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COMMUNICATION

Tandem Blaise–Nenitzescu reaction: one-pot synthesis of 5-hydroxy-α-(aminomethylene)benzofuran-2(*3H*)-ones from nitriles†

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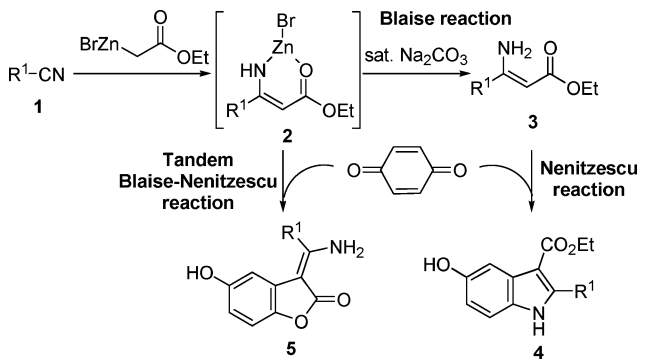
In contrast to the reaction of benzoquinones with β-enaminoesters providing indoles (Nenitzescu reaction), the tandem one-pot reaction of the Blaise reaction intermediate, zinc bromide complex of β-enaminoesters, with benzoquinone affords 5-hydroxy-α-(aminomethylene)benzofuran-2(*3H*)-ones in good to excellent yields (tandem Blaise–Nenitzescu reaction).

Tandem bond formations are highly attractive in modern synthetic design, as they enable the synthetic steps to be minimized, while also maximizing molecular complexity.[1] With regard to this arena, we have recently become interested in the possible use of the Blaise reaction intermediate, a zinc bromide complex of β-enaminoester **2**, as a potential platform for tandem reaction development.[2] During these studies, we observed that the chemoselectivity of the Blaise reaction intermediate **2** is quite different from the isolated Blaise reaction adduct, β-enaminoester **3**, providing an opportunity to discover a novel synthetic method that would not be generally feasible with **3**. Herein, we report an unprecedented novel tandem reaction of the Blaise reaction intermediate **2** with 1,4-benzoquinones (the Blaise–Nenitzescu reaction), affording the 5-hydroxy-(α-aminomethylene)benzofuran-2(*3H*)-ones **5** (Scheme 1).

The condensation of a 1,4-benzoquinone with β-enaminoesters **3**, usually prepared by the Blaise reaction, affording the substituted 3-carboxylated 5-hydroxyindole derivatives **4**, is known as the Nenitzescu indole synthesis,[3] which has been applied to the synthesis of biologically active indole derivatives.[4] In literature, there are very limited precedents for one-pot synthesis of 5-hydroxy-α-(aminomethylene)-benzofuran-2(*3H*)-ones **5** from nitriles: the recently developed Re-catalyzed cross-coupling of nitrile with benzofuranones is the only general one-pot method for this class of lactone compounds.[5] Although a stepwise reaction of β-aminocroton anilides with benzoquinone has also been reported, though the yields were low, to afford 5-hydroxy-α-(1-phenylaminoethyleidene)-benzofuran-2(3*H*)-one,[6] this case



Scheme 1 The Blaise, Nenitzescu, and tandem Blaise–Nenitzescu reactions.

simply reflect the effects of *N*-substituent on chemoselectivity for the specific β-enamino anilides, which is not generally observed in the β-enaminoesters **3**. In that context, our tandem process not only discloses the distinctive reactivity profile of the Blaise reaction intermediate, but also provides a one-pot method to synthesize benzofuranone derivatives **5** from nitriles with minimal steps.

In our first investigation, a solution of 1,4-benzoquinone (1.1 equiv) in THF was added to the Blaise reaction intermediate **2a** (R = Ph), formed from benzonitrile and a Reformatsky reagent, for 30 min at reflux temperature.‡

