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One-pot synthesis of 3,4-dihydropyridin-2-ones via tandem reaction of Blaise reaction intermediate and acrylic ester

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An efficient method for the synthesis 3,4-dihydropyridin-2-ones has been developed via tandem one-pot Michael-type addition and cyclization of the Blaise reaction intermediate and acrylic ester. A series of readily available nitriles, bromoacetic esters and acrylic esters have been employed to examine the scope of substrates for this method.

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Keywords: zinc; 3,4-dihydropyridin-2-ones; Blaise reaction; one-pot synthesis

Introduction

3,4-Dihydropyridin-2-ones are embedded as prominent substructures in numerous bioactive compounds exhibiting various activities such as antibacterial,[1] antifungal[2] and antitumor,[3] also serving as kinase inhibitors.[4] Moreover, the dihydropyridinone skeleton has often been used in natural product synthesis.[5] The usefulness of 3,4-dihydropyridin-2-one derivatives has made their quick and efficient synthesis the subject of much research.

So far, many methods have been developed. Among them, the aza-annulation of enamines and α,β-unsaturated carboxylic acid derivatives is the most commonly used method.[6] Furthermore, 3,4-dihydropyridin-2-one derivatives have been synthesized by intermolecular cyclization of 1-azadienes[7] with ketenes[8] or carboxylic acid derivatives.[9] In addition, aza Diels–Alder reactions between Brassard's diene and imines are also useful methods for their rapid synthesis.[10] Recently, multicomponent reactions have been applied as more step- and atom-economic pathways for their synthesis, which include the three-component reaction of aldehydes, cyanoacetamides and 1,3-dicarbonyl compounds developed by Lin and co-workers[11] and Das and co-workers,[12] four-component reaction of aromatic aldehydes, 1,3-diketones, aryl amines and dimethyl acetylenedicarboxylate reported by Yan and co-workers[13] as well as four-component reaction of phosphonates, nitriles, aldehydes and isocyanoacetates reported by the Orru group.[14] Although high yields can be obtained, the methods mentioned above either utilize substrates that are not readily available or require harsh reaction conditions. Thus, the search for a simple protocol for the construction of 3,4-dihydropyridin-2-one skeletons from readily available substrates is worth investigation.

The Blaise reaction is a classic reaction for the zinc-mediated transformation of nitriles and ethyl bromoacetate into the corresponding β-keto esters. In recent years, the Blaise reaction intermediates, zinc-bound β-amino-α,β-unsaturated esters, have been trapped with suitable partners such as acetic anhydride,[15] alkynes,[16] 1,3-enynes,[17] propiolates,[18] halogenated hydrocarbons,[19] nitriles,[20] isocyanates[21] and nitroolefins[22] in a tandem manner, which has provided access to a variety of nitrogen-containing heterocyclic compounds. Inspired by the works mentioned above, we report a tandem one-pot method for the synthesis of 3,4-dihydropyridin-2-one compounds through the sequential reaction of nitriles with Reformatsky reagents (the Blasie reaction) and α,β-unsaturated carboxylic esters.

Results and discussion

The reaction of Blaise reaction intermediate **Aaa**, which is formed from the reaction of benzonitrile (**1a**) with a Reformatsky reagent generated *in situ* from ethyl bromoacetate (**2a**; 1.5 equiv.) and zinc powder (2.0 equiv.) in tetrahydrofuran (THF), and ethyl acrylate (**3a**; 2.0 equiv.) was investigated for the synthesis of the 3,4-dihydropyridin-2-one **4aaa** as well as for optimization of reaction conditions (Table 1). No desired product is observed when the reaction is performed under non-catalytic conditions (Table 1, entry 1). We hypothesize that a Lewis acid catalyzes this addition and the sequential cyclization reaction. Screening of various Lewis acid catalysts reveals that the catalyst plays a significant role in this reaction. Only a trace amount of the desired product **4aaa** is obtained when zinc bromide is used as a catalyst (Table 1, entry 2). Boron trifluoride–diethyl ether complex is found to be the best of all catalysts tested (Table 1, entries 7–11). Further reducing the catalyst loading from 30 to 25 mol% results in a decrease in product yield from 81 to 63% (Table 1, entries 7 and 8). The effect of temperature on the reaction was studied. No desired product can be observed

