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The Blaise reaction

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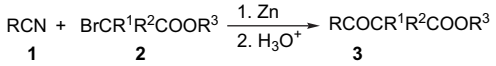
1. Introduction

Developments in the methodologies for the construction of the C–C bonds in the synthesis of complex non-natural and natural products have taken place in an incremental manner through pioneering studies made by eminent organic chemists for more than the past 150 years. Such reactions discovered, described and explored-in are generally named after their discoverers, e.g., Grignard reaction, Wittig reaction, Diels–Alder reaction, Friedel–Crafts acylation, etc.[1] One such named reaction is the Blaise reaction, discovered by Blaise in 1901.[2] In this reaction, a nitrile **1** is reacted with the zinc enolate of ethyl bromoacetate (or 2-alkyl-2-bromoacetates) **2** to yield the corresponding β-keto ester **3** (Scheme 1).



Scheme 1.

The Blaise reaction closely resembles the Reformatsky reaction in which the zinc enolate of an α-halo ester is reacted with a carbonyl compound to give the corresponding β-hydroxy esters.[3] Unlike the relatively more well-known Reformatsky reaction, the Blaise reaction has found little application in organic synthesis, due to problems of low yield and competing side reactions. Recent developments in organometallic chemistry, however, have rekindled interest in developing this reaction as a formidable tool for synthetic organic chemists, particularly because the starting materials like 2-bromoacetates and nitriles are easy to prepare or are commercially available and the β-keto ester functional group in the product is highly versatile for further transformations.[4] Moreover, the Blaise reaction can be truncated to produce β-amino-α,β-unsaturated esters, which are useful for the synthesis of heterocycles and β-amino acids. Overall, the Blaise conversion of nitriles into the corresponding β-keto esters or β-amino acrylates constitutes a two-carbon homologation. In this review, we present an account of the developments that have been reported for increasing the efficiency of the Blaise reaction and its application for the construction of complex molecules of biological interest. From each reference, one representative example has been selected to highlight the conversion and the reaction conditions.

2. Mechanism of Blaise conversions

The presently accepted mechanism for the Blaise reaction is shown in Scheme 2.[5] In the first step, an α-bromoacetate **2** reacts with activated zinc(0) to generate the zinc enolate, which adds to

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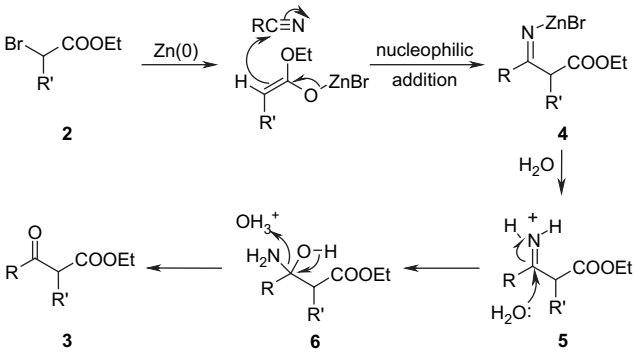


Scheme 2.

the nitrile to afford the zinc imino ester **4**. Acid hydrolysis of the zinc imino ester **4** furnishes the β-keto ester **3** via the intermediates **5** and **6**.[6] On the other hand, base hydrolysis of the intermediate **5** provides the β-amino-α,β-unsaturated esters.

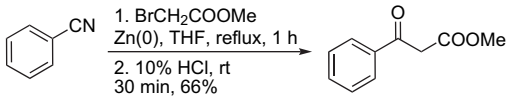
Almost 60 years after Blaise's initial disclosure of this important reaction, Cason and co-workers found that, by using excess zinc (1.5 equiv) and α-bromoacetate (1.5 equiv), the yield of β-keto esters can be increased to a maximum of 58% when the reaction was conducted in benzene reflux and in the presence of a catalytic amount of copper(II) bromide.[7] As an example, Blaise condensation of isobutyl α-bromopropionate **8** with hexanenitrile **7** provided isobutyl 2-methyl-3-oxooctanoate **9** in 57% yield (Scheme 3). Interestingly, steric hindrance in the bromo ester **8** appears to increase the yield of the β-keto esters, possibly by preventing self-condensation of the zinc enolate intermediates.

