

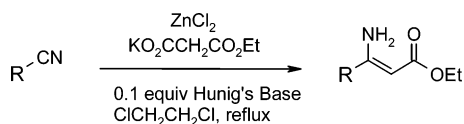
The Decarboxylative Blaise Reaction

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R = aryl, heteroaryl, cyclopropyl

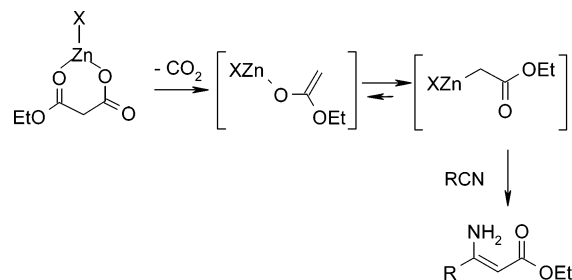
Reaction of aryl nitriles with potassium ethyl malonate in the presence of zinc chloride and a catalytic amount of Hünig's base provided β -amino acrylates in moderate to good yield. Compared to the classical Blaise reaction, this reaction is safer (endothermic), devoid of lachrymatory reagent, and is possible with 0.5–1.0 equiv of zinc chloride.

The Blaise reaction was introduced to synthetic organic chemists a century ago as an important method for the preparation of β -keto esters and β -amino acrylates by the reaction of the Reformatsky reagent with nitrile compounds. However, in spite of its straightforward introduction of versatile functionalities, this reaction has been under-exploited due to its narrow scope, low yields, and the formation of side products.¹ Although these shortcomings were significantly improved by several modifications of the original protocol,² there is still room for further refinements, particularly in eliminating the use of excess zinc metal, in avoiding the use of lachrymatory bromoacetate, and in suppression of the self-condensation side products of bromoacetate. In that context, we were intrigued by the feasibility of the decarboxylative³ Blaise reaction that would obviate the need for both zinc metal and bromoacetate.

Although there are several reports⁴ that the decarboxylation of malonic acid was accelerated by Cu(I) salts, there are scant

attempts to use this transient copper enolate intermediate in various conceivable reactions.⁵ By analogy to the copper enolate chemistry, we envisaged that the Reformatsky reagent could be formed from the zinc ethyl malonate species which would be readily prepared from the reaction of potassium ethyl malonate (**2**) with a zinc(II) salt, and further reaction with a nitrile would form a β -amino acrylate product (Scheme 1).

SCHEME 1



Initially it was found that when a mixture of zinc chloride (1.0 equiv), potassium ethyl malonate (**2**, 1.5 equiv), and benzonitrile in the polar aprotic solvents such as *N*-methylpyrrolidone (NMP) or DMF was heated at 90 °C, decarboxylation of the zinc ethyl malonate species gave ethyl acetate as the exclusive product. Since it is known that the rate of decarboxylation is dependent on the polarity of the medium,⁶ we tested the reaction in less polar media, which changed the profile of the reaction dramatically. In chlorinated solvents such as 1,2-dichloroethane (DCE) or chloroform, complete reaction was achieved in 18 h (Table 1, entries 3 and 4). On the other hand, ethereal solvents such as THF and dioxane showed limited conversion (entries 5 and 6).

With the optimal reaction medium determined, diverse metal salts were investigated for the decarboxylative Blaise reaction in DCE (Table 2). Among them, Zn(II), Cu(II), Ni(II), and In(III) salts showed moderate to excellent reactivity. Zinc chloride, bromide, or acetate (entries 1, 2, and 3) showed similar excellent reactivity, 98% conversion in 18 h, whereas zinc stearate (entry 4) showed marginal conversion; use of zinc triflate and oxide (entries 5 and 6) resulted in no conversion. Indium chloride or bromide (entries 9 and 10) exerted excellent reactivity, comparable to that of zinc. Cupric chloride and nickel bromide (entries 7 and 8) showed moderate reactivity, 73% conversion and 42% conversion in 100 h, respectively.