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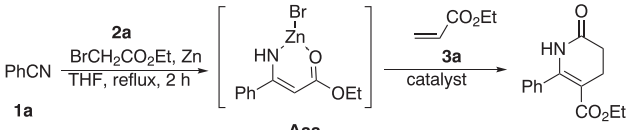
Table 1. Optimization of conditions for the one-pot synthesis of 3,4-dihydropyridin-2-one via the Blaise reaction[a]



Entry	Catalyst (mol%)	Solvent	T (°C)[b]	Yield (%)[c]
1	—	THF	80	0
2	$ZnBr_2$ (30)	THF	80	Trace
3	$FeCl_3$ (30)	THF	80	52
4	$AlCl_3$ (30)	THF	80	40
5	$Cu(OTf)_2$ (30)	THF	80	23
6	$In(OTf)_2$ (30)	THF	80	14
7	$BF_3{\cdot}OEt_2$ (30)	THF	80	81
8	$BF_3{\cdot}OEt_2$ (25)	THF	80	63
9	$BF_3{\cdot}OEt_2$ (20)	THF	80	52
10	$BF_3{\cdot}OEt_2$ (35)	THF	80	81
11	$BF_3{\cdot}OEt_2$ (30)	THF	60	35
12	$BF_3{\cdot}OEt_2$ (30)	THF	r.t.	0
13	$BF_3{\cdot}OEt_2$ (30)	Toluene[d]	100	36
14	BF_3 OEt_2 (30)	1,4-Dioxane[d]	100	76

[a]General conditions: benzonitrile (1.0 equiv.), ethyl bromoacetate (1.5 equiv.), zinc (2.0 equiv.), ethyl acrylate (2.0 equiv.), 8 h (after adding ethyl acrylate).
[b]Oil bath temperature.
[c]Isolated yields.
[d]After removing THF, toluene or 1,4-dioxane was added.

when the reaction is performed at room temperature, but the *β*-keto ester is mostly obtained (Table 1, entry 12). The reaction proceeds sluggishly at 60°C and is not completed even after 24 h (Table 1, entry 11). An examination of the importance of the solvents in this reaction reveals that THF is better than toluene and 1,4-dioxane (Table 1, entries 13 and 14).

With the optimized reaction conditions in hand, the scope and limitation of this reaction were then explored. We were pleased to find that intermediates **A**, formed from **2a** and aryl nitriles having various substituents on the aryl moiety, can react with **3a** to afford the corresponding 3,4-dihydropyridin-2-ones **4aaa–4kaa** in moderate to good yields (Table 2, entries 1, 4–13). In particular, the intermediate **A** derived from 4-(trifluoromethyl)benzonitrile affords 3,4-dihydropyridin-2-one **4kaa** in a good yield of 83% (Table 2, entry 13). However, pyridine nitriles do not afford at all the corresponding 3,4-dihydropyridin-2-ones. Aliphatic nitriles can also be transformed to the corresponding desired products in moderate yields via the tandem reaction of the Blaise reaction intermediate with **3a** (Table 2, entries 14–17). Methyl 2-bromoacetate (**2b**) and *tert*-butyl 2-bromoacetate (**2c**) react smoothly to give the corresponding 3,4-dihydropyridin-2-ones in good yields (Table 2, entries 18 and 19). Acrylic esters **3b** and **3c** give the desired product **4aaa** in 80 and 55% yields, respectively (Table 2, entries 2 and 3). These results suggest that the tandem reaction is sensitive to the steric hindrance of the acrylic esters **3**. In order to further expand the scope of the substrates **3**, ethyl cinnamate was added to the formed Blaise reaction intermediate **Aaa**, but no desired product is obtained. To increase the reactivity of the substrates **3**, more electron-deficient alkenes, arylidene malonates, were used. To our delight, various arylidene malonates can react smoothly with intermediate **Aaa** in the presence of boron trifluoride, affording the corresponding products in moderate to good yields (Table 2, entries 20–26). R^3 and R^4 in products **4aad–4aaj** are *trans*, which has been confirmed using X-ray crystallographic analysis.[23] Substituents on arylidene malonates influence the yields. Generally, arylidene malonates with electron-donating groups give poorer yields than those with electron-withdrawing groups (Table 2, entries 21 and 25). Due to the steric hindrance of the substituents on the aryl groups, *ortho*-substituted arylidene malonates provide products in poorer yields than *para*- and *meta*-substituted ones (Table 2, entries 21–23). Alkylidene malonates such as diethylethylidene malonate and diethylmethylidene malonate do not give the desired products.

