Synthetikal Archive

phenylpropanolamine from benzaldehyde

Name phenylpropanolamine from benzaldehyde

IndoleAmine assuming minimal isomerization of the alanine enantiomer being used in conjunction with the potassium cyanate route, one enantiomer of alanine will lead to the weakest of the four stereoisomers while the other will lead to the strongest.[/quote:d78ba16d94]

I think thats exactly what Bandil said a few posts earlier: either you'll get a mixture of the weakest and strongest diastereomers, or you will get a mixture of the almost equipotent two medium strong diastereomers.

In each case, you'll have a racemic mixture with approx. the same strength - but upon optical resolution with tartaric acid, one mixture would give crap and highly potent 4-MAR 50/50, while the other will give two almost equally potent stereomers 50/50.....

So maybe it would be the best to just not resolve any optical isomers at all, but rather enjoy it racemic "as is"....

i_a

IndoleAmine As said already, I'm really a dumbass when it comes to stereochemistry sometimes, but my impression was too that d,l-ala would be the best choice - unless we know which stereomer of ala to use in the akabori to arrive at the "correct" isomer, to produce the more active 4-MAR isomer with the cyanate route (I am somewhat **a bit**

Astrum Like other phenylisopropylamine derivatives, 4-methylaminorex is a central stimulant. The cis isomer of 4-methylaminorex ("U4Euh"; "ICE") has appeared on the clandestine market as a novel designer drug and was recently classified as a Schedule I substance. In the present investigation, the stimulus properties of racemic cis, racemic trans, and all four individual optical isomers of 4-methylaminorex were examined in rats trained to discriminate 1 mg/kg of S(+)amphetamine sulfate from saline. The S(+)amphetamine stimulus generalized to all of the agents investigated and the relative potencies of the optical isomers (followed by ED50 values) were as follows:trans(4S,5S) (0.25 mg/kg) > cis(4S,5R) (1.2 mg/kg) = cis(4R,5S) (1.5 mg/kg) > trans(4R, 5R). The trans(4R,5R) isomer did not completely substitute for S(+)amphetamine unless a longer (i.e., 60-min) presession injection interval was used, suggesting that it has a longer duration of onset that the other isomers of 4-methylaminorex. The results, which are consistent with established structure-activity relationships, suggest that the trans(4S,5S) isomer (which has not been scheduled) is similar in potency to (+)amphetamine (ED50=0.4 mg/kg) and is more potent than either of the cis isomers. [/quote:bdc5a1e65a]

[url=http://dx.doi.org/10.1016/0091%2D3057%2890%2990282%2DM] [b:bdc5a1e65a]Stimulus properties of a new designer drug: 4-methylaminorex ("U4Euh")[/b:bdc5a1e65a][/url]

I'm well aware that d,l-cis-4-MAR is the scheduled one. In fact all four stereoisomers of 4-MAR are active making this somewhat of a trivial point. However, I was correct in saying that the trans(4S,5S) stereoisomer was the most potent of the four.

Phenylpropanolamine (1-phenylpropan-1-ol-2-amine) has four stereoisomers; l-norephedrine, d-norephedrine, l-norpseudoephedrine, and d-norpseudoephedrine. Theoretically which enantiomer of alanine you use will determine which stereoisomer of PPA you get as described by this:

[URL=http://www.imageshack.us][img:bdc5a1e65a]http://img203.exs.cx/img203/9997/lisomer1op.gif[/img:bdc5a1e65a][/URL]
[URL=http://www.imageshack.us][img:bdc5a1e65a]http://img203.exs.cx/img203/5961/disomer9th.gif[/img:bdc5a1e65a][/URL]

The trans diastereomer is d,l-norephedrine where as the cis diastereomer is d,l-norpseudoephedrine. So basically l-alanine should condense with benzaldehyde to give you the trans(1S,2S) or cis(1S,2R) stereoisomers of PPA and likewise d-alanine should condense with benzaldehyde to give you the trans(1R,2R) or cis(1R,2S) stereoisomers. If however, d-alanine or l-alanine are in fact isomerized [i:bdc5a1e65a]in situ[/i:bdc5a1e65a] in this reaction (to equilibrium I assume) then you should get a mix of all four stereoisomers. In which case what you want really depends on the type of reaction you're going to perform (cyanogen bromide or potassium cyanate).

So if you're bold enough to work with cyanogen bromide you can use any or all of the four stereoisomers of PPA that can be produced. If you're using potassium cyanate you need to isolate only the trans diastereomer, either enantiomer or both will work. I'll look into this more when I've had some sleep; but assuming minimal isomerization of the alanine enantiomer being used in conjunction with the potassium cyanate route, one enantiomer of alanine will lead to the weakest of the four stereoisomers while the other will lead to the strongest. So until someone can figure out which enantiomer of alanine leads to trans(4R,5R)-4-MAR I would suggest using d,l-alanine. If the cis diastereomer is used with potassium cyanate it will make trans-4-methyl-5-phenyl-oxazolid-2-one which can be catalytically hydrogenated to (S)-amphetamine if so desired.

That being said I haven't slept in 24 hours. So if anything doesn't make sense or I've made an error somewhere (which I surely have), please point it out to me and I'll correct it in the morning.

jackoozzi Here is a pic prom the merck references

http://img208.exs.cx/img208/3704/aspthumb2ca.jpg[/img:f60c292398][/URL]

Astrum a) 1-phenylpropan-1-ol-2-amine (PPA) used in nasal decongestants (and cold medications) is the racemic d,l-ppa.hcl (no brand names; but there are MANY! Wink) [/quote:576c1bcc3f]

It used to be used as a nasal decongestant but has since been banned in the USA. So there's no hope in finding it in pills around here.

I was under the impression that that the trans(4S,5S) stereoisomer was more active than the cis(4S,5R/4R,5S) stereoisomers. In which case l-alanine or d,l-alanine would be

preferred. But I could be wrong, I'm [i:576c1bcc3f]dead[/i:576c1bcc3f] tired right now :wink: . I'll look into it in the morning.

phenylpropanolamine from benzaldehyde

jackoozzi I cut this out of a post at wd and was wondering if anyone has done this or has any more information

Uncle Fester says somewhere in SOMM that PPA can be made from benzaldehyde and alanine simply by heating the two together until CO2 evolution ceases. Hmmm. Cinnamon oil -> benzaldehyde, benzaldehyde -> PPA, PPA -> 4-MAR. OTC, and so simple that even pill-cooks might be able to do it. Is this the Next Big Drug Problem just waiting to happen?

Country: | Posts: 7

Astrum
New Dreamer

Posted - Mar 21 2005 : 3:27:22 PM

Alright, I did a little digging on making phenylpropanolamine from benzaldehyde and alanine. It's known as the Akabori-Momotani reaction. It's the aldol condensation of amino acids with aromatic aldehydes to give amino alcohols.

So the reaction we're looking at is:
C3H7NO2 + C7H6O -> CO2 + C9H13NO

jackoozzi And just witch isomer of alanine would you need there seems to be a few including

d alanine
l alanine
dl alanine
b alanine

Astrum Here's the diagram:

http://img108.exs.cx/img108/4304/akaborimomotani2ev.gif[/img:fcabb14e14][/URL]

CherrieBaby The references (from the 13th Merck) are:
E. Takagi et al., *J. Pharm. Soc. Japan***71**, 648 (1951); **72**, 812 (1952);
A. Lawson, H. V. Morley, *J. Chem. Soc*. **1955**, 1695;
A. Lawson, *ibid*. **1956**, 307;

K. Dose, *Ber*. **90**, 1251 (1957);
H. V. Belikov et al., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1969**
!!

IndoleAmine I haven't understood yet where the saturated 1-5C LOWER fatty acid should come from if the ala is racemized in situ - the only reagents I see are benzaldehyde and an amino acid - and no "fatty acid" lower/shorter than alanine which is required....
did you mean in-situ formed benzoic (this is longer than 5 carbons)? Or do you think the evolving CO2 could accomplish what is necessary?

However, nice find - and the "priced dextrorotary PPA" is suitable for the potassium cyanate route I would assume, right? (Bandil, Astrum?)