3. Modifications in reaction conditions to increase the efficiency of Blaise reaction

Kagan and Suen observed that the slow addition of a benzene solution of α-bromoacetate **2** to a refluxing benzene solution of alkyl nitriles in the presence of zinc provided increased yields (70–80%) of the α-mono- or α,α-di-substituted β-keto esters, but the yields of the α-unsubstituted β-keto esters rarely exceeded 40%.[8] Other workers, however, obtained only very low yields of the α-unsubstituted and α-monosubstituted-β-keto esters by this method.[9]

Kishi and Hannick were the first to recognise that pre-activation of zinc leads to an improvement in the yield of the β-keto esters.[10] Treatment of aliphatic/aromatic nitriles with pre-activated zinc dust and the α-bromoacetate in refluxing THF after base hydrolysis yielded the corresponding enamino esters or, after acid hydrolysis, the β-keto esters. The activated zinc was prepared by washing commercially available zinc dust with 3 N HCl, distilled water, ethanol and ether sequentially, followed by drying under vacuum. In one example, the reaction of benzonitrile **10** with methyl bromoacetate and pre-activated zinc provided benzoyl acetate **11** in 66% yield (Scheme 4). In the procedure developed by Kishi, employing an excess of α-bromoacetate was not required. The yields of the desired β-keto esters were between 55 and 80% in the two-step sequence.

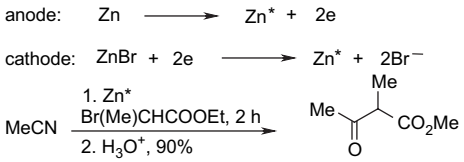
Subsequent to the discovery made by Kishi that the pre-activation of zinc was mandatory to get good yields in the Blaise reaction,



10 11

Scheme 4.

several researchers concentrated on finding better conditions for zinc activation to simplify the reaction. Zylber and co-workers reported an electrochemical method for zinc activation by the use of a zinc rod as the anodic material, zinc bromide, methyl α-bromoacetate and acetonitrile **12** in tetrabutylammonium tetrafluoroborate as the electrolyte (Scheme 5).[11] The electrolysis was carried out in a single-compartment cell fitted with gold cathode at −0.5 to −0.9 V versus SCE with a passage of 200 C. By this method, acetonitrile **12** was converted into methyl 2-methylacetoacetate **13** in 72% yield.

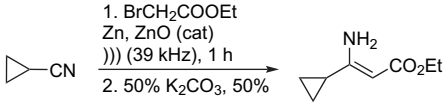


12 13

Scheme 5.

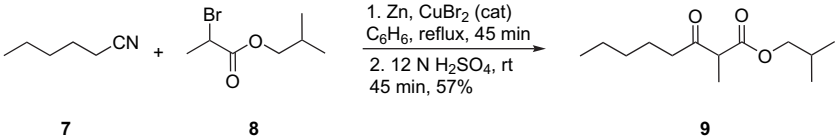
Lee and co-workers have reported a simple sonochemical activation of zinc,[12] using an ultrasonic cleaning bath,[13] to realise increased yields in the Blaise reaction (Scheme 6).[14] A solution of 1-cyclopropanecarbonitrile **14** and ethyl bromoacetate in THF with excess zinc powder and a catalytic amount of zinc oxide was sonicated in an ultrasonic cleaning bath operating at 39 kHz to provide the enamino ester **15** after basic work up. Activation of the zinc under sonochemical condition was very easy to perform and commercial bench-top zinc could be employed as such to make the reaction very facile. Interestingly, the presence of zinc oxide/titanium dioxide improved the efficiency of the sonochemical Blaise reaction, indicating a role for metal oxides in this reaction.[15]

Shin and co-workers reported in situ zinc activation by treatment with 1.0 mol % of a strong organic Brønsted acid such as CF_3COOH, $ClCH_2COOH$ or $MeSO_3H$ (MsOH) to increase the efficiency of the Blaise reaction for conversion of nitriles into β-keto esters.[16] As an example, (*S*)-4-chloro-3-trimethylsilyloxybutyronitrile **16** was converted into *tert*-butyl (*S*)-6-chloro-5-hydroxy-3-oxohexanoate **17** in 85% yield by pre-activation of zinc with a catalytic amount of methanesulfonic acid (Scheme 7).



