$EtN=P(NMe_2)N=P(NMe_2)_3$: An efficient non-ionic base catalyst for the isomerization of allylic compounds and methylene-interrupted dienes

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Dedicated to Professor Chengye Yuan on his 80th anniversary

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Abstract

Allylbenzene derivatives, allyl phenylsulfide, allylimidazole, 1,4-dihydronaphthalene, and several methylene-interrupted diene compounds are easily isomerized by the phosphazene strong base $EtN=P(NMe_2)N=P(NMe_2)_3$ (P_2-Et) in acetonitrile at 40 °C. This is the first report of such isomerizations catalyzed by a strong non-ionic strong base. The proposed methodology offers significant advantages over existing methods for most substrates, especially in terms of mild reaction conditions, experimental simplicity and high yields.

Keywords: Isomerization, non-ionic base, phosphazene base, allylic aromatics, conjugation

Introduction

The isomerization of allylic compounds and 1,4-dienes is of considerable interest in synthetic organic chemistry and in industrial applications. For example, the isomerization of safrole to isosafrole is an important step in the industrial synthesis of helitropin (3,4-methylene-dioxybenzaldehyde)[1] and a domino isomerization-hydroamination has been reported for the synthesis of a pharmaceutically interesting amphetamine.[2] Vegetable oils, in which the polyunsaturated fatty acids have been conjugated, show enhanced reactivity over their natural unconjugated forms in forming biodegradable polymers with improved mechanical and thermal properties.[3, 4]

The conjugation of double bonds is often carried out with a strong ionic base. For example, vegetable oils have been conjugated on an industrial scale by heating them with alkali metal hydroxides at elevated temperature.[5,6] However, soap formation is problematic in this process. The isomerization of such oils at room temperature mediated by an electrolytically generated cationic nickel(I) complex[7] or by triphenylmethyl anion[8] has also been reported, but conversions

were lower than 80% and significant amounts of reduction products were formed. Many organometallic systems have been shown to catalytically isomerize allylbenzene and other allylic compounds, but most of these approaches required high temperatures and/or harsh reaction conditions, and conversions were modest.[9]

Strong non-ionic bases (Figure 1) commonly used in organic transformations are, in order of generally increasing pK_a, proton sponge[10] (18.18[11]); amidine bases[12] such as DBN (23.79[11]) and DBU (24.32[11]); guanidine bases[13] such as TMG (23.3[11]), TBD (25.96[11]) and MTBD (25.43[11]); pro-azaphosphatranes[14] (32.9-34.49[15]); and phosphazene bases[16] (26.9-46[11,17]). Non-ionic but poorly nucleophilic bases having high pK_a values, such as pro-azaphosphatranes or phosphazenes, would be highly desirable for mediating double bond conjugation, since their low nucleophilic character could inhibit side reactions. Because of the strong basicity of such compounds, abstraction of a methylene proton from allyl aromatic compounds or methylene-separated double bond compounds, for example, could lead to migration of a double bond resulting in the formation of the thermodynamically more stable conjugated systems. Here we report that the non-ionic base P_2-Et (pK_a 32.74[18]) is an effective

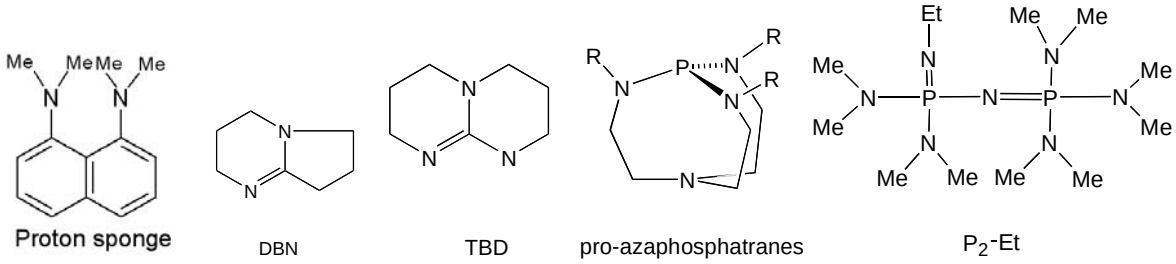
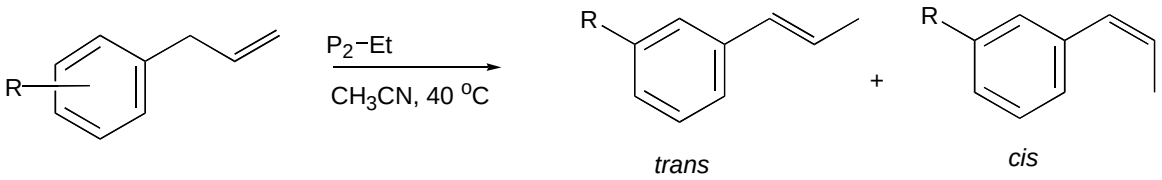