We initially anticipated that the tandem reaction of the Blaise reaction intermediate **2** with 1,4-benzoquinone would provide 5-hydroxyindoles **4** *via* sequential nucleophilic reactions of α-carbon and β-nitrogen as demonstrated in its reaction with propiolates affording 2-pyridones.[2d] Surprisingly, a lactonized product, 5-hydroxy-α-(aminomethylene)-benzofuran-2(*3H*)-one **5a** was isolated as a major product in 87% yield along with a trace amount of indole **4a** (R = Ph) (entry 1, Table 1). Later, we found that the Blaise reaction intermediate is reactive enough to carry out the the tandem reaction at room temperature with a slightly increased yield of 90% for 1.5 h (entry 2, Table 1). In contrast, the reaction between the isolated Blaise adduct β-enaminoester **3a** (R = Ph) and 1,4-benzoquinone in THF afforded the *N*-cyclized indole **4a** in 64% yield after 24 h at reflux temperature. Addition of 1.0 equiv of $ZnBr_2$ did not change the reaction pathway at all, but did increase the reaction rate and yield to afford the indole **4a** in 86% yield within 1 h at room temperature.

These results clearly suggested that the reaction profile of the Blaise reaction intermediate **2a** towards 1,4-benzoquinone is quite

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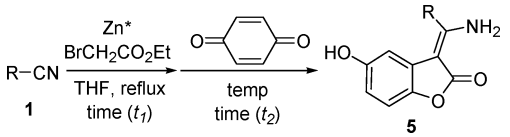
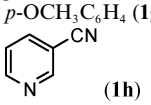
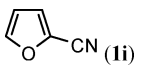
† Electronic supplementary information (ESI) available: Experimental details and spectral data of **5a**~**5n** and their ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c0ob01024c

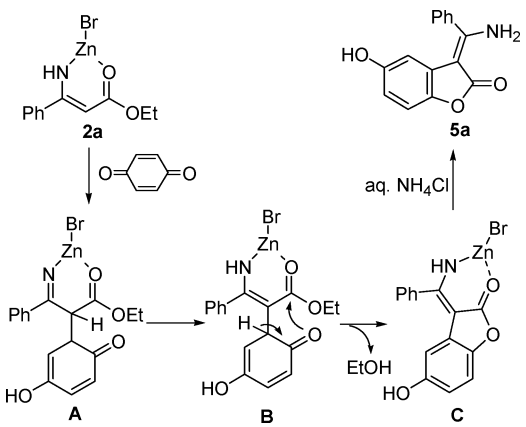
Table 1 The tandem Blaise–Nenitzescu reactions with various nitriles[a]



Entry	R_1(**1**)	t_1/t_2[b]	T/°C	**5** Yield (%)[c]
1	Ph(**1a**)	1 h/30 min	Reflux	**5a** (87)
2	**1a**	1 h/1.5 h	25	**5a** (90)
3	*o*-$CH_3C_6H_4$ (**1b**)	5 h/30 min	Reflux	**5b** (77)
4	**1b**	5 h/1.5 h	25	**5b** (86)
5	*m*-$CH_3C_6H_4$ (**1c**)	1 h/30 min	Reflux	**5c** (78)
6	*p*-$CH_3C_6H_4$ (**1d**)	1 h/30 min	Reflux	**5d** (80)
7	*p*-FC_6H_4 (**1e**)	1 h/15 min	Reflux	**5e** (88)
8	*p*-$CF_3C_6H_4$ (**1f**)	1 h/20 min	Reflux	**5f** (84)
9	*p*-$OCH_3C_6H_4$ (**1g**)	1 h/30 min	Reflux	**5g** (80)
10	 (**1h**)	1.5 h/40 min	Reflux	**5h** (70)
11		1.5 h/6 h	40	**5h** (82)
12	 (**1i**)	1 h/30 min	Reflux	**5i** (67)
13		1 h/1.5 h	25	**5i** (74)
14	$PhCH_2$ (**1j**)	1 h/30 min	Reflux	**5j** (78)
15	CH_3CH_2 (**1k**)	1 h/4 h	35	**5k** (82)
16	$(CH_3)_2CHCH_2$ (**1l**)	1 h/4 h	35	**5l** (80)

[a] Reaction conditions: see footnotes. [b] t_1: time for >98% conversion of nitrile to the Blaise intermediate, t_2:time for the disappeareance of the Blaise intermediate. [c] After silica column chromatography.

