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One-Pot Synthesis of 2-Pyridones via Chemo- and Regioselective Tandem Blaise Reaction of Nitriles with Propiolates

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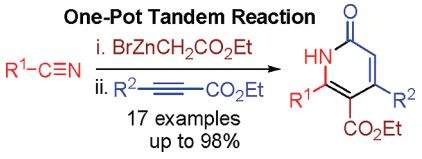

The Blaise reaction intermediate, generated in situ from Reformatsky reagent and nitrile, reacted with propiolates in a chemo- and regioselective manner to afford 2-pyridone derivatives in good to excellent yields

Pyridones are embedded as common structural units of many natural products and biologically active compounds.[1] As a result, the development of efficient synthetic methods for this class of heterocyclic compounds has become a long-standing subject in synthetic and medicinal chemistry.[2] The most commonly employed method is Michael addition of acetonitrile derivatives such as cyanoacetate ester, cyanoacetamide, or malonitrile to an appropriate α,β-unsaturated carbonyl substrate, and subsequent hydrolytic cyclization followed by oxidative aromatization of the resulting 3,4-dihydropyridones with use of DDQ,[3] molecular oxygen,[4] and HNO_2[5] as oxidants or by eliminative aromatization employing acetoamino and benzenetriazolyl leaving groups.[6] Alternatively, dienaminoesters prepared by the reaction of β-enaminoester with propiolate can be cyclized to 2-pyridones.[7] As an extension, Savarin and co-workers have recently reported that the reaction of *N*-arylated β-enamino ketones with methyl propiolates yielded the corresponding *N*-aryl 5-acyl-2-pyridones, which was utilized as a common template for naphthyridones and quinolines.[8] Although these methods are effective for the synthesis of pyridone derivatives, it is a prerequisite to prepare α,β-unsaturated carbonyl substrates or β-enaminocarbonyl derivatives beforehand from aldehydes or β-ketocarbonyl compounds, respectively. To improve on this, we devised a tandem one-pot synthesis of various 2-pyridone derivatives from nitriles via the Blaise reaction intermediate, which is very efficient in yield and operationally convenient.

The reaction of the Reformatsky reagent with nitrile, the so-called Blaise reaction, is known to proceed via a zinc bromide complex of a β-enamino ester.[9] Hydrolytic workup of this reaction intermediate under acidic or basic conditions provides the corresponding β-keto esters and β-enamino esters, which have been engineered to build a variety of molecules.[10] Recently, we were intrigued by the possible tandem use of the Blaise reaction intermediate as a bidendate organozinc nucleophile having two nucleophilic atoms, i.e., the α-carbon and β-nitrogen to the ester group, and found that the Blaise reaction intermediate acts as a carbon nucleophile toward anhydrides and terminal alkynes to give α-acylated and α-vinylated β-enaminoesters, respectively.[11]

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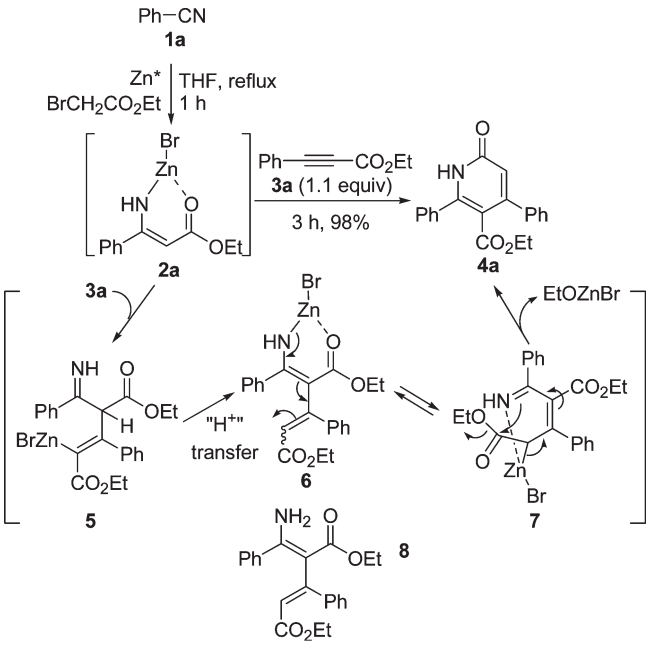
SCHEME 1. A Proposed Mechanism for the Tandem Synthesis of 2-Pyridone 4a