Figure 1

isomerization catalyst for the conjugation of allylic compounds and methylene interrupted double bonds in contrast to bases, such as TMG and DBU, which gave no observable conjugated product under our conditions.

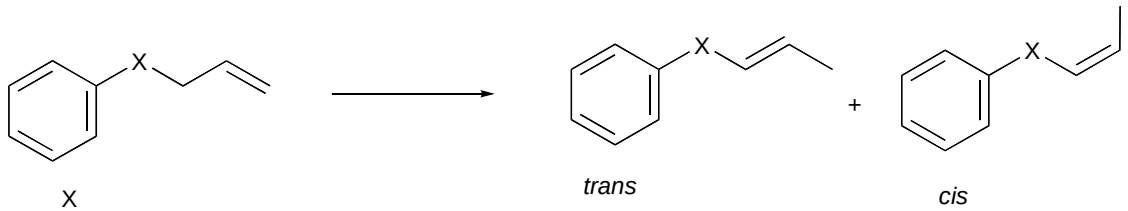
Results and Discussion

Conjugation of allyl aromatics in the presence of P_2-Et (10 mol %) took place smoothly, giving rise to the corresponding conjugated products in very good yield when acetonitrile was employed as solvent (entries 1-5 in Table 1). ^{1}H NMR spectroscopy revealed the disappearance of the CH_2 proton peak at 2.75 ppm and GC-MS measurements demonstrated the predominant presence of the presumably thermodynamically favored *trans* products ranging from 89.4% to 95.5%. In all cases isolated yields were over 90% and no side reactions were observed.



	R
1	H
2	3-methoxy
3	3,4-dimethoxy
4	3,4-methylenedioxy
5	2-allyloxy

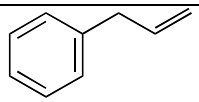
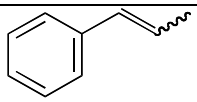
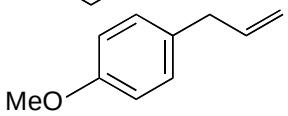
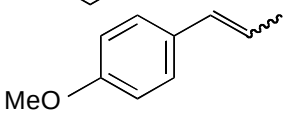
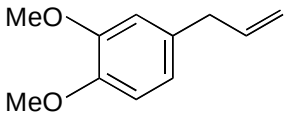
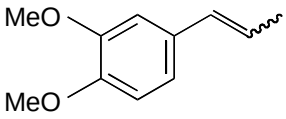
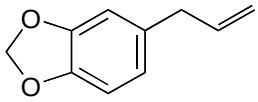
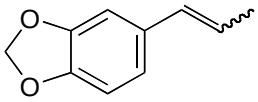
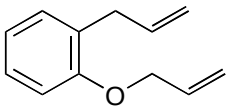
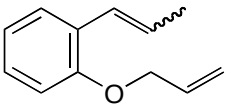
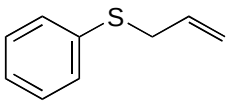
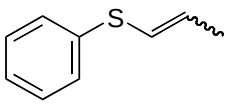
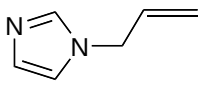
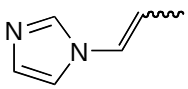
When allyl phenyl sulfide (entry 6 in Table 1) was subjected to the same conditions, the *cis* product isomer was somewhat predominant (*trans/cis* ratio 44.3:55.7). The *cis* product may be the kinetically favored species, but it is not obvious why this is the case. In contrast, when X is oxygen (**7**) or nitrogen (**8** and **9**) only starting materials could be recovered for reasons that are not clear. Assuming that isomerization occurs via an anionic



