Efficient Activation of Zinc: Application of the Blaise Reaction to an Expedient Synthesis of a Statin Intermediate

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Abstract: Efficient and practical in situ zinc activation was accomplished by treatment with catalytic amount of an organic acid. The protocol was applied successfully to the Blaise reaction of various nitriles. Noteworthy is the excellent Blaise transformation of (*S*)-4-chloro-3-trimethylsilyloxybutyronitrile (**2b**) into *tert*-butyl (*S*)-6-chloro-5-hydroxy-3-oxohexanoate (**1**), a key intermediate for the preparation of HMG-CoA reductase inhibitors (statins).

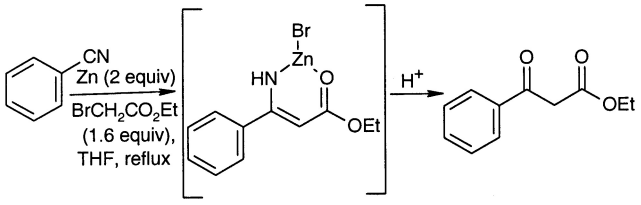
Key words: in situ zinc activation, Blaise reaction, statin intermediate

The Blaise reaction (Scheme 1) was introduced to synthetic organic chemists a century ago as an important method for the preparation of β-keto esters and their precursors, β-aminoacrylates. However, in spite of its straightforward introduction of versatile functionalities from nitrile group, its use in organic chemistry was limited due to low yield, narrow scope, and undesired side reactions.[1] These early problems were greatly improved by Kishi's modifications[2] that use activated zinc prepared by washing with a 3 N HCl solution and by adding the bromoacetate slowly to minimize self-condensation. Recently, ultrasonic assistance[3] and the use of added zinc oxide[4] have provided additional useful protocols for the Blaise reaction.

Although these modifications are significant improvements over the original procedure, there is a substantial need for further refinement of the reaction. A specific shortcoming of the existing methods is the need for preactivation of the zinc. Also, optimal reaction conditions typically require large excesses of zinc (usually 5–10 equiv) and of the bromoacetate (usually 3–5 equiv).

In this paper, we describe a practical and simple execution of the Blaise reaction using in situ activation of the zinc metal.

Since aqueous hydrochloric acid wash is effective for zinc activation removing the zinc oxide layer, it was thought that an organic acid having a similar acidity would serve the same function, and be compatible with the reaction conditions. Based upon this assumption, various organic acids have been tested for in situ zinc activation[5,6] and the



Scheme 1

results are gathered in Table 1. The Blaise reaction transformation of benzonitrile and ethyl bromoacetate into ethyl benzoylacetate was used to gauge the effectiveness of the activation.

Table 1 Effect of Acidity on the Activation of Zinc

Entry	Acid	pKa	Amount (mol%)	Conversion[a,b] (%)
1	unactivated (control)	–	–	35
2	CH_3CO_2H	4.75	1.0	80
3	$ClCH_2CO_2H$	2.85	1.0	98
4	CF_3CO_2H	0.23	1.0	99
5	CH_3SO_3H	–2.0	0.005	46
6	CH_3SO_3H	–2.0	0.05	55
7	CH_3SO_3H	–2.0	0.25	98
8	CH_3SO_3H	–2.0	0.5	99
9	CH_3SO_3H	–2.0	1.0	99
10	CF_3SO_3H	–13.0	1.0	99

[a] The analyses were performed using GC: HP-5 column; injector: 280 °C; initial time and temp: 2 min and 50 °C; gradient: 10 °C/min; final temp: 300 °C;, flow rate: 1 mL/min. Benzonitrile and ethyl benzoylacetate were detected at 10.6 and 19.7 min, respectively.
[b] All the reactions were quenched after 1.5 h and analyzed by GC.