Encouraged by these results, we envisioned that a chemo- and regioselective reaction of the Blaise reaction intermediate with propiolates bearing two electrophilic functional groups, alkyne and ester, would provide a new tandem synthetic route for 2-pyridone derivatives. Herein we present the results of our investigation on the development of a highly efficient one-pot synthesis of 2-pyridone derivatives via a chemo- and regioselective tandem reaction of the Blaise reaction intermediate, a zinc bromide complex of β-enamino ester **2**, with propiolates.

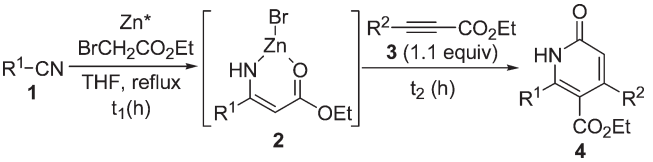
To begin our investigation, a Blaise reaction intermediate **2a** was prepared in situ by the addition of ethyl bromoacetate (1.5 equiv) to a solution of benzonitrile **1a** (1.0 equiv) and zinc powder (2.0 equiv, preactivated by using 5.0 mol % of CH_3SO_3H) in THF. To our delight, the tandem reaction of the intermediate **2a** with 1.1 equiv of ethyl phenylpropiolate **3a** for 3 h afforded the corresponding 2-pyridone **4a** in extremely high 98% yield (Scheme 1).

This result clearly indicated that the Blaise reaction intermediate **2a** has an ambivalent nucleophilic nature—both α-carbon and β-nitrogen can act as nucleophiles. As shown in Scheme 1, Michael addition of the Blaise reaction intermediate **2a** to the propiolate **3a** gave the vinyl zinc bromide **5**, which was isomerized to the α-vinylated zinc bromide complex **6** via inter- and/or intramolecular proton transfer of the acidic α-proton. Rearrangement of **6** to the Csp^3-ZnBr **7**, followed by intramolecular cyclization led to the 2-pyridone structure. Careful monitoring and quenching of the reaction in the early stage made possible the isolation of appreciable amounts of the α-vinylated β-enaminoester **8**, which supports our proposed reaction mechanism. The intermediate **8** can also be isolated in 45% yield when the reaction was carried out at 40 °C for 24 h.

We next explored the scope of the tandem Blaise reaction with propiolates **3** (Table 1).

A wide range of aromatic, heteroaromatic, and aliphatic nitriles could be transformed efficiently to the corresponding 2-pyridones **4a**−***l*** (entries 1−12, Table 1) with a 4-phenyl

TABLE 1. Synthesis of 2-Pyridones via Tandem Blaise Reaction with Propiolates[a]



Entry	**1** (R^1)	**3** (R^2)	t_1/t_2 (h)	**4** Yield (%)[b]
1	Ph	Ph	1/3	**4a** (98)
2	*p*-FC_6H_4	Ph	1/3	**4b** (97)
3	*p*-$CF_3C_6H_4$	Ph	2/3	**4c** (95)
4	*p*-$CH_3OC_6H_4$	Ph	1/3	**4d** (95)
5[c]	*o*-$CH_3C_6H_4$	Ph	5/4	**4e** (56)
6	*m*-$CH_3C_6H_4$	Ph	2/4	**4f** (81)
7	*p*-$CH_3C_6H_4$	Ph	1/4	**4g** (89)
8		Ph	1/6	**4h** (83)
9		Ph	1/4	**4i** (90)
10	$C_6H_5CH_2$	Ph	1/3	**4j** (92)
11	CH_3CH_2	Ph	2/4	**4k** (92)
12	$(CH_3)_2CHCH_2$	Ph	2/4	**4l** (88)
13	Ph	*p*-FC_6H_4	1/6	**4m** (92)
14	Ph	*p*-$CH_3OC_6H_4$	1/6	**4n** (94)
15	Ph	C_4H_9	1/5	**4o** (90)
16	Ph	*cy*-C_6H_{11}	1/8	**4p** (91)
17	Ph	H	1/24	**4q** (35)