	X	*trans*	*cis*
6	S	44 %	56%
7	O	0	0
8	HN	0	0
9	N allyl	0	0

intermediate formed from substrate deprotonation, the higher electronegativity of X = O and N in **5** and **6**, respectively, and resonance forms involving lone pair electron donation to the aromatic ring from these atoms, may be expected to lead to a reduced tendency to form a carbanion at the secondary carbon of the olefinic bond. These factors are expected to be considerably less important when X = S. When the allylic nitrogen in the substrate is part of an aromatic ring, as in entry 7 of Table 1, isomerization is expected to be facile as shown in this entry.

Table 1. Isomerization of allylic aromatic substrates

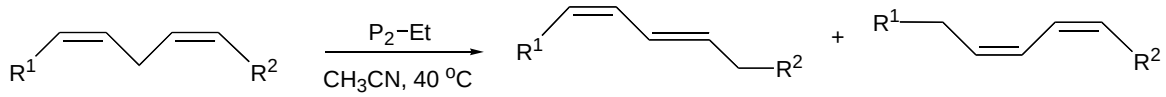
Entry	Substrate	Product	Yield (%)	E/Z ratio
1			91.5	95.5/4.5
2			95.3	89.4/10.6
3			97.9	90.3/9.7
4			96.4	91.2/8.8
5			96.9	92.9/7.1
6			97.1	44.3/55.7
7			94.2	15.1/84.9

Compared with acetonitrile, solvents such as hexane, benzene, valeronitrile and THF for the reactions in Table 1 did not function well or not at all. This observation may be attributed to the initial deprotonation of acetonitrile to form the CH_2CN ion which functions as the active species for deprotonation of the substrate. This suggestion is made reasonable by the direct observation of the deprotonation of acetonitrile by pro-azaphosphatranes using ^{31}P NMR spectroscopy[14a] and the fact that the pK_a value of P_2-Et in acetonitrile (32.74[18]) is quite close to those of pro-azaphosphatranes in the same solvent (32.9-34.49[15]). The poor performance of valeronitrile as a solvent for these reactions compared with acetonitrile could be due to the poorer ability of the former to lose a proton from the alpha methylene group owing to greater steric hindrance and/or to the inductive effect of the *n*-propyl moiety.

The structural similarity of 1,4-dihydronaphthalene to that of allylbenzene derivatives is expected to facilitate its isomerization to the conjugated 1,2-dihydronaphthalene product. Commercially available 1,4-dihydronaphthalene usually contains a substantial amount of the 1,2-isomer as an impurity. Our sample of this substrate (which contained 11% of the 1,2-isomer) in the presence of 20 mol% P_2-Et in acetonitrile at 40°C increased its content of 1,4-isomer to

79.4% over 24 hours (Table 2, entry 1). A significant amount (12.9%) of the dehydrogenated product naphthalene was also observed. When the amount of P_2-Et was increased to 50 mol%, the 1,4-isomer could still be seen, but the naphthalene contact increased to 43.5%. The greater catalyst loadings required in entry 1 of Table 2 compared with that for the allylbenzene substrates in Table 1 suggest that 1,4-dihydronaphthalene may be more reluctant to form an anionic intermediate owing to an increase in ring strain.

We also investigated the use of P_2-Et as a catalyst to conjugate the methylene-separated double bonds in long-chain compounds (Table 2). For the conjugation of *cis,cis*-3,6-tridecadiene (entry 2, Table 2), which was synthesized by a

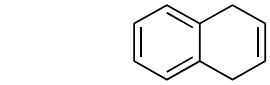
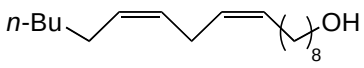
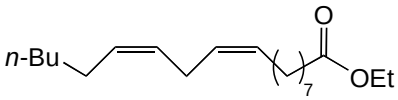
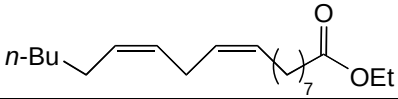