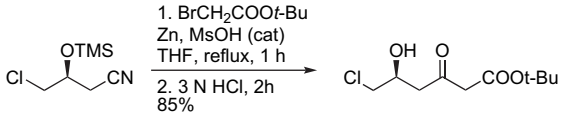
14 15

Scheme 6.



7 8 9

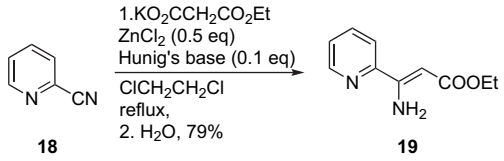
Scheme 3.



16 17

Scheme 7.

Subsequently, Shin and co-workers found appropriate conditions for the decarboxylative Blaise reaction between potassium ethyl malonate and aryl nitriles in the presence of zinc chloride and a catalytic amount of Hunig's base.[17] Compared to classical conditions, the reaction is endothermic, there is no need to employ lachrymatory bromoacetates and, in some cases, it is possible to use only 0.5–1.0 equiv of zinc chloride. By applying this method, 2-cyanopyridine **18** was converted into the corresponding β-amino acrylate **19** in good yield (Scheme 8).



18 19

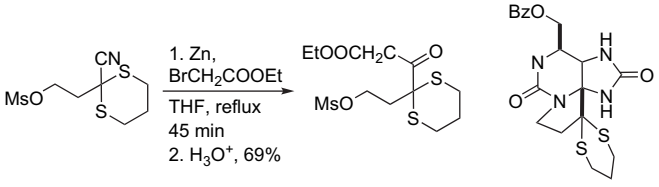
Scheme 8.

Thus, modifications of the reaction conditions of the Blaise reaction such as activation of zinc by pre-treatment with 3 N HCl/electrochemical methods/sonochemical methods/addition of catalytic amounts of Brønsted or Lewis acids make this reaction acceptable in organic chemistry for the synthesis of various biologically important compounds. Moreover, employment of the *tert*-butyl esters of α-bromoacetates or α-bromoacetate-like compounds appears to make the reaction efficacious.

In the following section, we present a review on the applications of the Blaise reaction in synthetic organic chemistry. We have arranged the references in chronological order. The references highlight the diversity of applications of the Blaise reaction.

4. Applications of Blaise reaction in synthesis of natural and non-natural products

Kishi has applied modified Blaise reaction conditions to the nitrile **20** to generate the intermediate β-keto ester **21** in the total synthesis of the natural product, saxitoxin **22** (Scheme 9).[10] Conversion of nitrile **20** into β-keto ester **21** shows that the reaction tolerates sensitive functional groups such as mesylate and thioketal.

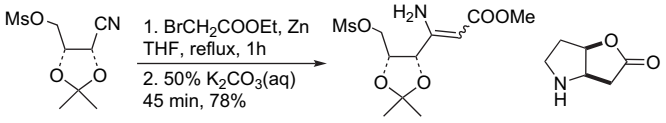


20 21 22

Scheme 9.

Doutheau and co-workers found the cyclisation of allenic compounds of the type **24** lead to heterocyclic compounds of the type **25**, which are useful precursors for further synthetic elaborations (Scheme 10).[18] The allenic β-keto ester **24** was prepared by making use of the Blaise reaction. The reaction of allenic nitrile **23** with zinc and ethyl bromoacetate in THF under reflux led to the allenic β-keto ester **24**, which on further treatment with yellow mercuric(II) oxide and *p*-toluenesulfonic acid gave the heterocyclic compound **25**.