Would be too kewl if the cheapest alternative would be the best here.... :D

i_a

Amino acids

synthetika I cautiously assume this is why L- alanine can be used, since it becomes racemic(dl-alanine) in situ,

This is good reading, the akabori, has quite a destiny,

Abstract of JP11322684
PROBLEM TO BE SOLVED: To improve the isomerization process, in other words, racemization and epimerization for optically active amino acids, typically alanine, &alpha - aminobutanoic acid, valine, leucine, isoleucine, phenylalanine, tryptophane and methionine, in the presence of a lower fatty acid and an aldehyde and provide an high-efficiency isomerization process for amino acids with lowered energy consumption and easy recycle of the lower fatty acid and aldehyde as the isomerization catalyst. SOLUTION: An optically active amino acid is dispersed in an inert solvent that substantially does not dissolve amino acids, preferably an aromatic hydrocarbon such as benzene, toluene, xylene or halogenated benzene. A lower fatty acid, preferably a 1-5C saturated fatty acid as acetic acid, propionic acid or butanoic acid and an aliphatic aldehyde or an aromatic aldehyde, preferably an aromatic aldehyde such as benzaldehyde or salicylaldehyde are allowed to act on the dispersion to effect the isomerization. The mixture of the optical isomers of the crystallized amino acid separating from the solvent are collected by the solid-liquid phase separation.

Abstract of JP57123150
PURPOSE:The racemization of an optically active aminoacid is effected in the presence of a lower fatty acid and an aromatic aldehyde to give the racemi aminoacid in high yield through one step and this process is applicable to a variety of aminoacids and the racemization rate is high. CONSTITUTION:An optically active aminoacid such as alanine, arginine, asparaginic acid or proline is racemized in the presence of a saturated fatty acid of 1-3 carbon atoms and an aromatic aldehyde such as benzaldehyde which may be a substituent such as hydroxyl, nitro, amino, methoxy or the like wherein the amount of the aldehyde is about 0.001-0.3mol and the lower fatty acid is more than 10 (V/V)% based on the optically active aminoacid.

Very interesting reading,

syn

IndoleAmine Since

a) 1-phenylpropan-1-ol-2-amine (PPA) used in nasal decongestants (and cold medications) is the *racemic*

did I already say I LOVE pictures?

IndoleAmine Lets see, hope I got this right:

(edit: I just noticed that the second rxn depicted above is in fact an esterification - the whole thing is acid-catalysed, and two hydrogens and one oxgen have to leave the carbamoyl molecule before it can close this oxazole-type ring - and after this dehydration has occured, we have a C-O-C structure, which all together represents the classical definition of an esterification, if I'm not completely debile...(:?:) - :lol:
- Now the next question: what type is the rxn I didn't include, the one between PPA/"norephedrine" and KOCN? I didn't include it because I don't understand it, maybe someone can help?)

i_a

IndoleAmine No, the d,l-*cis*

isomers

synthetika I believe both isomers of 4-mar are active,
As the L-alanine would be racemerized to DL-alanine in situ,

Wouldn't this them mean you would have then dl-PPA,

But then what happens to L-PPA in the KOCN,

What happens when L-alanine insitu becomes DL-alanine,
does the dl-alanie, keep getting processed until it all D-alanine, or D-PPA?

IS there only one optical molecular configuration for PPA?

SO accoring to the patents,
If you wanted all d-alanine, you would have to separate out D-isomer, and reprocess, a few times the remaing L-alanine?

What process to we have for separation of stereo isomers?

Tartaric acid?

I don't think it's of too much concern,
As long as you are happy with a racemic mix,
Which Is probably a good mix

syn

64bandil The cyanate route with norephedrine gives the *trans* isomer, whereas norephedrine with cyanogenbromide yields cis. norpseudoephedrine with CNBr gives trans and norpseudoephedrine with cyanogen bromide yields a crappy amide, thats completely inactive... phew! cyanate

IndoleAmine Nice. So stereochemistry is not much of a concern in the PPA->4MAR step, I would say - right? 8)

And my understanding is that the akabori-momotani gives only 1-phenylpropan-1-ol-2-amine (PPA), regardless which d, l or racemic stereomer of alanine you use, although it is possible that only one optical isomer will give 100% conversion - but since alanine is dirt cheap, it really shoudln't matter, since there is no "wrong" compound produced that could present a waste of aldehyde...

I think I will just try, visit my local pharmacy right after easter and tell'em I need a LOT of alanine, all isomers they have in stock (maybe I will have a serious nutrition disequilibrium, have a little sister with apoor ill rabbit, or wanna become a 200pound muscle monster by ingesting amino acids or something like that, what do you think?), and try and decarboxylate them with some BzCHO - maybe one ala isomer will give nearly double yields compared to the others, or maybe even 2x as much as the racemic and one wont work at all - we'll see....

(any stereochemistry expert wanna comment?)

i_a

that would be good

synthetika It would be nice to see a bit of real world experimentation on this alanine species,

L-alanine comes in the HCL salt, i believe?
As i have sometimes noticed on the packaging,

syn

Astrum I'm also wary of using cyanogen bromide, even if it would be more effective at converting both diastereomers of PPA. I'll work on seeing which enantiomer of alanine would best be suited for the job though. If it does turn out to be l-alanine then that would be pretty awsome 8) . If not then it can easily be isomerized so it's no big deal.

> **Quote**
> I think thats exactly what Bandil said a few posts earlier: either you'll get a mixture of the weakest and strongest diastereomers, or you will get a mixture of the almost equipotent two medium strong diastereomers.
>
> In each case, you'll have a racemic mixture with approx. the same strength - but upon optical resolution with tartaric acid, one mixture would give crap and highly potent 4-MAR 50/50, while the other will give two almost equally potent stereomers 50/50.....

> So maybe it would be the best to just not resolve any optical isomers at all, but rather enjoy it racemic "as is"....

stereo chemistry

synthetika It sounds ok to me,

And the chances are that if yo do use L-alanine anyway,
You will most likely end up with dl-Alanine in-situ , and then that will go to dl.PPA, even even that dl.PPA gets a few more d's than l's by again further isomerization,

So I would tend to think that L-alaine, is going to give DL-PPA, with probably a higer=her % of D-isomer,

If the akabori, is stated to yield only 15%, that is 15% of BzCHO used, not alanine, Since alanine would be the liniting reacteant(cost wise)
then You would say that you get a 50% yield, based on Alanine used,

That is definately not so bad,

syn
(i can't help but think there is a way once we find, which isomers(s) of PPA are best, then we could probably easily get the isomerizing to that isomer without too much trouble, if need be at all)

indole

synthetika Even if you start with L-alanine, it will be changed to dl-alanine insitu,
Resulting in racemic PPA,

l-alanine will be fine,

posted at wd.

> **Quote**
>
> Why has no one picked up the glaring error with regards to chirality of the alanine. In the reaction the aldehyde and amino acid condense to form an addition product before loosing CO2 to form PPA. This means that the chiral centre of the alanine has been inverted to give the opposite stereocentre. So to obtain the prized dextrorotary PPA we would need to use the freely available L-alanine.

Process for the production of serine derivatives, USP 450191

CherrieBaby Process for the production of serine derivatives[/b:2ee8be0809], USP 4501919.

Abstract: [color=green:2ee8be0809]Serine derivatives are synthesized by the condensation of an alkali metal salt of a glycine derivative and a carbonyl compound in the presence of a phase transfer catalyst.[/color:2ee8be0809]

(1) Patent image. Go to:
http://l2.espacenet.com/espacenet/viewer?PN=US4501919&CY=ep&LG=en&

DB=EPD
then click the link to "[b:2ee8be0809]Requested Patent[/b:2ee8be0809]"

(2) Patent text. Go to:
http://patft.uspto.gov/netahtml/search-adv.htm
and enter "[b:2ee8be0809]pn/4501919[/b:2ee8be0809]" as your query. Click [b:2ee8be0809]Search[/b:2ee8be0809].

PS: Phenylpropanolamine is a serine derivative. Alanine is a glycine derivative (see patent abstact).

Astrum Yeah, I caught what Rumplestiltskin said. He might be right but I'm not sure right now, I'll look at it later. I did do that late one night after a full day at university, so I might have made a dumb mistake like he said.

He didn't back up his post with any substantial information, sources, or work so I'm not sure if he just assumed the dextro enantiomer* will give you trans(4S,5S)-4-MAR or not**.

*Only one of the dextro enantiomers are suitable to be used with potassium cyanate. The other dextro enantiomer is cis and wouldn't give you 4-MAR at all. trans(1R,2R)-1-phenylpropan-1-ol-2-amine being d-norephedrine (debatable, but would agree with rhodium's, bandil's, and Rumplestiltskin's posts).
**This is assuming "..prized dextrorotary PPA.." insinuates the end product will be the most potent stereoisomer of 4-MAR. His post wasn't exactly clear on that.