[a]The reaction was carried out on a 7.6-mmol scale of nitrile **1**, and propiolate **3** was added after >98% conversion of nitrile unless otherwise noted. [b]Isolated by silica chromatography. [c]Propiolate **3a** was added at 93% conversion of nitrile.

group with good to excellent yields through the tandem reaction with ethyl phenylpropiolate. The structures of 2-pyridones are unambigously characterized by spectroscopic methods and further confirmation was obtained from the X-ray structure of the 6-ethyl-substituted 2-pyridone **4k** prepared from propionitrile.[12] In general, the electronic properties of nitriles did not affect the reactivity. However, the sterically more demanding *o*-methylbenzonitrile showed diminished reactivity, resulting in a relatively lower yield of 2-pyridone **4e** (56%, entry 5, Table 1). Various propiolates such as aryl and alkyl propiolates have also been investigated by the tandem reaction of the Blaise reaction intermediate, prepared from benzonitrile **1a** and ethyl bromoacetate (entries 13−16, Table 1). Tandem reaction with aryl propiolate having either electron-withdrawing 4-fluoro- or electron-donating 4-methoxyphenyl groups (**3b** and **3c**) showed comparable results in providing the corresponding 4,5-diarylated 2-pyridones **4m** (92%, entry 13, Table 1) and **4n** (94%, entry 14, Table 1), respectively. The ethyl hexynoate **3d** reacted very effectively to afford the corresponding 4-butyl 2-pyridone **4o** in 90% yield (entry 15, Table 1). The sterically more demanding **3e** (R^2 = *cy*-C_6H_{11}) required prolonged reaction time (8 h) to achieve high yield of **4p** (entry 16, Table 1). In contrast, the reaction of ethyl propiolate **3f** (R^2 = H) resulted in **4q** in a poor yield of 18%, which

(12) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 742379. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk). For details, see the Supporting Information.

was marginally increased to 35% with 2.2 equiv of **3f** even after 24 h. Significant amounts of the Blaise adduct, β-enaminoester, were isolated, reflecting facile proton transfer of the acidic acetylenic proton to the Blaise reaction intermediate (entry 17, Table 1).

In summary, we developed a highly efficient, one-pot procedure for the synthesis of 2-pyridones through the tandem reaction of the Blaise reaction intermediate of nitriles with propiolates. This methodology not only allows direct use of nitriles, but also provides quick buildup of high diversity of pyridone derivatives.

General procedure for the tandem reacton of the Blaise reaction intermediate of nitrile with propiolate: To a stirred suspension of commercial zinc dust (10 μm, 1.0 g, 15.3 mmol) was added methanesulfonic acid (3.7 mg) in anhydrous THF (4.0 mL). After 10 min of reflux, benzonitrile (0.8 mL, 7.6 mmol) was added all at once. While maintaining reflux temperature, ethyl bromoacetate (1.26 mL, 11.4 mmol) was added over 1 h with use of a syringe pump, and the reaction mixture was further heated at reflux for 1 h. To this reaction mixture was added ethyl phenylpropiolate (1.4 mL, 8.4 mmol). After being stirred for 3 h at reflux temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl at room temperature and extracted with ethyl acetate (3×30 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica chromatography to yield the 2-pyridone **4a** (98%, 2.65 g). Yellow solid; mp 208−210 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.75 (t, J = 7.1 Hz, 3H), 3.80 (q, J = 7.2 Hz, 2H), 6.45 (s, 1H), 7.26−7.41(m, 5H), 7.45−7.52 (m, 5H), 12.21(br s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.2, 61.2, 114.3, 118.5, 127.2, 128.2, 128.4, 128.7, 128.8, 130.3, 132.9, 138.1, 147.2, 154.0, 163.7, 166.7.

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Supporting Information Available: Experimental procedure and spectroscopic data and copies of the ^{1}H NMR and ^{13}C NMR spectra for **4a**−**p** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.