In spite of having optimized both the metal salts and reaction medium, we encountered occasional problems such as an unpredictable induction period of up to a few hours, and poor overall reproducibility of the reaction. The former issue was resolved by the addition of Hünig's base (*N,N*-diisopropylethylamine): addition of 0.1 to 1.0 equiv of Hünig's base consistently initiated the reaction as the reaction mixture reached

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(6) Please refer to ref 4b.

TABLE 1. Solvent Effect on the Conversion of the Decarboxylative Blaise Reaction of Benzonitrile

entry	solvent	reaction time (h)	conversion (%)
1	NMP	18	NR ^a
2	DMF	18	NR ^a
3	DCE	18	100
4	CHCl ₃	18	100
5	THF	72	5
6	dioxane	72	29

^a Only decarboxylation of potassium ethyl malonate was observed.

TABLE 2. Effect of Metal Salts on the Decarboxylative Blaise Reaction of Benzonitrile^a

entry	metal salt	time (h)	conversion (%)
1	ZnCl ₂	18	>98
2	ZnBr ₂	18	>98
3	Zn(OAc) ₂	18	>98
4	Zn(stearate) ₂	72	67
5	Zn(OTf) ₂	48	NR
6	ZnO	48	NR
7	CuCl ₂	72	72
8	NiBr ₂	72	42
9	InCl ₃	18	>98
10	InBr ₃	18	>98

^a A mixture of benzonitrile (1.0 equiv), 2 (1.5 equiv), and metal salt (1.0 equiv) in DCE was heated at reflux.

reflux. Also, after careful experiments we found that the poor reproducibility resulted from a slowing of the reaction rate, depending on the water content of the reaction mixture. Control experiments with various water contents revealed that 1200 ppm water in the reaction mixture completely stopped the progress of the reaction; 550 ppm water caused a slowdown of the reaction rate to approximately half (35 h for completion); and with a 30 ppm water level (accomplished by Dean–Stark azeotropic distillation), the reaction was consistently completed in 18 h. Interestingly, addition of molecular sieves completely inhibited the progress of the reaction.

In general, nitriles conjugated with aromatic systems showed good to moderate reactivity, while alkyl nitriles show no conversion (entry 12) as shown in Table 3. Electron-withdrawing groups on the aryl ring accelerated the reaction exemplified by entry 8, while electron-donating groups retarded the reaction (entries 4 and 6). The reaction was very sensitive to steric changes in the substrate: ortho substituted aryl nitriles showed remarkably lowered reactivity (entries 3 and 5) than their para isomers (entries 4 and 6). Heteroaryl nitriles such as 3-furonitrile (entry 10) and 2-cyanopyridine (entry 9) showed excellent reactivity (>98% conversion within 6 h). Interestingly, cyclopropyl nitrile showed good conversion to provide 79% yield of product (entry 11).

To check the possible catalytic turnover of zinc chloride, we reduced the amount of zinc chloride to 0.5, 0.2, 0.1, and 0.05 equiv, respectively (Table 4). Reduction of the equivalency below 0.5 equiv led to incomplete reactions (entries, 1, 2, and 3) despite prolonged reaction times. However, it clearly showed that the reaction was catalytic in zinc chloride with marginal turnover number. In contrast, 10 mol % of indium chloride showed only 3% conversion (entry 5); however, the use of 50

TABLE 3. Substrate Scope of the Decarboxylative Blaise Reaction^a

Entry	RCN	Equiv of ZnCl ₂ / 2	Time (h)	Product	Yield (conv.)
1	1a	0.5/1.5	18	3a	86
2	1b	1.0/2.0	18	3b	82
3	1c	1.0/2.0	72	3c	(6)
4	1d	1.0/2.0	72	3d	42 (49)
5	1e	1.0/2.0	72	3e	(0)
6	1f	1.0/2.0	40	3f	62 (67)
7	1g	1.0/2.0	18	3g	73
8	1h	0.5/1.2	4	3h	78
9	1i	0.5/1.2	4	3i	79
10	1j	1.0/2.0	6	3j	78
11	1k	1.0/2.0	18	3k	79
12	1l	1.0/2.0	120	3l	(0)

^a All the reactions were performed in DCE at reflux, with a Dean–Stark trap, and in the presence of 0.1 equiv of Hünig's base. The progress of the reactions was checked by ¹H NMR.

mol % of indium chloride (entry 6) led to complete conversion comparable to that of the zinc chloride example.