CherrieBaby I would expect the end product to have a racemic mixture due to racemization during the reaction in a similar way to how reactants of the corresponding **C-alkylation of amino acids**

IndoleAmine Something I have found over at WD: Fishinabottle clarifies on the chirality issue and answers the question quite good I think:

> **Quote**
> Norephedrine is the isomer of PPA which can be converted into
> 4-MAR by potassium or sodium cyanate (not the toxic cyanide).
> PPA is +/- norephedrine and +/- norpseudoephedrine.
> Norpseudoephedrine requires cyanogen bromide - nasty stuff this is.
> Norephedrine yields trans-4-MAR, the most potent isomer.
> Norpseudoephedrine yields cis-4-MAR.
>
> Oh, yes - cyanogen bromide also works on norephedrine, the
> cyanate works not on norpseudoephedrine though.
>
> Confusion completed?
> Ok. ;)

IndoleAmine

IOC
(Stranger)
12-07-01 04:28

No 245275
Akabori run Bookmark

crap, at best 15% using 100 g BnZ, 40g l-alanine.
Heat to 140 seems best, extracted into H2o and evaperate, then clean up.
would decarboxylation of a methylamino over the amino maybe improve results?
How about a base and high bp solvent with C5H5N??
as suggested in tfse.
could some one please explain the reaction mechanics for the reaction:
,on heating BzH and DL-alanine directly; PhCH2NH2, PhCH(OH)CHPhNH2 (2 dl-compds.), AcH, and CO2 are formed.
Is this a condensation (no H2o) or a decarboxylation?
what conditions would be pref?
any ed imput would be great, cheers

jim
(Hive Bee)
12-07-01 05:53
No 245287
Re: Akabori run Bookmark

Give references.

Personnally I don't know of this reaction, and am wondering why you would even attempt it? Get phenylalanine and decarboxylate instead...

Aurelius
(Hive Bee)
12-07-01 10:15
No 245346
Re: Akabori run Bookmark

complicated rxn mechanism for just words. you'd have to look up the actual article.
(btw- your yeild will go up if you calculate according to the converted benzaldehyde, and recover the rest for a second go)

IOC
(Stranger)
12-08-01 01:33
No 245572
Re: Akabori run Bookmark

An otc way to PPA, what I,ve dug up so far

Synthesis of aminoalcohols by aldol condesation of aminoacids with aromatic aldehydes.
The alanine is reduced via -COOH => -CH2-OH

Reaction between aromatic aldehydes and a-amino acids. I. New facts on the Akabori reaction. Takagi, Eiichi. J. Pharm. Soc. Japan (1951), 71 648-51. Journal written in Unavailable.

Abstract
The Akabori reaction (I) (C.A. 41, 3774g) on BzH and dl-MeCH(NHMe)CO2H (II) with and without pyridine and removal of the unreacted BzH by steam distn. gave dl-ephedrine and dl-y-ephedrine. Similarly, direct heating of piperonal and II gave 2 dl-1-(3,4-methylenedioxyphenyl)-2-methylamino-1-propanols. A new reaction (III), differing from I, takes place on heating BzH and DL-alanine directly; PhCH2NH2, PhCH(OH)CHPhNH2 (2 dl-compds.), AcH, and CO2 are formed. It is considered that the I-type reaction occurs when the N of the amino acid is secondary and the III-type reaction when it is primary.

Fester5 sites that direct heating of 20g N-methyl-alanine
with 50g Bnz at 150deg untill fizzing stops, produces
12g of a mixture 3g ephedrine and 9g pseudoephedrine isomers.

Reactant BRN 471223 benzaldehyde
1720250 DL-alanine
Product BRN 3196917 (1RS,2RS)-2-amino-1-phenyl-propan-1-ol

Reaction Details
Reaction Classification Preparation
Temperature 140 #65533;C
Other conditions Erwaermen des Reaktionsprodukts mit wss.-aethanol. HCl
Ref. 1 2262852; Journal; Takagi et al.; YKKZAJ; Yakugaku Zasshi; 73; 1953; 1086; Chem.Abstr.; 1954; 12021;

As promised, here are some more refs on the interesting condensation reaction between aromatic aldehydes and glycine/alanine:
BER 25: 3445 (1892) + 52 :1734 ('19)
ANN. 284: 36 + 307: 84
JCS 1943 ('26) + 2600 ('22)
JACS 76: 1322 ('54)
J.PHARM.SOC.JAP. 67: 218 ('47)
Most of the articles are pretty old to say the least but they contain some interesting stuff on the reaction we're interested in here. I'm especially interested in the J.Pharm.Soc.Jap article, which describes the preparation of a methylenedioxy-substituted phenylserine. But the practical way to go is definitely as mentioned in a certain patent, that is using a two-phase solvent system. This prevents the benzylidene phenylserine from crystallising and makes sure that the reaction mixture can be stirred at all times.
After decarboxylation, these phenylserine derivates turn into amino alcohols, the perfect substrates for aminoxazolines. By substituting the benzaldehyde, a lot of phenylserine and amino alcohol derivates can be made and thus a lotta aminoxazolines!

So with some 10x experiments with 20g alanine + 50g BnZ
a massive 15% return sux, any suggestions besides learn how to make nitroethane?

java
(Hive Bee)
12-04-02 08:24
No 386214
Re: akabori: Bookmark

Did I read this correctly then one can then make ephedrine using this method.....well have you tried it and what are the conditions since I can't find the article ,,,anyone?

Akabori
Also known as Akabori-Momotani
Synthesis of aminoalcohols by aldol condesation of aminoacids with aromatic aldehydes.

[image]

Bibliography

Akabori S., Momotani K., J. Chem. Soc. Japan, 1943, 64, 608; C. A., 1947, 41, 3774
Dose K., Ber., 1957, 90, 1251.
Belikov V. M., Izv. AN SSSR. OHN, 1969, 2536.

This I was able to locate.

Rhodium
(Chief Bee)
12-04-02 08:53
No 386225
Akabori Bookmark

Yes, it's correect that you can make ephedrine very simply with the Akabori reaction between Benzaldehyde and N-methylalanine. Ordinary alanine would give phenylpropanolamine.

The only one of the above articles I could locate was J. Am. Chem. Soc. 76, 1322 (1954) (https://www.rhodium.ws/pdf/akabori.phcho.glycine.pdf).

I doubt that the original reference has been retrieved as it is written in Japanese, and "IOC" is not likely to answer you either, as he hasn't been logged in since June.

----------[/quote:46de70c811]

and

[quote:46de70c811]
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dormouse
(Member)
04-22-00 02:13
No 108531
phenylpropanolamine from benzaldehyde and alanine -drone 342 Bookmark

the Hive BB
Novel Discourse
phenylpropanolamine from benzaldehyde and alanine

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Author Topic: phenylpropanolamine from benzaldehyde and alanine
drone 342
Member posted 10-15-98 09:18 AM

Reactant BRN 471223 benzaldehyde
1720250 DL-alanine
Product BRN 3196917 (1RS,2RS)-2-amino-1-phenyl-propan-1-ol

Reaction Details

Reaction Classification Preparation
Temperature 140 #65533;C
Other conditions Erwaermen des Reaktionsprodukts mit wss.-aethanol. HCl
Ref. 1 2262852; Journal; Takagi et al.; YKKZAJ; Yakugaku Zasshi; 73; 1953; 1086; Chem.Abstr.; 1954; 12021;

This informative post was brought to you by drone(tm) #342, who reminds you: euphoria -- its what's for dinner.

-drone #342

Rhenium
Member posted 10-15-98 10:20 AM

Drone,
I have a similar paper here, it's in Japanese and was published around 1942. I can't read it, but the pictures suggest that they reflux the two and get the PPA and CO2 produced. They have a little picture of piperonal as well, but I can't figure out what they're trying to do with it.

Take care,

Rhenium

beagle boy
unregistered posted 10-15-98 10:50 AM

Shwing! I like what I hear. But I only hear the basic outline. Can anyone (please) fill in the details. Like what solvent? How long a reaction time? Japanese writing looks cool, but thats about all I get out of it.

Labrat
Member posted 10-15-98 10:51 AM

This is great and shit at the same time, great because it's one beautiful method of making PPA from simple reagents, shit because the article is in Japanese!
There are professional translators on the Net. How about paying one to translate the experimental section of the two Yakugaku Zasshi articles we have? If we share the costs, it won't be that expensive. Lr/

drone 342
Member posted 10-15-98 03:38 PM

I have a friend who's a Japanese native. The problem is she knows nothing of chemistry. I sat down with her, and we went through the Yakugaku Zasshi article from a while back, but they really didn't say anything too intersting that I hadn't read elsewhere.
I could talk to her about translating the the two papers, but you'll have to send me the second one, Rhenium. Hope you have a scanner.

