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A Simple and Highly Efficient Synthesis of β-Amino-α, β-unsaturated Ester via Sonochemical Blaise Reaction

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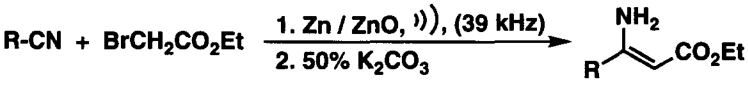
Abstract: β-Amino-α,β-unsaturated ester is produced by a sonochemical Blaise reaction of nitrile, zinc powder, zinc oxide and ethyl bromoacetate in THF in a commercial ultrasonic cleaning bath.

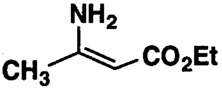
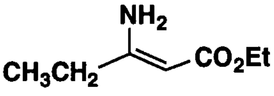
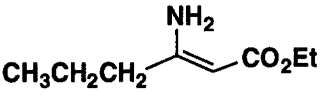
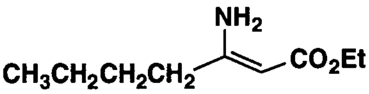
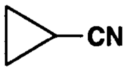
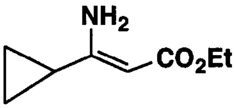
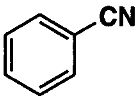
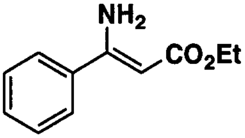
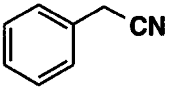
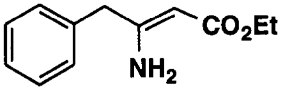
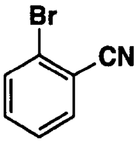
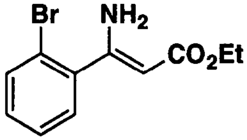
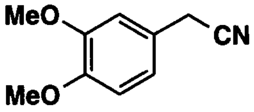
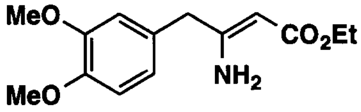
Since the discovery of the addition of zinc ester enolates to nitriles by Blaise in 1901[1], this potentially useful β-keto ester[2] synthesis has found little application in organic synthesis. The easy introduction of functionalities and the straightforward nature of the conversion have been hampered by the narrow scope of low yields obtained, the requirement for excess α-bromo ester (3-5 molar) and competing self-condensation problems.[3-6] It has been reported that β-amino-α,β-unsaturated ester can be obtained in moderate to good yield by using magnesium enolate of *t*-butyl acetate.[7] Some modifications of the zinc ester enolate (Blaise reaction) have been reported and reasonable yields were obtained for α,α-di- and α-monosubstituted β-keto esters. However, only in some cases did the yields for α-unsubstituted β-keto esters exceed 40%.[4,7-9] In those particular cases, the self-condensation appeared to have been minimized by the slow addition of the α-bromo ester and the required excess of the bromoacetate increased in the order *t*-butyl < isopropyl < etrhyl ~ methyl esters.[10] Although the result of these modifications seemed to be a substantial improvement in the yield of α-monosubstituted β-keto esters, however the major problem of the inconsistent reaction of the bromoacetates to give an α-unsubstituted product still remained. In addition, two steps were found to be necessary to ensure the success of these modifications. Herewith, we wish to report a novel one-step synthesis of β-amino-α,β-unsaturated ester via sonochemical Blaise reaction (Scheme 1).

Scheme 1



The typical procedure for the preparation of β-amino-α,β-unsaturated ester from the corresponding nitrile is as follows: A solution of nitrile (1.0 mmol), zinc powder (5.0 mmol), zinc oxide (0.5 mmol), and

Table 1. Synthesis of β-amino-α,β-unsaturated ester[a]

Entry	Substrate	Product	Yield[b]
1	CH_3-CN		67%
2	CH_3CH_2-CN		52%
3	$CH_3CH_2CH_2$-CN		70%
4	$CH_3CH_2CH_2CH_2$-CN		62%
5			50%
6			90%
7			80%
8			N.R.%[c] 60%[d]
9			10%

(a) The general reaction conditions are described in the text.

(b) The yields were determined after chromatographic purification.

(c) No reaction but recovered 2-bromobenzonitrile when ZnO was used.