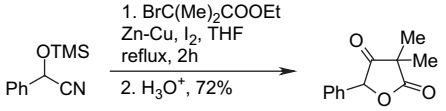
The Geismman–Waiss lactone **28** is an important intermediate in the synthesis of several pyrrolizidine alkaloids. Buchanan and co-workers considered its enantioselective synthesis from carbohydrate precursors.[19] In this effort, the nitrile **26** derived from D-erythrose was subjected to a Blaise reaction with ethyl bromoacetate and zinc to provide the β-amino-α,β-unsaturated ester **27** in 78% yield after basic work up (Scheme 11). Intramolecular displacement of the mesyl group provided the required pyrrolidine framework.



26 27 28

Scheme 11.

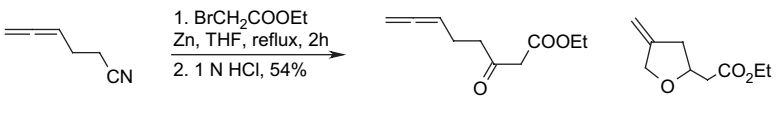
The Blaise reaction is a convenient method for the synthesis of tetronic acid **30** from readily available starting materials such as *O*-trimethylsilyl (TMS)-protected cyanohydrins **29** and α-bromoacetates.[20] In one example, the *O*-trimethylsilylated cyanohydrin of benzaldehyde **29** reacted with ethyl α-bromopropionate in the presence of activated zinc dust and traces of iodine to provide tetronic acid **30** in good yield (Scheme 12). Addition of a trace amount of iodine to the reaction mixture caused a mildly exothermic reaction. The Blaise reaction proceeded only with zinc dust and not with zinc flakes. Ethyl α-bromopropionate was, however, used in excess to force complete conversion of the cyanohydrins.



29 30

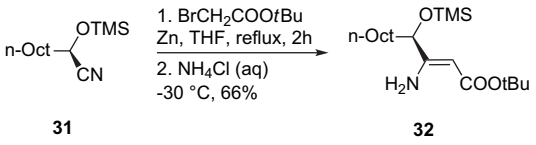
Scheme 12.

Under normal Blaise reaction conditions, i.e., treatment of the intermediate zinc-coordinated imines with protic acids, it is difficult to isolate intermediate β-amino-α,β-unsaturated esters. Effenberger and co-workers have worked out appropriate conditions for engineering intermediates from the Blaise reaction of cyanohydrins **31** towards β-amino-α,β-unsaturated esters **32** without racemisation, by using *tert*-butyl α-bromoacetates and a saturated aqueous solution of ammonium chloride at −30 °C for hydrolysis of the intermediate.[6b] As an example, the TMS-protected cyanohydrin **31** was transformed into the enamino ester **32** in good yield under these modified conditions (Scheme 13).



23 24 25

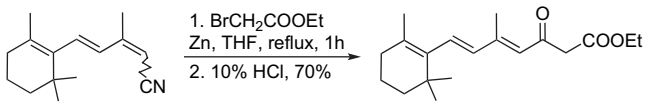
Scheme 10.



31 32

Scheme 13.

Giraud and co-workers reported that the β-keto ester **34**, a key intermediate in the synthesis of vitamin A, can be made by employing the Blaise reaction on α,β-unsaturated nitrile **33** (Scheme 14).[21] β-Ionone was converted into β-ionylidene acetonitrile **33** in a two-step reaction sequence.



33 34

Scheme 14.