-drone #342

Cherrie Baby
Member posted 10-15-98 04:48 PM

US patent 4501919 describes the reaction of glycine with p-nitrobenzaldehyde (in a two phases: H2O-DCM with MeBu3NCl as a PTC and concn. NaOH as a base, at 5-7#65533;C) to give b-hydroxy,p-nitro-tyrosine.
What would happen if alanine were used in place of glycine? The a-methyl analog?, which could be decarboxylated to p-nitro-norephedrine? Your guess is as good as mine. This looks like an interesting patent to explore as all the reagents are OTC.

It would work with other ring-substituents apart from nitro-, but I only discovered the Chem. Abstract tonite [CA:102, 204296] and I've not yet read the patent!

beagle boy

unregistered posted 10-15-98 08:48 PM

Just checked that patent and saw that they were getting 70+% yield of the #65533;-hydroxy phenylalanine derivative from this easy procedure. And makes sense that alanine gives the alpha-methyl derivative, which should be more readily decarboxylated, no?
So if just refluxing these cpds. in say, xylene, will decarboxylate in good yields, this is one dandy scheme. Easy access to both ethanolamines and propanolamines for that comprehensive aminorex study.

Rhenium
Member posted 10-16-98 10:22 AM

Drone : My friend with the scanner will be back in a couple of days. I will try sending it to you after that. This could be a very interesting procedure, hopefully the yields will be nice...
Take care,

Rhenium

Cherrie Baby
Member posted 10-16-98 05:56 PM

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beagle boy
In one of my references that quotes this they said that it was an Aldol condensation between the aldehyde and the amine forming an imine - which was subsequently hydroysised back to an amine, after condensation with a further 1 mol of glycine. So it looks like a different reaction mechanism to the one Drone's talking about - theres only a slight possibility that it might work with alanine. [I don't think so - I'm almost sorry I posted it - but it looked good to me when I first saw it.

[no don't ask me I never thought that amines underwent Aldol condensations either!]

beagle boy
unregistered posted 10-16-98 10:12 PM

Cherrie:
I believe the patent you gave claims alanine could be used. Checkitout:
http://www.patents.ibm.com/cgi-bin/viewpat.cmd/US04501919__
Wierd amine aldol condensation, different from what I was thinking. The question about decarboxylation remains, but I think these serine derivatives should decarboxylate quite a bit easier than tryptophan.

One downside to the above condesation is that the benzaldehyde would have to be in twofold XS. The extra benzaldehyde is claimed to be recovered for recycling after the reaction, but I'm not so keen about letting precious aldehydes stir around in aq. NaOH and then trying to recover them. Maybe the other route will turn out better.

Wouter
(Stranger)
01-28-03 17:40
No 402127
Full text journal of the akabori-momotani reaction Bookmark

Has any one the Full text journal of the akabori-momotani reaction?
Akabori S., Momotani K., J.Chem.Soc.Japan, (1943), 64, 608; C.A., (1947), 41, 3774
Is it possible to copy it and send it to me (wouter@chemist.com). Please??

java
(Hive Bee)
01-28-03 18:24
No 402132
Re : Akabori..... Bookmark

This is all that is currently available....Akabori
Also known as Akabori-Momotani
Synthesis of aminoalcohols by aldol condesation of aminoacids with aromatic aldehydes.
Bibliography
Akabori S., Momotani K., J. Chem. Soc. Japan, 1943, 64, 608; C. A., 1947, 41, 3774
Dose K., Ber., 1957, 90, 1251.
Belikov V. M., Izv. AN SSSR. OHN, 1969, 2536.
although not available there is this at Rhodium's place.....https://www.rhodium.ws/pdf/akabori.phcho.glycine.pdf.
this ofcourse combined with Rhegis's post Post 367468 (Regis: "The most interesting

CTH reaction ever documented?", Novel Discourse)
makes for a nice package for the synthesis for amphetamines.....java

Rhodium
(Chief Bee)
01-29-03 01:00
No 402201
Lots of threads on Akabori Bookmark

Post 122768 (dormouse: "Condensations of benzaldehyde and alanine", Serious Chemistry)
Post 245275 (IOC: "Akabori run", Novel Discourse)
Post 278820 (ChemicalSolution: "alanine and Akabori???", Chemistry Discourse)
Post 300434 (not existing)
Post 329052 (Aurelius: "Akabori-Momotani reaction", Chemistry Discourse)
[/quote:46de70c811]

Hope this helps!?

i_a

IndoleAmine And here's the corresponding thread over at WD, together with the original article on the Akabori-Momotani rxn:

http://www.wetdreams.ws/forum/topic.asp?TOPIC_ID=1716

The preparation of Hydroyphenylserines from Benzyloxyaldehydes and Glycine (William A. Bolhofer)

nzbee So has anyone sucessfully completed this reaction?? Would be keen to see a write up of a this if it was sucessful.

DrugPhreak Shouldn't a solvent be used? All the patents I've read that use similar compounds, which give a good yield etc do so. The posts that state the yield was low just mixed the two together and maybe they didn't heat it high enough also. Details are non-existent.

Astrum Yes it has been successfully completed.

Yes a solvent should be used.

Lep.CON Origianally posted at the hive by Aurelius and write up by Driven

Quote

"PPA via Akabori of benzaldehyde and alanine.

1) 100g of benzaldehyde was placed in a 250 ml rbf and 40g of dl-alanine (molecular bio grade) was added with stirring.
2) The mixture refluxed at 140 degrees C with heavy stirring for 3

hrs. The reaction mixture went through notable characterisitics. When the temperature of the liquid reached 115 deg, the mixture evolved CO2, emanating particularily around the alanine and condensate was apparent in the condenser. At 140 deg, T=0 the solution was lime green. At T=15min, pee yellow, at T=30 min, deep orange, T=40 min, red-orange,
3) At T= 3hrs, the solution was a deep red colour. Another solution phase was apparent and was of fluffy consistency and crème in colour. It was unclear at this point whether the reaction was finished. Previous reports have suggested ceasing of gas evolution as an end point however this was difficult to tell since the solution was boiling as well.
4) The post-reaction was cooled to 4 degrees and slowly with good stirring 30% HCl was added until the solution was ph= 2.
5) The mixture was vacuum filtered twice to remove insolubles. There was about 1 tablespoon. (unreacted alanine?).
6) The filtrate was washed with 2 X 100ml of DCM. Much of the red colour present in the filtrate moved into the DCM. The aqueous took on a light, clear yellow.
7) The aqueous was basified to ph=13 slowly with 30% NaOH. Solution progressed from yellow to cloudy white with a deep orangy oil falling to the bottom of the beaker. Only about 5-10 ml of this oil was present.
8) The basified solution was extracted with 3 X 50 ml of DCM, extracts combined and fractionally distilled at atmospheric pressure.
9) After the DCM had come off, the heat had to be cranked up quite a bit for the next fraction (PPA?) to come over at 85 deg C. (quite a bit off from bp of PPA being 100 deg C. as published?). It condensed much like water and had a strong amine smell to it. Only 3g of distillate came over.
9) Upon continued heating the remaining liquid in the boiling flask sublimed into a deep red chunk. No other fractions besides the one at 85 deg C. came over.
10) As a check, the original DCM washes were back extracted with acidic aqueous, basified, extracted with DCM and distilled. The 85 Deg C fraction was absent and once again the remnants in the boiling flask sublimed. Urgh!"

IndoleAmine Concluding it doesn't work just because he fucked up a vacuum distillation of an amine freebase? No no - we'll see. :D

(he made a small error in the workup, for example...)

i_a

Lep.CON I hope your right

java Here is the whole thread with comments on it's viability .....java

---

DRIVEN
(Stranger)
06-18-03 09:40
No 440837
PPA via Akabori of benzaldehyde and dl-alanine Bookmark

Hi everyone,

D was very excited to see Bandils' success with the synthesis of 4-MAR with the use of KOCN. D is deeply intrigued by this substance and would like to dream up its existence and was wondering if someone could possibly offer some advice about the production of the precursor, dl-PPA. Though it may seem more appropriate to derive PPA from the reaction of nitroethane and benzaldehyde, it would be nice to derive dl-PPA through the Akabori rxn of benzaldehyde and dl-alanine for practical reasons. If this direction seems futile, please by all means speak your mind and D will get off the train here as he doesn't have any experience with this reaction.

IOC performed a run by combining 100g BnZ and 40g l-alanine, heating the mixture to 140 (until fizzing stops),extracted the post reaction with H2O, concentrated, then cleaned up the crude product (how it was cleaned wasn't specfied). In this case there was 15 % yield - which was low but for D, 15% yield would suffice if properly purified. Given PPA is produced, D thinks the next issue is to determine the nature of side products and how to separate them from the target especially when they are likely to be in large quantities from a low yielding reaction. According to Takagi et al (1): When BzH and DL-alanine are heated directly; PhCH2NH2, PhCH(OH)CHPhNH2 (2 dl-compds.), AcH, and CO2 are formed.