We were delighted to have an immediate success. When 1 mol% of methanesulfonic acid was added for in situ activation of commercial zinc (5 equivalents), complete conversion in the Blaise reaction of benzonitrile with ethyl bromoacetate (4 equivalents) was observed by GC analysis. Further optimization on the reduction of the use of zinc and bromoacetate led to the conclusion that only 2

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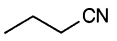
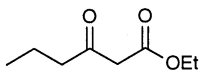
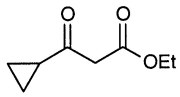
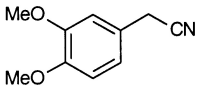
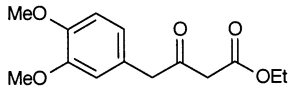
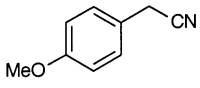
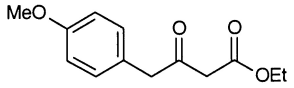
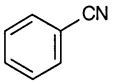
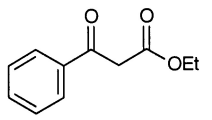
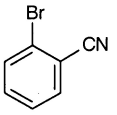
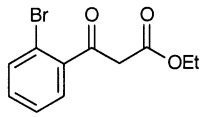
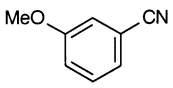
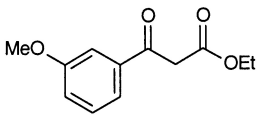
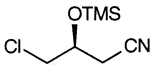
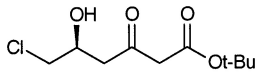
equivalents of zinc and 1.6 equivalents of bromoacetate are sufficient for complete conversion. The influence of the acidity and the stoichiometry of organic acids were studied and it was found that the acidity of an organic acid is critical for proper activation of zinc. Addition of acetic acid provided 80% conversion (Table 1, entry 2), while stronger acids such as chloroacetic, trifluoroacetic, methanesulfonic, and trifluoromethanesulfonic acids led to complete conversion. Using methanesulfonic acid as the organic acid, we next examined the optimal amount of acid required (Table 1, entries 5–8): A minimum of 0.25 mol% of methanesulfonic acid was necessary for complete conversion (Table 1, entry 7). However, 0.5 mol% of methanesulfonic acid (Table 1, entry 8) was generally employed to ensure consistent results. We have also observed that the Blaise reaction is quite tolerant of moisture. We used commercial THF as solvent, which contained 420 ppm of water by Karl Fisher titration. Even THF with a water of up to 0.2% (wt/wt) gave consistently successful results.

The optimized Blaise reaction protocol was examined with various nitriles and the results are summarized in Table 2. Good to excellent isolated yields were observed with aliphatic nitriles (Table 2, entry 1 and 2) as well as benzylic nitriles (Table 2, entries 3 and 4). Aromatic nitriles also showed good yields regardless of their electronic character.

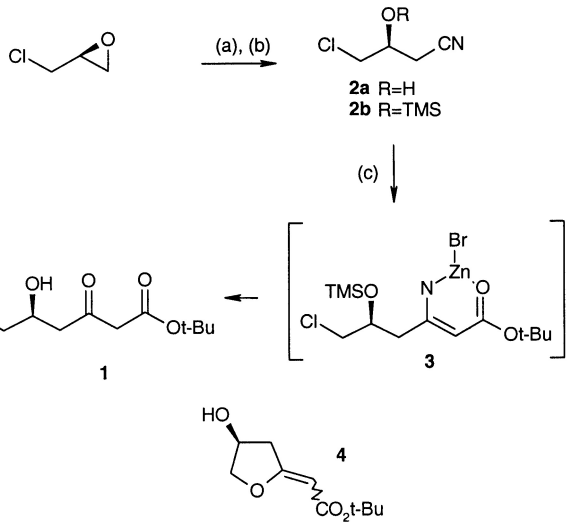
Noteworthy is the conversion of (*S*)-4-chloro-3-trimethylsilyloxybutyronitrile (**2b**) to *tert*-butyl (*S*)-6-chloro-5-hydroxy-3-oxohexanoate (**1**), a key intermediate for the preparation of HMG-CoA reductase inhibitors[7] (Table 2, entry 8 and Scheme 2). The known methods are based upon the Claisen condensation of ethyl (*S*)-4-chloro-3-hydroxybutyrate with an excess of the lithium enolate of *tert*-butyl acetate[8] and enzyme-mediated enantioselective reduction of *tert*-butyl 6-chloro-3,5-dioxohexenoate,[9] respectively. The former route is complicated by the formation of the side product **4**. The latter method suffers the limitation of being able to access only one of the two possible enantiomers.