A possible reaction mechanism that accounts for the formation of products **4** is shown in Scheme 1. The first step involves a Michael-type addition of the Blaise reaction intermediate **Aaa** to **3a** to form an intermediate **B**,[22] followed by tautomerization and proton transfer to give intermediate **C**. Then, intermediate **C** undergoes tautomerization to give the enamine intermediate **D**, which liberates **4aaa** and BrZnOEt after classic intramolecular nucleophilic cyclization and elimination reaction.

Conclusions

We have developed an efficient one-pot protocol for the synthesis of 3,4-dihydropyridin-2-ones based on BF_3-catalyzed tandem Michael-type addition and cyclization between Blaise reaction intermediates and acrylic esters. Considering the ready availability of the starting materials, the one-pot operation and the mild conditions, the present protocol could be a useful method for the synthesis of 3,4-dihydropyridin-2-ones. Further investigations of the mechanism and synthetic applications of the reaction presented here are in progress.

Experimental

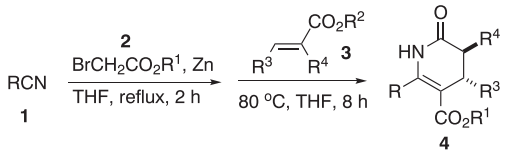
General

All the tandem reactions were performed under an argon atmosphere using oven-dried Schlenk flasks. The chemicals were purchased from Alfa Aesar and Acros Chemicals. All solvents and materials were pre-dried, redistilled or recrystallized before use. ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded using a Bruker Avance 400 spectrometer with $CDCl_3$ as the solvent. Chemical shifts were measured in ppm by assigning tetramethylsilane resonance in the ^{1}H NMR spectra as 0.00 ppm and $CDCl_3$ resonance in the ^{13}C NMR spectra as 77.0 ppm. All coupling constants (*J* values) were measured in hertz. Column chromatography was performed on silica gel 200–300 mesh. Melting points were measured using a WC-1 microscopic apparatus and were uncorrected. Fourier transform infrared spectra were recorded using KBr pellets in the range 400–4000 cm^{-1} with a Nicolet 5DX spectrometer. Mass spectra were obtained with an Agilent LC-MSD-Trap-XCT instrument. Arylidene malonates **3d–3j** were prepared using published procedures.[24]

General procedure for synthesis of 3,4-Dihydropyridin-2-ones

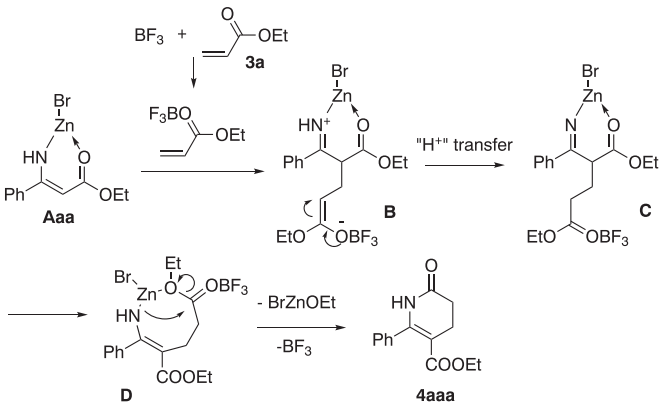
To a stirred suspension of commercial zinc dust (10 mmol, 0.65 g) in THF (2.0 ml) was added 1,2-dibromoethane (10 mol%) and the reaction mixture was heated to 65°C until the solvent began to reflux. Two minutes later it was cooled to room temperature and trimethylchlorosilane (10 mol%) was added. After stirring for 15 min at room temperature, nitrile (5.0 mmol), THF (2 ml) and