D searched for the physical data on PPA and these side products. These (incomplete) data are indicated below (2).

Proposed cleanup (a work in progress): After extracting the post reaction with water, it would be expected that at least benzylamine (PhCH2NH2), being water soluble, would travel along with the PPA. Since the bp of benzylamine, 182 - 185 deg C (760mmHg), is about 80 degrees higher than PPA base then the mixture could be distilled to collect a fraction at 100-105 deg C containing PPA base and water. D is unsure about how to subsequently separate the PPA base from water given their bp's are so close. D had difficulty finding the bp or solublity data for 2-amino-1,2-diphenylethanol (PhCH(OH)CHPhNH2) so D is still unsure about how to predict its removal.

My questions are:

1) It is assumed that the post reaction will be basic and therefore PPA in its base form, is this correct?
2) Could one separate PPA base from water by acidifying it (making PPA-HCL which has a higher bp than water) and concentrating the mixture?
3) Does anyone know where to find the solubility and bp data for the 2-amino-1,2-diphenylethanol contaminant?
4) Can benzylamine be removed from the reaction mixture as proposed above?
5) What does "AcH" abbreviate?

Any input, directions and comments would be much appreciated!

Take care

DrIvEnwink

References and Data:

(1) Reaction between aromatic aldehydes and a-amino acids. I. New facts on the Akabori reaction. Takagi, Eiichi. J. Pharm. Soc. Japan (1951), 71 648-51.

(2) Physical Data of Various Chemicals Produced by the Akabori Reaction of Benzaldehyde and dl-alanine

Phenylpropanolamine (racemic mix of d- and l-norephedrine)

Base Bp: 101-101.5°
HCl Bp : 190-194°
HCl (+)-form Bp : 171-172°

PhCH2NH2 is benzylamine:

Physical State:
Liquid Appearance: clear colorless to slightly yellow
Odor: ammonia-like
pH: Not available.
Vapor Pressure: 0.6 mbar @ 20 deg C
Viscosity: mPas 20 deg C
Boiling Point: 182 - 185 deg C @ 760.00mm Hg
Freezing/Melting Point: 10 deg C
Solubility in water: > 500 G/L (20°C) IN WATER
Specific Gravity/Density: .9810g/cm3

d,l-PhCH(OH)CHPhNH2 is 2-amino-1,2-diphenylethanol:

This compound has several racemic forms, (1R,2R)(1S,2R)(1RS,2RS),(1RS,2SR)

For example: (1R,2R)-(+)-2-Amino-1,2-diphenylethanol:

Product Number 523704 CAS Number 88082660 Formula C14H15NO Formula Weight 213.3 APPEARANCE WHITE POWDER MELTING POINT 143.8-146.8 DEGREES CELSIUS INFRARED SPECTRUM CONFORMS TO STRUCTURE. PROTON NMR SPECTRUM CONFORMS TO STRUCUTRE. TITRATION 99.1 % (WITH HCLO4) OPTICAL ROTATION +7.5 DEGREES (C=0.6198%, ETOH)
It just seems to go faster...

Aurelius
(Active Asperger Archivist)
06-18-03 11:50

No 440858
Information Bookmark

Hey DRIVEN, take a look.

Post 422067 (Aurelius: "Ephedrine Compilation", Stimulants)

Just about anything you ever wanted to know about the subject. If you've read all of this, let me know and I'll help you out with your questions.

1. Yes, the mixture begins basic, probably ends that way too. Depends on the reaction conditions mostly.

2 & 4. You should clean the reaction mixture by first acidifying the mixture with 10-30% HCl until strongly acidic to litmus. Then filter the whole mess twice to remove any nastiness that we don't want. extract the mix twice with 2x50ml of DCM (or other suitable non-polar) and Separate any layers present and keep the aqueous layer. slowly add NaOH solution (10-30%) until stongly basic to litmus. Extract the mixture with DCM 4x50ml and keep the extract. Combine the extracts and remove the solvent. Fractionally distill the remainder.
benzylamine will be removed when you fractionally distill.

3. try the merck, lang's handbook, CRC handbook, or any of the other very common handbooks with chemical data. It'll be in at least one of them, if not all.

5. AcH is just another way to write Acetic acid. It is more commonly abbreviated as AcOH.
Act quickly or not at all.

DRIVEN
(Stranger)
06-18-03 18:39
No 440932
PPA via Akabori of benzaldehyde and dl-alanine Bookmark

Thanks for being so helpful Aurelius.

Your awsome!wink
It just seems to go faster...

Rhodium
(Chief Bee)
06-19-03 10:41
No 441066
Ac signifies acetyl, CH3CO- not acetoxy, CH3COO-
(Rated as: Good Read) Bookmark

Ac is most often an abbreviation for acetyl { CH3(C=O)- } - not acetoxy { CH3(C=O)O- / AcO- } nor acetate { CH3COO- / AcO- }.

For example, Ethyl Acetate is properly abbreviated EtOAc (and not EtAc) as its structure is CH3CH2O(C=O)CH3.
EtAc is the abbreviation of CH3CH2(C=O)CH3 - methylethylketone (MEK)!

From the above follows that AcOH is a correct designation for CH3COOH, or acetic acid, and that the often incorrectly interpreted AcH really designates { CH3(C=O)H / MeCHO } - acetaldehyde, or etanal!

Aurelius
(Active Asperger Archivist)
06-19-03 11:09
No 441072
Rhodium Bookmark

I'm not going to say you're wrong, but given the large number of newbees around here, I still think that the abbreviation was probably meant to be understood as acetic acid.

Driven, could you please post the article in which you found the abbreviation and use a colored markup to point it out? (surround the word with word But without ANY of the spaces and you get word.
Act quickly or not at all.

Rhodium
(Chief Bee)
06-19-03 12:18
No 441098
Ac nomenclature Bookmark

The earliest mention of at the hive together with Akabori discussions is in the abstract in the first CA citation in Post 227827 (foxy2: "Re: P2P - 100% OTC !?!", Chemistry Discourse) - The reaction seem much more likely to produce acetaldehyde than acetic acid.

PhCHO + CH3CH(NH2)COOH -> PhCH2NH2 + PhCH(OH)CH(NH2)Ph + AcH + CO2

My main point wasn't to only correct this instance of possible Ac-nomenclature confusion, but also to write a post which to refer back to in the future, should confusion happen again. Regardless of what newbees may write by mistake, it is imperative that we teach them the correct nomenclature now, before we cannot find anything we can be sure of in the archive...

Astrum Alright, well SWIM tried this reaction a few days ago. Not the traditional one, but this one:

Quote

Water (400 g), 212 g of benzaldehyde and 120 g of toluene were added to 60 g of glycine. With stirring at 10 DEG to 15 DEG C., 177.8 g of 45% sodium hydroxide was added dropwise over the course of 2 hours. Then, the reaction temperature was gradually raised to 20 DEG C., and the reaction was carried out at 20 DEG to 25 DEG C. for 20 hours. After the reaction, 292.0 g of 35% hydrochloric acid was added dropwise at a temperature of not more than 40 DEG C., over 45 minutes. The mixture was further stirred at room temperature for 1 hour. After standing, the lower aqueous layer was separated and analyzed by high-performance liquid chromatography. The ratio of formation of .beta.-phenylserine was 92.6% (based on glycine). The aqueous layer was neutralized to a pH of 6 with 45% sodium hydroxide, cooled to 0 DEG to 5 DEG C., stirred at the same temperature for 1 hour, filtered, washed with cold water, and then dried under reduced pressure at 50 DEG C. to give 131.4 g of white crystals of .beta.-phenylserine. The purity of this product analyzed by high-performance liquid chromatography was 90.5%. Differential thermal analysis showed that the product had one molecule of water of crystallization. The yield of the product (based on glycine) was 82.0%. Melting point: 198 DEG-200 DEG C. (decomposition).

As described in this patent. SWIM used the same molar ratios for everything and obviously replaced glycine with alanine (levorotary isomer only).

SWIM did this mainly because it sounded too easy to be true. Well after adding the HCl(aq) SWIM had a sudden influx of work and was delayed at getting back to it until today (two days later). Well it seperated into two layers, a bottom aqueous layer and a top layer that literally looked and behaved like diarrhea which is quite disturbing. Anyway there was some crystallization, not a ton, but the bottom started to needle out as well as right under the diarrhea layer. So obviously *something*

PPA via knoevenagel - maybe easier?