Our route depicted in Scheme 2 eradicated the problems associated with the precedents. Ring opening of (*S*)-epichlorohydrin by sodium cyanide[10] and subsequent protection of the secondary hydroxyl group by trimethylsilyl group[11] afforded (*S*)-4-chloro-3-trimethylsilyloxybutyronitrile (**2b**) in good yield. At the epoxide opening stage, maintaining the pH of the reaction in the range of 7.7 to 7.9 was critical to the success of the reaction because under more basic conditions the formation of 3-hydroxyglutaronitrile predominates. Blaise reaction of **2b** with *tert*-butyl bromoacetate provided the β-amino-α,β-unsaturated ester intermediate **3**, which was hydrolyzed by aqueous HCl to cause concomitant hydrolysis of the enamine moiety and deprotection of the trimethylsilyl group to afford the β-keto ester **1** in 85% yield. Complete absence of the side product **4** clearly demonstrates the high functional group compatibility of the optimized Blaise reaction conditions.

Table 2 The Blaise Reactions of Various Nitriles[a]

Entry	Substrate	Product	Yield (%)
1			77
2			86
3			66
4			91
5			75
6			67
7			77
8			85

[a] All the reactions were performed with 2 equiv of zinc and with slow addition of 1.6 equiv of bromoacetate over 1 h. After addition, the mixture was refluxed for 0.5 h in THF.



Scheme 2
Reagents and conditions: (a) NaCN, H_2SO_4, pH 7.7–7.9, –20 °C, 87%; (b) TMSCl, HMDS, 98%; (c) $BrCH_2CO_2Bu$-*t* (1.6 equiv), Zn (2 equiv), MsOH (0.5 mol%), then 3 N HCl, 85%.

In conclusion, we have developed an efficient and practical in situ activation of zinc metal[12] by treatment with an catalytic amount of organic acid. The effectiveness of this activation (use of 0.5 mol% of methanesulfonic acid) leads to a significant reduction in the equivalents of zinc and bromoacetate in the Blaise reaction to 2 and 1.6 equivalents, respectively. The established protocol was successfully applied to the Blaise reactions of various nitriles and the expedient synthesis of *tert*-butyl (*S*)-6-chloro-5-hydroxy-3-oxohexanoate (**1**).

β-Keto Esters; General Procedure

To a stirred suspension of commercial zinc (zinc dust, <10 micron, Aldrich, 2.0 equiv) in THF (5 mL/g) was added $MeSO_3H$ (1 mol%) at r.t. The mixture was refluxed for 10 min and nitrile was added. To the mixture was added ethyl bromoacetate (1.6 equiv) over 1 h using syringe pump. After 30 min, the mixture was cooled to 0–5 °C and aq 3 N HCl (4 mL/g) solution was added dropwise. After 3–24 h, all the organic volatiles are removed in vacuo and the remaining mixture was extracted with EtOAc (10 mL/g). The separated organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated. Column chromatography of the residue afforded the desired product (Table 2).

Ethyl 3-Oxoheptanoate[13]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20 (q, *J* = 7.2 Hz, 2 H), 3.43 (s, 2 H), 2.54 (t, *J* = 7.2 Hz, 2 H), 1.59 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 0.91 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0, 167.3, 61.3, 49.3, 42.7, 25.5, 22.1, 14.1, 11.7, 13.8.

MS (ESI): *m*/*z* = 367 (2 M + Na), 195 (M + Na), 173 (M + H).

Ethyl 3-Cyclopropyl-3-oxopropionate[14]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 (q, *J* = 7.2 Hz, 2 H), 3.57 (s, 2 H), 2.04 (m, 1 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.12 (m, 2 H), 0.97 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.8, 167.2, 61.3, 50.0, 20.7, 14.1, 11.7.