different from that of the isolated β-enaminoester **3a**. For isolated β-enaminoester **3a**, the added $ZnBr_2$ may activated the carbonyl group of the benzoquinone, and the indole **4a** was formed more efficiently according to the original Nenitzescu reaction mechanism. In contrast, the zinc bromide complex of the Blaise reaction intermediate **2a** could activate the ester carbonyl group favoring formation of benzofuranone **5a**, which implies that the Blaise reaction intermediate **2a** possesses dual nucleophilic/electrophilic character: *i.e.*, the C2-carbon is nucleophilic and the carbonyl of the ester group is electrophilic allowing tandem C–C/C–O bond formations. As shown in Scheme 2, the first step would be the Michael addition of the Blaise reaction intermediate **2a** to the 1,4-benzoquinone providing the imino ester **A**, which could isomerize

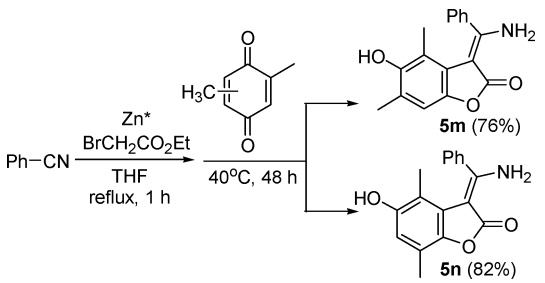


Scheme 2 Proposed mechanism for the formation of **5**.

to the enamino zinc complex **B** *via* fast proton transfer of the acidic α-proton. In the zinc bromide complex **B**, the carbonyl group of the ester may become highly electrophilic *via* activation by zinc coordination, which favors the *O*-cyclization affording the lactone ring in **C** instead of the nucleophilic condensation by the nitrogen atom to the carbonyl group of quinone, as observed with the isolated β-enaminoester **3a** affording indole **4a**.

This novel tandem reaction showed a broad range of substrate generality (Table 1). The tandem reactions with aromatic and heteroaromatic nitriles provided the corresponding benzofuranones **5a–5i** (entries 1~11, Table 1) in good to excellent yields.

Electronic and steric properties of the substituents did not significantly effect reactivity. The yields were substantially increased in prolonged reaction times at lowered reaction temperatures (compare entries 1 and 2, 3 and 4, 10 and 11, 12 and 13). All aliphatic nitriles also converted to the corresponding benzofuranones in high yields (entries 12~14, Table 1). The tandem reactions of other substituted 1,4-benzoquinones such as 2,5-dimethyl- and 2,6-dimethylbenzoquinones with the Blaise reaction intermediate derived from benzonitrile also proceeded well to give the corresponding 5-hydroxy-(α-aminomethylene)benzofuran-2(*3H*)-ones **5m** (76%) and **5n** (82%), respectively, at 40 °C for 48 h (Scheme 3a).



Scheme 3 Tandem Blaise–Nenitzescu reaction with substituted 1,4-benzoquinones.

In conclusion, we have demonstrated an unprecedented, highly efficient tandem one-pot synthesis of 5-hydroxy-α-(aminomethylene)benzofuran-2(*3H*)-ones from nitriles. These results underscore the high potential of the Blaise reaction intermediate as an amphiphilic organozinc complex for forming carbon-carbon bonds and provides a divergent synthetic platform towards benzofuran-2(*3H*)-ones and 5-hydroxyindoles from nitriles. Further studies extending the range of tandem reactions by modulating the Blaise reaction intermediate are currently underway in our laboratory.

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Notes and references

‡ Typical procedure: To a stirred suspension of zinc dust (1.0 g, 15.3 mmol) in anhydrous THF (4.0 mL) was added methanesulfonic acid (3.7 mg). After 10 min reflux, benzonitrile (**1a**, 7.6 mmol) was added. To the solution, ethyl bromoacetate (11.4 mmol) was slowly added over 1 h, and the reaction mixture was heated at reflux for an additional 1 h to afford the Blaise reaction intermediate (>98% conversion by GC analysis). To this reaction mixture, a solution of 1,4-benzoquinone (7.6 mmol) in anhydrous THF

(8.0 mL) was added for 10 min at either reflux or at room temperature. The reaction was continued for the given time in Table 1, and quenched by addition of saturated aqueous NH_4Cl. The reaction mixture was extracted with ethyl acetate (3 × 40 mL), and the combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by silica column chromatography to afford benzofuranone **5a** (1.94 g, 90%).

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