Preliminary experiments have been executed to understand the mechanism of the reaction. In the absence of the nitrile, a mixture of zinc chloride, potassium ethyl malonate, and Hünig's base in DCE was heated at reflux to show negligible decarboxylation. This indicates that the decarboxylation occurs after the addition of the zinc malonate species to the nitrile group. Although not conclusive, this result could be related to a congested transition state that was manifested with the limited progress of the reaction of sterically hindered nitriles such as *o*-bromobenzonitrile and *o*-tolunitrile (Table 3, entries 3 and

TABLE 4. Effect of Amount of Metal Salt on the Conversion^a

entry	metal salt (mol %)	time (h)	conversion (%)
1	ZnCl ₂ (5)	72	39
2	ZnCl ₂ (10)	72	58
3	ZnCl ₂ (20)	72	74
4	ZnCl ₂ (50)	18	>98
5	InCl ₃ (10)	72	3
6	InCl ₃ (50)	18	> 98

^a A mixture of benzonitrile (1.0 equiv), potassium ethyl malonate (1.5 equiv), and Hünig's base (0.1 equiv) and the designated amount of the metal salts in DCE was heated at reflux with a Dean–Stark trap.

5). Moreover, the sterically more demanding potassium ethyl 2-methylmalonate gave no reaction, consistent with this interpretation.

In conclusion, we have discovered conditions for the decarboxylative Blaise reaction which are endothermic, devoid of lachrymatory reagents, and use only 0.5–1.0 equiv of zinc chloride. It showed dichotomous selectivity toward alkyl and aryl nitriles and is marginally catalytic in zinc chloride, providing a platform for further investigation targeting a catalytic version of this reaction with a higher turnover number.

Experimental Section

General Procedure for the Decarboxylative Blaise Reaction.

A mixture of nitrile (10 mmol), ZnCl₂, potassium ethyl malonate, and *N,N*-diisopropylethylamine (1.0 mmol, 0.18 mL) in 1,2-dichloroethane (10 mL) was heated at reflux. After complete

conversion was confirmed by NMR analysis, the mixture was cooled to room temperature. To the mixture was added saturated aqueous NH₄Cl (10 mL). The organic layer was separated, dried over MgSO₄ and concentrated *in vacuo*. Chromatography of the residue provided pure product.

(Z)-3-Amino-3-(3-methoxy-phenyl)acrylic acid ethyl ester (3g): ¹H MNR (400 MHz, CDCl₃) δ 7.30 (t, 1 H), 7.12 (d, 1 H), 7.05 (m, 1 H), 6.96 (m, 1 H), 4.96 (s, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 160.3, 159.7, 139.1, 129.8, 118.4, 115.8, 111.6, 84.6, 58.9, 55.3, 14.5; LC–MS (ESI) *m/z*: 222.1 (*M* + 1); HRMS (ESI) Calcd for C₁₂H₁₆NO₃: 222.1124. Found 222.1119 (*M* + H⁺).

(Z)-3-Amino-3-(2,4,5-trifluoro-phenyl)acrylic acid ethyl ester (3h): ¹H MNR (400 MHz, CDCl₃) δ 7.33 (m, 1 H), 7.00 (m, 1 H), 4.83 (s, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 154.9 (ddd, *J* = 248, 90, 2.4 Hz), 153.4, 150.8 (ddd, *J* = 252, 150, 126 Hz), 146.8 (ddd, *J* = 243, 126, 4.2 Hz), 121.6 (m), 117.3 (m), 106.6 (dd, *J* = 236, 168 Hz), 87.4, 59.1, 14.4; LC–MS (ESI) *m/z*: 246.1 (*M* + 1); HRMS (ESI) Calcd for C₁₁H₁₁F₃NO₂: 246.0736. Found 246.0733 (*M* + H⁺).

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Supporting Information Available: Characterization data and ¹H and ¹³C NMR spectra of **3a,b**, **3d**, **3f–3k**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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