MS (ESI): *m*/*z* = 335 (2 M + Na), 179 (M + Na), 157 (M + H).

Ethyl 4-(3,4-Dimethoxyphenyl)-3-oxobutyrate[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85–6.71 (m, 3 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 3.87 (s, 6 H), 3.76 (s, 2 H), 3.44 (s, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 167.1, 149.2, 148.4, 125.6, 121.8, 112.5, 111.4, 61.4, 55.9, 49.6, 48.0, 14.1.

MS (ESI): *m*/*z* = 289 (M + Na), 267 (M + H).

Ethyl 4-(4-Methoxyphenyl)-3-oxobutyrate[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (m, 2 H), 6.87 (m, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 3.80 (s, 3 H), 3.76 (s, 2 H), 3.43 (s, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 167.1, 158.9, 130.6, 125.2, 114.3, 61.3, 55.2, 49.1, 48.1, 14.0.

MS (ESI): *m*/*z* = 495 (2 M + Na), 259 (M + Na), 237 (M + H).

Ethyl 3-(2-Bromophenyl)-3-oxopropionate[13]

^{1}H NMR (400 MHz, $CDCl_3$): δ (keto form, 60%) = 7.64–7.24 (m, 4 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 4.02 (s, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H). δ (enol form, 40%) = 12.42 (s, 1 H), 7.64–7.24 (m, 4 H), 5.45 (s, 1 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (keto form) = 195.6, 166.8, 140.0, 133.9, 132.3, 129.5, 127.5, 119.2, 61.5, 48.8, 14.0. δ (enol form) = 172.6, 171.1, 135.8, 133.8, 131.2, 130.2, 127.3, 121.0, 93.2, 60.6, 14.3.

MS (ESI): *m*/*z* = 367 (2 M + Na), 195 (M + Na), 173 (M + H).

Ethyl 3-(3-Methoxyphenyl)- 3-oxopropionate[13]

^{1}H NMR (400 MHz, $CDCl_3$): δ (keto form, 75%) = 7.50–7.35 (m, 3 H), 7.14 (m, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 3. 98 (s, 2 H), 3.86 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H). δ (enol form, 25%) = 12.57 (s, 1 H), 7.50–7.35 (m, 3 H), 5.65 (s, 1 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 3.84 (s, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (keto form) = 192.4, 167.5, 160.0, 137.4, 129.8, 121.2, 120.4, 112.5, 61.5, 55.5, 46.1, 14.1. δ (enol form) = 173.2, 171.3, 159.7, 134.9, 129.6, 118.5, 117.3, 111.2, 91.8, 60.4, 55.4, 14.3.

MS (ESI): *m*/*z* = 467 (2 M + Na), 245 (M + Na), 223 (M + H).

(*S*)-4-Chloro-3-hydroxybutyronitrile (2a)

To a stirred solution of NaCN (92.6 g, 1.89 mol) in H_2O (560 mL) was added dropwise conc. H_2SO_4 (92.0 g, 0.94 mol) over 1 h at –25 °C to adjust the pH of the reaction mixture in the range of 7.7 to 7.9. To the mixture was added dropwise (*S*)-epichlorohydrin (139.8 g, 1.51 mol). After 12 h, the formed solid was filtered and the filtrate was extracted with CH_2Cl_2 (370 g). Concentration of the separated organic layer and vacuum distillation of the residue provided 157.5 g (87%) of **2a** as a colorless oil; bp 110 °C/1 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 (m, 1 H), 3.71 (dd, *J* = 11.6, 4.8 Hz, 1 H), 3.67 (dd, *J* = 11.6, 5.6 Hz, 1 H), 2.74 (dd, *J* = 16.8, 6.0 Hz, 1 H), 2.69 (dd, *J* = 16.8, 6.4 Hz, 1 H), 2.61 (d, *J* = 5.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.0, 67.2, 47.2, 23.2.