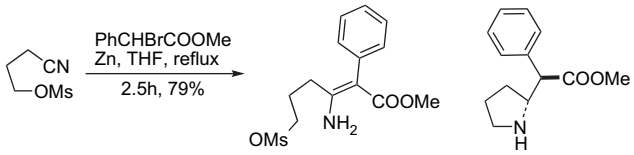
Hiyama and co-workers reported a convenient synthesis of the β-keto ester **36** via a Blaise reaction on the nitrile **35** (Scheme 15).[22] The β-keto ester **36** served as an intermediate in the synthesis of a highly potent HMG-CoA reductase inhibitor NK-104. For a successful Blaise reaction, 4 equiv of *tert*-butyl bromoacetate and 5 equiv of zinc were used in the transformation of nitrile **35** into β-keto ester **36**.

Uracil analogs such as **39** are medicinally important molecules for targeting the retrovirus HIV-1. Pedersen and co-workers studied the synthesis of analogs of a known drug, emivirine, a non-nucleoside inhibitor of HIV.[23] In this effort, the Blaise reaction was used for the conversion of nitrile **37** into the β-keto ester **38** in quantitative yield by employing 2.5 equiv of ethyl bromoacetate and 6.7 equiv of activated zinc (Scheme 16). Condensation of the β-keto ester **38** with thiourea and subsequent reaction of the thiourea derivative with chloroacetic acid provided the target uracil analog **39**. In a continuation of this type of work for the synthesis of uracil derivatives, Pedersen and co-workers found that the activation of zinc could be carried out conveniently with iodine.[24]

Pyrazole and pyrimidine C-nucleosides of the type **42** are among a class of compounds showing antiviral and antitumour activities.[25] In a quest for the synthesis of such molecules, Veronese and Morelli contemplated a Blaise reaction for the preparation of their intermediates.[26] In this transformation, 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide **40** reacted with ethyl bromoacetate in the presence of zinc dust under Blaise conditions to give the enamino ester, which on acid hydrolysis provided the unstable D-ribofuranosyl β-keto ester **41** in good yield (Scheme 17).

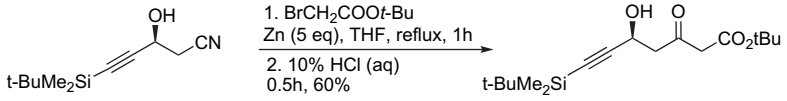
Abuse of the stimulant drug, cocaine, is a major social problem. Cocaine blocks the re-uptake of dopamine (DA) into the presynaptic neuron and, as a consequence, there is a local build up of DA in the synapse. This acute problem can be treated by developing organic molecules that interact with the DA transporter. Methyl phenidate **45** is a promising candidate as it binds potently and somewhat selectively to the DA transporter. Deutsch and co-workers reported a new methodology for the synthesis of methyl phenidate **45** involving the Blaise reaction (Scheme 18).[27] The Blaise reaction of α-bromophenylacetate, zinc and cyanomesylate **43** gave a stable enamine **44**, which on further reduction, cyclisation and manipulation of the ester stereochemistry provided methyl phenidate **45**.

The 2,6-dichloro-5-fluoronicotinoyl acetate structural unit **47** is a useful intermediate in the synthesis of a number of antibiotics such as enoxacin, tosufloxacin, trovafloxacin, gemifloxacin, etc. Shin and co-workers reported a facile, single-step method for its synthesis by using the Blaise reaction.[28] In this reaction, ethyl bromoacetate was reacted with 3-cyano-2,6-dichloro-5-fluoropyridine **46** and activated zinc to provide the key structural unit **47** (Scheme 19). In order to make this reaction viable for large-scale



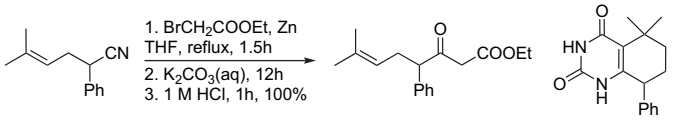
43 44 45

Scheme 18.



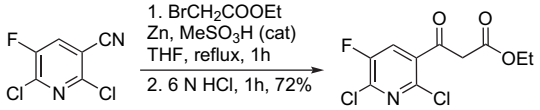
35 36

Scheme 15.