Table 2. One-pot synthesis of 3,4-dihydropyridin-2-ones from acrylic esters[a]



Entry	Nitrile 1	Bromoacetic ester 2	Acrylic ester 3	Product 4	Yield (%)[b]
1	R = Ph (1a)	R^1 = Et (2a)	R^2 = Et, R^3 = H, R^4 = H (3a)	4aaa	81
2	1a	2a	R^2 = Me, R^3 = H, R^4 = H (3b)		80
3	1a	2a	R^2 = *t*-Bu, R^3 = H, R^4 = H (3c)		55
4	R = 3-MePh (1b)	2a	3a	4baa	75
5	R = 2-MePh (1c)	2a	3a	4caa	69
6	R = 4-ClPh (1d)	2a	3a	4daa	79
7	R = 2-ClPh (1e)	2a	3a	4eaa	75
8	R = 3-FPh (1f)	2a	3a	4faa	78
9	R = 4-FPh (1g)	2a	3a	4gaa	79
10	R = 2-FPh (1h)	2a	3a	4haa	65
11	Piperonylonitrile (1i)	2a	3a	4iaa	71
12	Cinnamonitrile (1j)	2a	3a	4jaa	63
13	R = 4-F_3CPh (1k)	2a	3a	4kaa	83
14	R = 4-ClPhCH_2 (1l)	2a	3a	4laa	62
15	R = 2-ClPhCH_2 (1m)	2a	3a	4maa	53
16	R = Et (1n)	2a	3a	4naa	44
17	R = Me (1o)	2a	3a	4oaa	41
18	1a	R^1 = Me (2b)	3a	4aba	76
19	1a	R^1 = *t*-Bu (2c)	3a	4aca	70
20	1a	2a	R^2 = Et, R^3 = Ph, R^4 = CO_2Et (3d)	4aad	76
21	1a	2a	R^2 = Et, R^3 = 4-MeOPh, R^4 = CO_2Et (3e)	4aae	56
22	1a	2a	R^2 = Et, R^3 = 3-MeOPh, R^4 = CO_2Et (3f)	4aaf	64
23	1a	2a	R^2 = Et, R^3 = 2-MeOPh, R^4 = CO_2Et (3g)	4aag	45
24	1a	2a	R^2 = Et, R^3 = 2-ClPh, R^4 = CO_2Et (3h)	4aah	68
25	1a	2a	R^2 = Et, R^3 = 4-ClPh, R^4 = CO_2Et (3i)	4aai	80
26	1a	2a	R^2 = Et, R^3 = 4-MePh, R^4 = CO_2Et (3j)	4aaj	61

[a]General conditions: nitrile (5.0 mmol), bromoacetic ester (7.5 mmol), zinc (10 mmol, 0.65 g), BF_3·OEt_2 (30 mol%), acrylic ester (10 mmol), 8 h (after adding ethyl acrylate), 80°C (oil bath temperature).
[b]Isolated yields after flash column chromatography.



Scheme 1. Proposed mechanism.

bromoacetic ester (7.5 mmol) were added successively. The mixture was refluxed for 2 h. After the reaction mixture was cooled to room temperature, BF_3·OEt_2 (30 mol%) and acrylic ester (10 mmol) were added, and the reaction temperature was raised to 80°C. After 8 h of stirring, the mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (30 ml) and extracted with ethyl acetate (30 ml). The organic layer was washed with brine (30 ml), dried over by anhydrous $MgSO_4$ and evaporated under vacuum. The desired 3,4-dihydropyridin-2-ones were obtained after purification by flash chromatography on silica gel with petroleum ether–ethyl acetate as the eluent.

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