IndoleAmine Just wanted to remark that you can as well condense benzaldehyde with nitroethane using KOH catalyst to yield the nitro alcohol 1-phenyl-2-nitropropan-1-ol (P2NPol), which is easily reduced with Zn/HCOOH to yield phenylpropanolamine... :wink:

Quote

(c) Method of Kamlet (3). Benzaldehyde (106 g., 1 mole) was vigorously agitated with sodium bisulfite (110 g., 1.06 mole) in 500 ml of water until the formation of the addition compound was complete. Simultaneously, nitroethane (or nitromethane) (82.5 g., 1.10 mole) was dissolved in a solution made from sodium hydroxide (45 g., 1.125 moles) dissolved in 200 ml of water. This solution was gradually added, with agitation and at room temperature, to the addition product of benzaldehyde and sodium bisulfite. After stirring for a half hour, the mixture was allowed to stand overnight. The

> lower layer was discarded and the upper layer was dissolved in ether and washed with sodium bisulfite solution. The ethereal solution was dried over Drierite, and after removal of ether, distilled (bp 120-130 @ 2-4 mm). The usual conversion is 90-100g. (50-55%) and the yield, based on benzaldehyde which reacts is nearly quantitative.
>
> Preparation of 2-amino-phenyl-1-propanol. (a) With zinc and sulfuric acid. Sulfuric acid (375 g of 30% acid) was added with stiring to a mixture of 2-nitro-1-phenyl-1-propanol (54.3 g., 0.3 mole), zinc dust (90 g., 1.37 mole of 80 mesh zinc), and 100 ml of 95% ethanol. The acid was added at such a rate that the temperature remained at 45 deg C or below. Usually 10 to 12 hours were required. Agitation was continued for 1-2 hours after completing the addition of acid, then after extracting the acidic solution with ether to remove non-basic materials, a large excess of sodium hydroxide (as a 50% solution) was added. The product which was freed was extracted with ether. Three extractions, with a total of 500 ml of ether, sufficed. The ether solution was dried, ether was removed, and the product was distilled (b.p. 122 deg C at 4 to 5 mm); 29-32 g resulted (yield 65-70%). The viscous liquid solidified on standing, and m. 46-50 deg C.
>
> According to the article, "The unmethylated amino alcohol was obtained by reduction of the nitro alcohol either with zinc and sulfuric acid, tin and hydrochloric acid, sodium amalgam and acetic acid . . . "

http://12.162.180.114:90/synthetika/hiveboard/chemistrydiscourse/000242981.html

I would guess that the bisulfite adduct is just used to stabilize the BzCHO somehow, and that this base-catalysed henry rxn will work fine with just plain BzCHO, KOH and C2H5NO2.

EDIT: just noticed that it is supposed to be Zn/H2SO4 originally; don't see any reason why formic wouldn't work as well though, since Zn nitro->amine reductions generally leave OH groups untouched IIRC.

See also:

Journal of Chemical Research, Synopses, 2003, 6, 332-334 "Zinc/ammonium formate: a new facile system for the rapid and selective reduction of oximes to amines" (K. Abiraj; D. Channe Gowda)

Indian Journal of Chemistry, section B: Organic Chemistry (2001), 40B(1), 75-77 "Zinc-catalysed ammonium formate reductions: rapid and selective reduction of aliphatic and aromatic nitro compounds" (D. Channe Gowda; B. Manesh; Shankare Gowda)

Then there's always the possibility of a NH4COOH/Pd-C CTH reduction of the nitro alcohol...

> **Quote**
>
> Experimental:
> A typical procedure is as follows: to a solution of the nitro alcohol (3b) in THF and methanol (50:50, 10ml) was added 10% Pd/C (50mg) followed by ammonium formate (0.35g, 5 eq). The mixture was stirred at RT until all the starting nitro alcohol had been consumed. (TLC). The mixture was diluted with Et2O (100ml), filtered, and the filtrate was evaporated in vacuo to yield the crude amine. Flash column chromatography gave the amine (4b) .

http://12.162.180.114:90/synthetika/hiveboard/methods/000435002.html

(for another NH4COOH/PD-C CTH on nitro compounds, see also *Tetrahedron Letters 25(32), 3415-3418 (1984): "A general procedure for mild and rapid reduction of alipathic and aromatic nitro compounds using ammonium formate as a catalytic hydrogen transfer agent" (S. Ram; R. E. Ehrenkaufer)*

IndoleAmine Astrum: the BzCHO dissolves in the toluene, the l-alanine dissolves in the water - you'll need a PTC or other surfactant to accomplish any appreciable rxn rate I think, or at least vigorous stirring...

> **Quote**
>
> "As required, a phase transfer solvent may be added to the reaction system. This promotes the reaction and the yield of the .beta.-phenylserine increases. The effect of adding the phase transfer catalyst is particularly remarkable when the amount of the alkali used is not more than 1.5 equivalents based on the starting glycine."

Bluechip Bandil has had success with simular using trethylamine as catalyst.He also explains why this is favourable over NaOh catalyst, for producing the wanted isomer.

THE NEW VERSION.

.
http://v3.espacenet.com/textdes?DB=EPODOC&IDX=US5750802&F=0&QPN=US5750802

Nitroethane (10.2 g., 0.132 mole) was mixed with triethylamine (17.1 g., 0.169 mole), cooled to a temperature of -8 DEG C. and benzaldehyde (5.1 g., 0.047 mole) added. After 2.7 hours at -10 DEG C., the mixture was neutralized. HPLC analysis showed a conversion of 8.25 g. (96.9%) of total 2-nitro-1-phenyl-1-propanol. 6.40 g of the 2-nitro-1-phenyl-1-propanol was the (1R*,2S*)-stereoisomer (77.6%).

EXAMPLE 2

Nitroethane (15.6 g., 0.208 mole) was mixed with triethylamine (17.1 g., 0.169 mole),

cooled to a temperature of -8 DEG C. and benzaldehyde (5.02 g., 0.047 mole) added. After 2.25 hour reaction time, at -10 DEG C., the mixture was neutralized. HPLC analysis showed a conversion of 8.30 g (96.9%) of total 2-nitro-1-phenyl-1-propanol with a (1R*,2S*)-stereoisomer content of 6.11 g. (74.1%).

Hydrochloric can alkso be used for the zinc reaction
REDUCTION AND RESOLUTION.

http://v3.espacenet.com/textdes?DB=EPODOC&IDX=US5962737&
F=0&QPN=US5962737

EXAMPLE 1

A racemic mixture of threo nitroalcohols was prepared by combining freshly distilled benzaldehyde (1 mole), nitroethane (2.5 moles), and triethylamine (0.05 mole) in ethanol (150 ml.) with water (75 ml.). This mixture was allowed to stand at room temperature in the dark for twenty-four hours. The mixture was then ice-cooled and acetic acid (0.05 mole) was added to the reaction mixture. Alcohol and excess nitroethane were evaporated (vacuum). Water (75 ml.) was added and the nitro alcohol extracted with ethyl acetate, dried over anhydrous sodium sulfate and the solvent evaporated (vacuum) to give the product, a viscous oil (yield 70-80% based on the benzaldehyde). GC/MS and NMR data were consistent with proposed structures. NMR indicates pure threo isomer on the basis of the coupling constant of the benzylic proton
.

EXAMPLE 2

The nitro alcohols were reduced by two methods, a zinc and acid method and a lithium aluminum hydride method as described below:

(A) Zinc and Acid

Hydrochloric acid (4 moles) is added (with stirring) to a mixture of nitroalcohol (1 mole), zinc dust (4 moles), and 400 ml. of 95% ethanol. The acid is added at such a rate that the temperature remains at 45 degrees or below (several hours are usually required). Stirring is continued for 1-2 hours after completing the addition. The acid solution is extracted with ether to remove non-basic materials. Excess NaOH solution is then added and the free base extracted with ether. The ether solution is dried (MgSO4) evaporated, and the product distilled or crystallized in the usual manner (70-80% yield

The reaction mixture of reduced nitro alcohols was resolved into optically pure isomers by the following process.

A mixture of a DL-threo-2-amino-1-phenylpropanol (1 mole) in dichloromethane (600 ml.), dibenzoyltartaric acid (0.5 mole) in distilled water (30 ml.), and sodium hydroxide (0.5 mole) in distilled water (50 ml.) is stirred rapidly for two hours and allowed to stand for two hours. The dichloromethane phase is separated using a separating funnel over anhydrous magnesium sulfate. Rotary evaporation of the dichloromethane phase

gives the L-threo isomer in nearly quantitative yield.