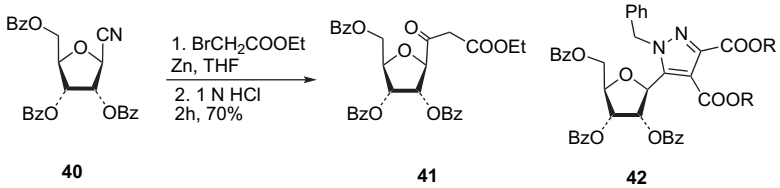
37 38 39

Scheme 16.



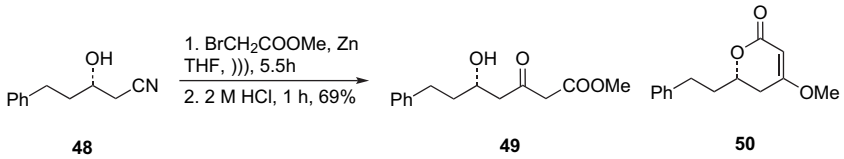
46 47

Scheme 19.



40 41 42

Scheme 17.



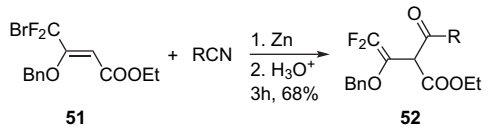
48 49 50

Scheme 20.

preparation, in situ zinc activation was carried out with methanesulfonic acid.

The natural product (*S*)-(+)-dihydrokavain **50** is a useful entity for the treatment of TNF-α related diseases. Wang and Yue reported a facile synthesis of this natural product from the D-glyceraldehyde-derived nitrile **48**.[29] Blaise conversion of the nitrile **48** using methyl bromoacetate and zinc under ultrasonic activation provided the β-keto ester **49** in good yield after hydrolysis of the intermediate with dilute hydrochloric acid (Scheme 20). Routine functional group interconversions (FGIs) provided the natural product **50**.

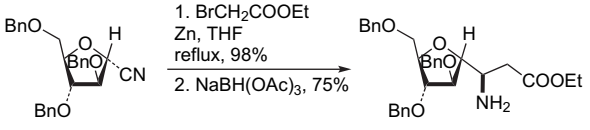
Zhu and co-workers reported the Blaise reaction between ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate **51** and a variety of nitriles to furnish a series of α-difluoro-substituted β-enamino esters, which provided the corresponding β-keto esters **52** on acid hydrolysis (Scheme 21).[30]



51 52

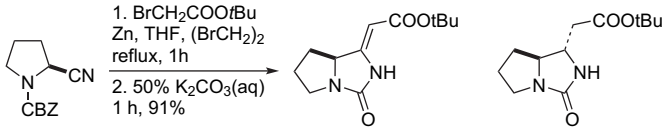
Scheme 21.

The Blaise reaction could serve as a convenient method for the synthesis of β-amino acids. Dondoni and co-workers demonstrated the synthesis of *C*-glycosyl-β-amino acids by employing *O*-perbenzylated glycosyl nitriles.[31] As an example, the reaction of nitrile **53** with excess ethyl bromoacetate (4 equiv) and zinc (6 equiv) provided the intermediate enamino ester, which on reduction with sodium triacetoxyborohydride resulted in the desired β-amino acid **54** with low diastereoselectivity (de=35%, Scheme 22).



53 54

Scheme 22.



55 56 57

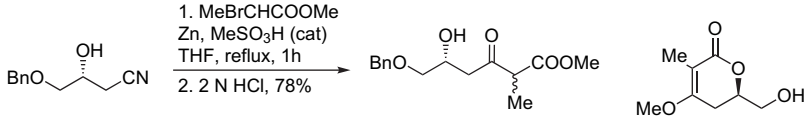
Scheme 23.