EI-MS: *m*/*z* = 122 (M + H + 2), 120 (M + H), 81 (M + 2 – CH_2CN), 79 (M – CH_2CN).

(*S*)-4-Chloro-3-trimethylsilyloxybutyronitrile (2b)

To a stirred solution of **2a** (150 g, 1.25 mol) in toluene (700 mL) was added hexamethyldisilazane (HMDS, 121 g, 0.75 mol) at 0 °C. To the mixture was added Me_3SiCl (6.9 g, 0.05 mol) and the mixture was warmed to r.t. After 8 h, aq 10% NH_4Cl solution was added and the organic layer was separated. Concentration of the separated organic layer provided 229.5 g (98%) of **2b** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (m, 1 H), 3.54 (dd, *J* = 11.4, 4.8 Hz, 1 H), 3.48 (dd, *J* = 11.4, 7.2 Hz, 1 H), 2.70 (dd, *J* = 16.6, 4.6 Hz, 1 H), 2.62 (dd, *J* = 16.6, 6.6 Hz, 1 H), 0.21 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.8, 68.5, 46.5, 24.1, 0.0.

EIMS: *m*/*z* = 367 (2 M – CH_3), 284 (2 M + H – TMS – CN), 264 (2 M – H – TMS – CN – H_2O), 176 (M – CH_3), 93 (M + H – TMS – CN), 75 (M + H – TMS – CN – H_2O), 73 (TMS).

***tert*-Butyl (*S*)-6-Chloro-5-hydroxy-3-oxohexanoate (1)**

To a stirred suspension of commercial zinc dust (8.3 g, 126 mmol) in THF (60 mL) was added $MeSO_3H$ (60 mg, 0.6 mmol) at r.t. The mixture was refluxed for 10 min and (*S*)-4-chloro-3-trimethylsilyloxybutyronitrile (**2b**; 12.0 g, 63 mmol) was added. To the mixture was added *tert*-butyl bromoacetate (19.7 g, 101 mmol) over 1 h using a syringe pump. After 30 min, the mixture was cooled to 0–5 °C and aq 3 N HCl (40 mL) was added dropwise. After 2 h, all the organic volatiles were removed in vacuo and the remaining mixture was extracted with EtOAc (60 mL). The separated organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated. Column chromatography (EtOAc–hexane, 1:3) of the residue afforded 12.1 g (85%) of **1** as a viscous oil; $[\alpha]_D^{25}$ –24.4 (*c* = 1.0, $CHCl_3$) {Lit.[9b] $[\alpha]_D^{25}$ –24.9 (*c* = 1.4, $CHCl_3$)}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (enol form, 5%) = 12.40 (s, 1 H), 5.01 (s, 1 H), 4.19 (m, 1 H), 3.62 (dd, *J* = 11.2, 4.8 Hz, 1 H), 3.58 (dd, *J* = 11.2, 5.6 Hz, 1 H), 2.56 (m, 1 H), 2.48 (br s, 1 H), 2.46 (m, 1 H), 1.48 (s, 9 H). δ (keto form, 95%) = 4.32 (m, 1 H), 3.62 (dd, *J* = 11.2, 4.8 Hz, 1 H), 3.58 (dd, *J* = 11.2, 5.6 Hz, 1 H), 3.42 (s, 2 H), 3.00 (d, *J* = 3.2 Hz, 1 H), 2.91 (dd, *J* = 17.6, 4.4 Hz, 1 H), 2.85 (dd, *J* = 17.6, 7.2 Hz, 1 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (enol form) = 193.2, 166.1, 93.1, 79.2, 69.0, 49.0, 39.7, 28.3. (keto form) = 202.7, 166.0, 82.5, 67.4, 51.1, 49.0, 46.4, 28.0.

ESI-MS: *m*/*z* = 496 (2 M + Na + 2), 494 (2 M + Na), 261 (M + Na + 2), 259 (M + Na).

HRMS-ESI: *m*/*z* calcd for $C_{10}H_{17}ClO_4Na$: 259.0713; found: 259.0712.

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