R^1	R^2
C_2H_5	C_6H_{13}
C_5H_{11}	$(CH_2)_7CH_2OH$
C_5H_{11}	$(CH_2)_7CH_2OCH_3$
C_5H_{11}	$(CH_2)_7COOCH_3$
C_5H_{11}	$(CH_2)_7COOC_2H_5$

reported method,[19] a 93.6% conversion was achieved in the presence of 10 mol % of P_2-Et, although 72 hours was required. The product was a mixture of isomers which we believe to be chiefly *cis,trans*-3,5-tridecadiene and *trans,cis*-4, 6-tridecadiene according to the ^{1}H and ^{13}C NMR assignments. The *cis,trans*/*trans,cis* ratio was 45/55, indicating a small preference for the conjugated double bonds to locate nearer to the center of the molecular chain. When the hydrocarbon chains contained a terminal hydroxy or methoxy group (entries 3 and 4, Table 2, respectively) good conversions and high yields of isomeric mixtures of conjugated product were obtained. The alcohol, *cis,cis*-9,12-octadecadiene-1-ol, was conjugated in 100% conversion after 72 h. Here it is likely that deprotonation of the methylene group between the double bonds of the substrate was also accomplished by alkoxide ions formed by deprotonation of the OH group of the substrate. Alkoxide formation from alcohols in the presence of pro-azaphosphatranes has been directly observed by ^{31}P NMR spectroscopy.[15] *cis,cis*-18-Methoxy-6,9-octadecadiene was somewhat sluggish to conjugate under the same conditions, showing only 84.3 percent conversion after 72 hours (entry 4, Table 2). Complete conversion in 72 hours was realized by increasing the P_2-Et concentration to 20 mol%. From a comparison of the isomer ratios in entries 2 and 4 of Table 2, it is apparent that the presence of the terminal OH group is of little consequence. Similar product isomer ratios were obtained for substrates in entries 2, 3 and 4. An examination of the behavior of methyl and ethyl linoleate in the presence of P_2-Et (entries 5 and

6, respectively) by ^{1}H NMR and ^{13}C NMR spectroscopy of the complicated mixture of products formed suggested that the ester functionality was being nucleophilically attacked by the CH_2CN at the carbonyl carbon and/or that this ion was deprotonating the carbon alpha to the carbonyl. Poor conversions to desired product were observed and only about 46-47 % of a mixture of conjugated product and unconjugated starting materials could be recovered.

Table 2. Isomerization of 1,4-dihydronaphthalene and methylene-interrupted dienes

Entry	Substrate	Base (mol%)	Time (h)	Conversion (%)	Yield (isomer ratio)
1		20	24	91.3	84.6(7.7/79.4/12.9[a])
		50	24	94.2	85.1(5.2/51.3/43.5[a])
2		10	72	93.6	87.4(45/55)
3		10	72	100	90.2(45/55)
4		10	72	84.3	98.7(44.6/55.4)
		20	72	100	99.1(47.2/52.8)
5		10	72	55	46.7
6		10	72	47	47.5

[a] Ratio is 1,4-dihydronaphthalene/1,2-dihydronaphthalene/naphthalene.

In summary, the application of commercially available P_2-Et offers an efficient strategy for the isomerization of allylic compounds and other methylene–interrupted double bond systems in acetonitrile, provided functional groups that are nucleophilically sensitive to the CH_2CN are absent. The proposed methodology is attractive because of its mild reaction conditions, experimental simplicity and high conversions. It has been reported that P_2-Et can be extracted with aqueous acid and recovered upon subsequent deprotonation.[20] The results of conjugations carried out with pro-azaphosphatranes will be reported in due course.

Experimental Section

In acetonitrile (5 mL) 1 mmol of substrate and 10 mol % of P_2-Et (Fluka) were stirred under nitrogen at 40 ^{o}C for the times indicated in the tables. Conversions after 24 hours to products in Table 1 were 100% in all cases as determined by ^{1}H NMR spectroscopy. Conversions in Table 2, after the times indicated in this table, were determined by ^{1}H NMR spectroscopy. After evaporation of the solvent, the residues were subjected to silica gel column chromatography for

isolation of the products. Isomer ratios were obtained from ^{1}H NMR spectroscopic and GC-MS measurements.

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