The α-amino acids could serve as precursors for nitriles, the starting compounds in the Blaise reaction. Kouklovsky and co-workers explored the stereoselective synthesis of 1,2-diamines from amino acids via the corresponding nitriles.[32] In one example, the carbobenzyloxy (CBZ)-protected proline was elaborated into nitrile **55**, which on Blaise reaction with *tert*-butyl bromoacetate and activated zinc provided an intermediate that on treatment with 50% aq potassium carbonate generated the enamino ester. Intramolecular cyclisation involving amino and CBZ groups furnished the imidazoline **56** in excellent yield (Scheme 23). In the Blaise transformation, dibromoethane served as a convenient reagent for the activation of zinc. Diastereoselective reduction of the double bond in **56** with sodium cyanoborohydride under acidic conditions and at low temperature provided the protected diamine **57**.

The microbial natural products, jerangolids, show promising antifungal activities. Marko and Pospisil have used the Blaise reaction to synthesise a key intermediate towards the lactone **60**, which served as one of the components in the convergent synthesis of the natural product.[33] The hydroxynitrile **58** was reacted with methyl 2-bromopropionate in the presence of activated zinc to furnish the β-keto ester **59** in 78% yield. Interestingly, the reaction tolerated the free hydroxyl group in **58** (Scheme 24).

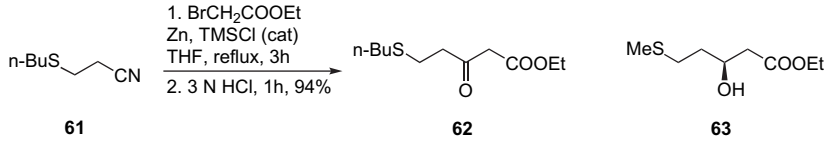
In some respects, the natural product gonyol **63** (present as the sulfonium salt), a δ-sulfido-β-hydroxy ester, resembles the amino acid β-methionine. Nakamura and co-workers reported a facile baker's yeast-mediated asymmetric reduction of the β-keto ester **62** for the synthesis of gonyol-like products.[34] We have prepared the β-keto ester **62** from the corresponding nitrile **61** by using ethyl bromoacetate and bench-top zinc activated by 3 mol % of TMSCl (Scheme 25).[35] The β-keto esters of the type **62** could serve as precursors for methyl ketones, some of which are fragrance and flavour materials.

The β-keto ester **66**, well known as the Nazarov reagent, is employed extensively in Robinson annulation reactions. It can be prepared from the stable β-keto ester precursor **65** via the oxidative elimination of thiophenol. We have prepared the β-keto ester **65** from the nitrile **64** by reacting with ethyl bromoacetate (1.1 equiv) and zinc (1.1 equiv) activated with TMSCl (3 mol %) in THF reflux in 87% yield (Scheme 26).[35] Activation of zinc with methanesulfonic acid according to the procedure described by Shin and co-workers[17] leads to competitive elimination of thiophenol to give **66**, which polymerised readily under the reaction conditions. Activation of zinc according to the method of Kishi[10] provided the β-keto ester **65** in only 20% yield.



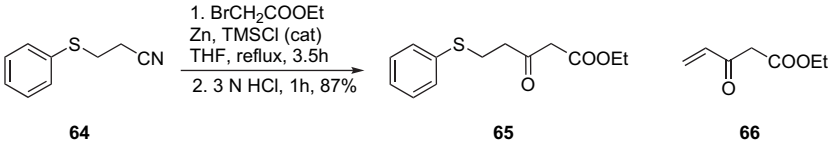
58 59 60

Scheme 24.



61 62 63

Scheme 25.



64 65 66

Scheme 26.

5. Concluding remarks

The Blaise reaction is an important carbon–carbon bond-forming reaction that has found its rightful place in synthetic organic chemistry in recent years, particularly due to the developments in employing activated zinc. This reaction is useful for two-carbon homologation of nitriles to β-keto esters or enamino esters of diverse structures. Further functional group modifications should provide a large variety of molecules. Moreover, the Blaise reaction conditions tolerate a wide range of functional groups and strained rings. Future research on this reaction should focus on the catalytic efficacy of metals to be employed, the diversity of α-substituted bromoacetates and intramolecular versions to provide ring structures.

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