The aqueous phase is made alkaline with ammonia to pH 13 and extracted with dichloromethane. The dichloromethane extract is dried over anhydrous magnesium sulfate and evaporated to give the D-threo isomer in nearly quantitative yield. The enantiomeric purity of the products is 96-99% based on GLC analysis of the D or L-.alpha.-methoxy-.alpha.-trifluromethylphenylacetamide (MTPA) derivatives.

****

Astrum,

Thankyou for trying this out and posting your results.
Over at WD I posted a ref for a French patent in the same post.
It is in french(duh) but a quick babelfish translation shows that the reaction is conducted in ethanol with higher yield.
MAybe give this a try also please?
Im thinking that these are different mechanisms to the claimed Akabori.
Im not sure that PPA would even be produced with these.Just going by what Cherriebaby hinted at.
I did see another patent in which they did as IA suggested and used an emulsifier as apposed to PTC with O>K results.
Without PTC as like CHerriebaby posted,the french patent is the next best yield I could fine.

Cheers

Bluechip I had to go all the way over to WetDreams to retrieve this. :lol:

Ballzofsteel
Dreamer

Posted - Mar 30 2005 : 03:26:55 AM

Drug freak,
Please look at and test some of these out,like Cherriebaby suggests.
USing your alanine of course.

Abstract of GB932837

A process for the manufacture of optically active methylamino carboxylic acids comprises reacting in aqueous solution a salt formed from a strong base and an optically active amino carboxylic acid (a second amino group if present being protected if it is not to take part in the reaction) with benzaldehyde or a substituted benzaldehyde, reducing the resulting N-benzylidene or N,N1-dibenzylidene compound in a basic medium to the corresponding N-benzyl or N,N1-dibenzyl compound and then

methylating the latter at the benzylated amino group or groups (i.e. unselective monomethylation or otherwise dimethylation in the case of the N,N1-dibenzyl compound) and subsequently splitting off the N-benzyl group of N,N1dibenzyl groups and any protecting group by hydrogenolysis in a neutral or acidic medium. An alkali metal salt of the amino carboxylic acid is preferably used as the starting material. The reduction of the N-benzylidene or N,N1-dibenzylidene compound may be carried out using catalytically activated hydrogen or a complex metal hydride. The methylation is preferably carried out using formaldehyde in the presence of a reducing agent, preferably formic acid. Many suitable amino carboxylic acids are specified. Suitable substituted benzaldehydes specified are salicylaldehyde, tolualdehyde, vanillin, and nitro-benzaldehydes such as p-nitrobenzaldehyde. Examples 1-5 describe the stepwise preparations of the N-methyl derivatives of L-valine, L-phenylalamine, L-alanine, L-leucine and L-serine. Example 6 describes the preparation of Ne -carbobenzoxy-Na -benzyl-L-lysine from Ne -carbobenzoxy-L-lysine and its subsequent conversion to Na -methyl-L-lysine.

http://v3.espacenet.com/textdes?DB=EPODOC&IDX=GB932837&F=0&QPN=GB932837" target="_blank"> br / br / http://v3.espacenet.com/textdes?DB=EPODOC&IDX=GB932837&F=0&QPN=GB932837

By reactionof L-alanine with benzaldehyde and reduction of the so obtained benzylidene compound with sodium borohydride according to the procedure of the preceding examples, N-benzyl-L-alanine was obtained in a yield of 71%; melting point 255~ C. (decomposition)D22=+12.6~ (c=1.0 in 6-N hydrochloric acid).

http://v3.espacenet.com/textdes?DB=EPODOC&IDX=KR8700738&F=0&QPN=KR8700738" target="_blank"> br / http://v3.espacenet.com/textdes?DB=EPODOC&IDX=KR8700738&F=0&QPN=KR8700738

Water (400 g), 212 g of benzaldehyde and 120 g of toluene were added to 60 g of glycine. With stirring at 10 DEG to 15 DEG C., 177.8 g of 45% sodium hydroxide was added dropwise over the course of 2 hours. Then, the reaction temperature was gradually raised to 20 DEG C., and the reaction was carried out at 20 DEG to 25 DEG C. for 20 hours. After the reaction, 292.0 g of 35% hydrochloric acid was added dropwise at a temperature of not more than 40 DEG C., over 45 minutes. The mixture was further stirred at room temperature for 1 hour. After standing, the lower aqueous layer was separated and analyzed by high-performance liquid chromatography. The ratio of formation of .beta.-phenylserine was 92.6% (based on glycine). The aqueous layer was neutralized to a pH of 6 with 45% sodium hydroxide, cooled to 0 DEG to 5 DEG C., stirred at the same temperature for 1 hour, filtered, washed with cold water, and then dried under reduced pressure at 50 DEG C. to give 131.4 g of white crystals of .beta.-phenylserine. The purity of this product analyzed by high-performance liquid chromatography was 90.5%. Differential thermal analysis showed that the product had one molecule of water of crystallization. The yield of the product (based on glycine) was 82.0%. Melting point: 198 DEG-200 DEG C. (decomposition).

http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=DE3642475&F=0" target="_blank"> br / http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=DE3642475&F=0

ss-Phenylserine is prepared by condensation of glycine with benzaldehyde in the presence of an alkali metal hydroxide in a medium consisting of water and a benzaldehyde-immiscible silicone oil and subsequent treatment of the alkali metal salt of N-benzylidene-ss-phenylserine formed in this way with an acid. As a result of the additional use of silicone oil, the reaction mixture remains stirrable during the condensation reaction and the work-up is facilitated by the acid treatment.

Babelfish translation:

75 g glycine were solved in 350 g water and with 220 g Benzaldehyd and 200 ml silicone oil M 3 (manufacturer: Bavarian AG) shifts. Then 250 g 40 of a weight-per cent caustic soda solution were admitted at one time. It was ensured by occasional cooling that the reaction temperature did not rise over 50 DEG C. Subsequently, over night at ambient temperature one agitated. Then at a temperature of any more than 40 DEG C 360 g 35 of a weight-per cent hydrochloric acid were not course-dripped, still another one hour was agitated long and then the aqueous phase separated. The aqueous phase was brought with 50 to weight-per cent caustic soda solution on pH 7.5, cooled down on 0 DEG C and filtered after one hour at this temperature. The Phenylserinkristalle was washed with ice water and dried under decreased pressure with 60 DEG C up to the constant weight. The colorless Phenylserin contained then still 1 mol of crystal water. Yield: 157.8 g (79% of the theory, related to assigned glycine). Melting point: course-dripped, the cooling and was removed for 180-182 DEG C caustic soda solution still 15 hours were agitated long at ambient temperature. Then 360 g 35 of a weight-per cent hydrochloric acid course-dripped that the interior temperature did not rise to any more than 40 DEG C, it were agitated in such a way still another one hour long and then the aqueous phase separated. The aqueous phase was brought with 50 to weight-per cent caustic soda solution on pH 7.5, on 0 DEG C cooled down and 1 hour long at this temperature stands left. Then the separated crystals were filtered off, washed with ice water and dried under decreased pressure with 60 DEG C up to the constant weight. The colorless beta Phenylserin contained then still 1 mol of crystal water. Yield: 161.4 g (81% of the theory, related to assigned glycine). Melting point: 180-182 DEG C.

This is in french,Performed in alcohol.
http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=FR1017396&F=0" target="_blank"> br / http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=FR1017396&F=0

Bluechip Please read this if interested in the phenylserines.
A very interesting thread indeed.

http://12.162.180.114:90/synthetika/hiveboard/methods/000448052.html

:D

TY

IndoleAmine Wow - thanks for the heaps of interesting information you provided us with!

If every bee would solely contribute in such a way, we would have the most comprehensive chemical database related to the chemistry of mind-altering compounds, within one or two years - I would bet... :lol:

(keep up the good work!)

i_a

IndoleAmine Of course you don't appear like being a smartass, why do you think so?
(post has been removed, hope your happy with the freed bandwith)

i_a

IndoleAmine Means that the nitroalcohol route to PPA allows for **stereoselectivity**

Funny

Bluechip Sure you have permission.

Funny thing is I posted the exact same patented, "redundant" info a couple of posts up! :lol:

Click on the link I posted.Same as yours yeah?
Now stop that eating up of precious banwidth will you?

Off topic,
Any thought on the reduction of the isonitropropiophenone?Is catalytic hydrogenation a must do you think?

IndoleAmine The links you posted don't contain the same things at all - they are all original text patents, and one hive thread - no link to any rhofium mirror.

Note: I searched this thread for the patent number EP960,876 with Ctrl+F, and found just my own post... :roll:

(or I'm just temporarily blinded, and you have to point me to it :wink:)

Show me where, and I will delete my post (provided its really redundant).