(d) TiO_2 was used to replace ZnO under the reaction condition.

ethyl bromoacetate (1.0 mmol) in anhydrous THF (4 mL) is sonicated for two hours in a commercial ultrasonic cleaning bath (Crest 575-D, 39 kHz).[11] A green color appeared after 10-30 minutes and the solution was sonicated for 2 hours to ensure the completion of the reaction. After the sonication, the solution was passed through a short silica gel column to remove zinc and zinc oxide. The eluate was added to a 50% K_2CO_3 solution (10 mL) and immediately extracted with ethyl acetate (3 x 10 mL). The organic layer was collected, washed with brine (10 mL), dried with $MgSO_4$, filtered, and the organic solvent removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexane. This type of β-amino-α,β-unsaturated esters are known to exist predominantly as Z-isomers.[10,12] A series of β-amino-α,β-unsaturated esters were synthesized and the results are shown in Table 1.

A solution of Zn (10.0 mmol), acetonitrile (2.0 mmol) and ethyl bromoacetate (2.2 mmol) in 8 mL anhydrous THF was refluxed for two hours and the formation of the self-condensation compound[13] was observed. As it is known that the activation of zinc[14,15] can be improved under ultrasound,[16-20] we therefore used ultrasound to activate the zinc metal instead of by the classical activation method.[21] A solution of Zn (5.0 mmol), acetonitrile (1.0 mmol) and ethyl bromoacetate (1.2 mmol) in 4 mL anhydrous THF was sonicated for two hours and the desired product obtained indeed was of a 52% yield. Despite success under this condition, other nitriles (e.g., phenylnitrile, Entry 6) were overshadowed by the formation of the self-condensation compound as the major product. Other activating agents, 1,2-dibromoethane[22], trimethylsilyl chloride[23], boron trifluoride[24], iodine[25] were also added for investigation under this ultrasonic reaction condition, however, only the self-condensation compound was the major product obtained.[26]

Fortunately, the above problem can be overcome by using a commercial 90% zinc instead of a > 99% pure zinc. A solution of 90% Zn (6.0 mmol), phenylnitrile (1.0 mmol) and ethyl bromoacetate (1.2 mmol) in 4 mL anhydrous THF was sonicated for two hours and the β-phenylenamino ester was produced with a 90% yield (Entry 6). We hypothesize that the remaining 10% untitled contents are the oxygenated compounds of zinc. Thus, a solution of zinc (5.0 mmol), zinc oxide (0.5 mmol), phenylnitrile (1.0 mmol) and ethyl bromoacetate (1.2 mmol) in 4 mL anhydrous THF was sonicated for two hours and the expected product was obtained with a 90% yield. It is worthwhile to note that the 90% zinc can also be an effective reagent in traditional reflux reaction conditions. A solution of Zn (10.0 mmol), acetonitrile (2.0 mmol) and ethyl bromoacetate (2.2 mmol) in 8 mL anhydrous THF was refluxed for ten hours and β-methylenamino ester (Entry 1) was produced with a 50% yield and a small amount of self-condensation compound (< 5%).[27]

Other metal oxides, such as CuO, Al_2O_3[28], SiO_2, and PtO_2 were also investigated and the desired products obtained had very low yield or negligible yields. The main product obtained appeared to be self-condensation compounds. Interestingly, titanium oxide (TiO_2)[29] was also found to improve the above sonochemical Blaise reaction (Table 1, Entry 8).[30] The mechanism for the addition of zinc oxide or titanium oxide is still unclear and needs further investigation.

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11. The bath should be filled with water containing some 3-5% detergent. In our laboratory, we use Decon 90 which permits much more even cavitation in the bath water.
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26. A solution of zinc (5.0 mmol), 1,2-dibromoethane (1.1 mmol), acetonitrile (1.0 mmol) and ethyl bromoacetate (1.2 mmol) in 4 mL dry THF was sonicated for two hours and the major product was a self-condensation compound as well as the desired product which had a 15% yield.
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30. A solution of zinc (5.0 mmol), TiO_2 (0.5 mmol), 2-bromobenzonitrile (1.0 mmol) and ethyl bromoacetate (1.0 mmol) in 4 mL dry THF was sonicated for two hours and β-amino ester (Entry 8) was produced with a 60% yield and a small amount of self-condensation compound.

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