Next time you could say "its already here; look HERE" and give a quick link, instead of letting me search every link you posted recently, that would be nice.

And a propiophenone has a C=O instead of that C-OH we want - so yes, you have to reduce it to arrive at PPA, no way around it.

Either with cat.hydrogenation, or other reduction methods.

cheers,

i_a

Bluechip http://v3.espacenet.com/textdes?DB=EPODOC&IDX=US5750802&
F=0&QPN=US5750802[/url]

Click and compare if you want.

POST 38 by me.
It is already here.Same patent different number is all. :wink:

Not meaning to be a smartarse btw.

On the reduction of the propiophenone oxime
I realise some kind of reduction is indeed needed but,I recall foxy posting a procedure at the hive describing the direct reduction of isonitrosopropiophenone leading to Cathinone,which if Im not mistaken is usually considered norpseudoephedrine.
I am wondering about the ideal conditions ie catalyst for the reduction so as to obtain norephedrine.I cant seem to find any refs for this,or any notes on the industrial methods.
Any ideas.

Hex There is one of the Akabori reaction samples:

http://synthetikal.com/synthforum/viewtopic.php?p=3549#3549

Astrum Well SWIM took another run at this using ethanol instead of toluene this time. SWIM added the 45% NaOH solution dropwise to the ethanol, benzaldehyde, dH2O, and l-alanine over an hour at roughly 0C. A clear yellow solution was present after the addition which was allowed to warm to room temperature with stirring. It was further stirred at room temperature for five hours where CO2 evolved. At five hours a **lot**

IndoleAmine Hm - sounds like a carbonate has formed if you ask me.

http://physchem.ox.ac.uk/MSDS/NO/l(-)-norephedrine.html

(the best I could find; but no word about solubility! :cry:)

PPA freebase is a crystalline solid at room temp., but I would say since it has that OH and NH2 and phenyl ring, it should be very soluble in EtOH....

Carbonates OTOH have a limited solubility in EtOH, and since a lot of CO2 was evolved, I think there is a great chance that carbonates of the starting material and product are formed, as well as some sodium carbonate etc..

(Anyone know about the solubility of PPA.carbonate in EtOH? :D)

I would try and add lots of acidic H2O, remove the solvent and residual BzCHO through distillation/steam distillation, and then proceed with basifying, extraction and vacuum distillation and then you see what you are left with... :wink:

Good luck!

IndoleAmine Thanks to Shib, the following very interesting document is available here:
Schiff bases. I. Thermal decarboxylation of alpha-amino-acids in the presence of ketones. (Al-Sayyab AF, Lawson A.)
J Chem Soc

Astrum Well SWIM did some tests. First off the percipitated crystalls were filtered off. The substance was slightly soluble in ethanol (more so than sodium benzoate). Next SWIM tested for the presence of sodium which turned out positive. This shouldn't be a suprise

since NaOH should be present to some extent. It's mp was roughly that of phenylpropanolamine (base). University is taking over again so SWIM will see what he can do next week perhaps.

Anyone else running experiments? :wink:

IndoleAmine Yes - me with n-BuOH solvent (and a few percent H2O) and heating to 140°C... (and maybe KOH? better not?)

(as soon as my alanine arrives at least :( )

Willie And what about the benzaldehyde and alanine condensation itself? I mean time, temperature, catalists, acid or alcaline medium. Who knows the exact conditions of this reaction?

akabori cont.

java Here is a thread on the subject and enclosed some articles in japanese and one in english to help understand the problems, if any.....java

Direct Link URL: http://home.ripway.com/2005-1/247174/akaborirun.html
Alternate URL: http://host.picturewizard.com/2005-1/247174/akaborirun.html

These are articles in Japanese that deal with akabori synthesis of ephedrine and norephedrine.....

Direct Link URL: http://home.ripway.com/2004-11/211899/YakugakuZasshi.zip
Alternate URL: http://host.picturewizard.com/2004-11/211899/YakugakuZasshi.zip

How to get N-methylalanine from alanine

java In the study "Studies on /reaction between aromatic Aldehydes and alpha-amino Acids.v. Results obtained by Paper chromatography" one of the papers inclosed in the post above; the only one in english, reviews the synthesis of ephedrine by mixing bezaldehyde and N-methylalanine and the result is ephedrine .

So my question is how does one get from alanine to n-methylalanine.....can it be done with formic acid then reduced either with catalytic hydrogenation or by any of the other methods mentioned in
rhodium's page on methylation of amphetamine.....

It seems to me that with the information privided by WizardX on the reducing phenylalanine to benzaldehyde by a simple procedure .....

> **Quote**
>
> http://www.ajinomoto.co.jp/amino/e_aminoscience
> /bc/amino_13.html
> Phenylalanine when heated in 5N sodium hydroxide at 110~115°
> for 5 hours, it decomposes forming benzaldehyde.

Bumblebee some info i told someone not long ago about the Akabori.
ithink it belong in this thread:

when you start with:

-d,l-alanine (the racemic stuff) would give you d,l-pseudoephedrine and after reducing Benzedrine (dl-amphetamine)

-l-alanine food grade would give you l-pseudoephedrine and would end with Dexedrine (l-amphetamine)

-N-methyl-d,l-alanine would give a mixture of dl-pseudoephedrine and dl-ephedrine that is reduced to racemic chili along with some Benzedrine! :wink:

I found out that N-methylalanine is nearly impossible to get anywhere. An if it is in the case of the n-methyl stuff as also as hard to dissolve the stuff in the reaction as it is with l-alanine i would forget about it.

but l-ephedrine is much easier to extraxt from the reaction mixture as the PPA is. It doesnt dissolve that good in H2O... :)

jackoozzi I think you will find that alanine will make PPA not pseudoephedrine and the PPA will reduce to amphetamine

java Bumblebee[/b:77afd319cc] ..although you may be close but as you said it's been a while but here is a table from on of the articles I posted where you can see the end result ..... java

[quote:77afd319cc="Bumblebee"]some info i told someone not long ago about the Akabori.
ithink it belong in this thread:

when you start with:

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-N-methyl-d,l-alanine would give a mixture of dl-pseudoephedrine and dl-ephedrine that is reduced to racemic chili along with some Benzedrine! :wink:

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but l-ephedrine is much easier to extraxt from the reaction mixture as the PPA is. It doesnt dissolve that good in H2O... :)[/quote:77afd319cc]

[URL=http://www.imageshack.us][img:77afd319cc]http://img123.echo.cx/img123/237/typesofreactionsinbenzandalani.jpg[/img:77afd319cc][/URL]

[URL=http://www.imageshack.us][img:77afd319cc]http://img158.echo.cx/img158

/4646/benzaldehyde7sp.jpg[/img:77afd319cc][/URL]

IndoleAmine Do you maybe have more details about the rxn nr. three (benzaldehyde/dl-alanine /pyridine) mentioned in your table? It seems as a base catalyst would be needed in order to avoid biphenyl compnd. formation and favor phenylpropanolamine production..

article quoted on the excerp table

java I've had several request for more on the exerp posted, the information has been posted and the articles are there I guess I will have to pull it out and repost it as it was included with the other articles that were in japanese.....

pdf

Stinger It seems as a base catalyst would be needed in order to avoid biphenyl compnd. formation and favor phenylpropanolamine production..[/b:6150256c68]

I wonder if the short reaction time plays a part in the success of reaction 3, and the failure of reaction 2, to obtain PPA?

Changes depend on translation of articles.....

java One would need to translate the articles and study them in order to make some comments on the reaction since they did 3 other papers prior to the one's I posted.

There needs to be someone with some japanese to english translating program....so we can all find out.....java

: phenylpropanolamine from benzaldehyde

IndoleAmine Without any knowledge in japanese: reactions 2 and 3 both run 40 minutes - only difference is pyridine... :D

But it would indeed be really very helpful if someone could translate those cryptic signs...

re: phenylpropanolamine from benzaldehyde

java This is another study in the series of benzaldehyde and amino acids reactions for which there is a whole series that need translating.....java

Studies and Reactions between Aromatic Aldehydes and alpha-amino Acids I. New Facts on Akabori Reaction
Takagi; Yakugaku Zasshi;]
[color=red:0ad651b73b]The Pharmaceutical Society of Japan Study #185,vol. 71, no. 7, pg 648, 1951 [/color:0ad651b73b]

[url=http://rapidshare.de/files/1746380/takagi4.djvu.html]djvu[/url]

Note : thanks to [b:0ad651b73b]Lugh[/b:0ad651b73b] for securing the citation

- Synthetikal Forums - Main - Misc. Stimulants -