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$Cu(OAc)_2$-Catalyzed Tandem Blaise/Pinner-Type Reaction for One-Pot Synthesis of Pyrimidin-4-ones

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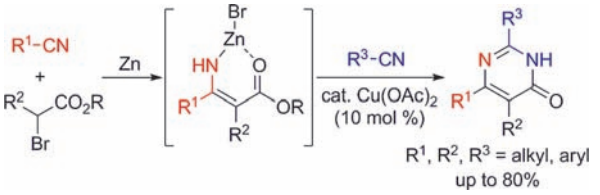
ABSTRACT



A novel tandem Blaise/Pinner-type reaction for the one-pot synthesis of pyrimidin-4-ones is described. The Blaise reaction intermediate, formed by addition of a Reformatsky reagent to a nitrile, reacted with a second nitrile chemoselectively in the presence of a catalytic amount of $Cu(OAc)_2$ to afford pyrimidin-4-ones.

Reactions that run in tandem can deliver substantial increases in molecular complexity *via* one-pot operations without the need for the isolation of intermediates, minimizing waste generation.[1] Herein, we report an unpreceedented tandem Blaise/Pinner-type reaction for the one-pot synthesis of 2,5,6-trisubstituted pyrimidin-4-ones (Scheme 1).

Pyrimidinone is a key scaffold in many natural compounds and pharmaceuticals and represents physiochemically an excellent drug-like template in many drug discovery studies.[2] Although many different methods have been developed to synthesize pyrimidinones,[3] the most technically feasible synthesis of these heterocyclic compounds still relies on the classical condensation between β-ketoester and amidines, and both of these compounds can be synthesized from nitriles *via* the Blaise[4] and Pinner

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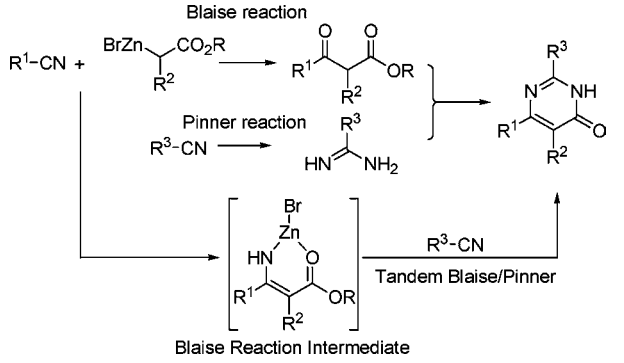
reactions,[5] respectively. In the course of our ongoing study on the tandem use of Blaise reaction intermediates,[6] we envisioned that a chemoselective tandem coupling reaction with a second nitrile could be a novel method for one-pot synthesis of pyrimidin-4-ones.

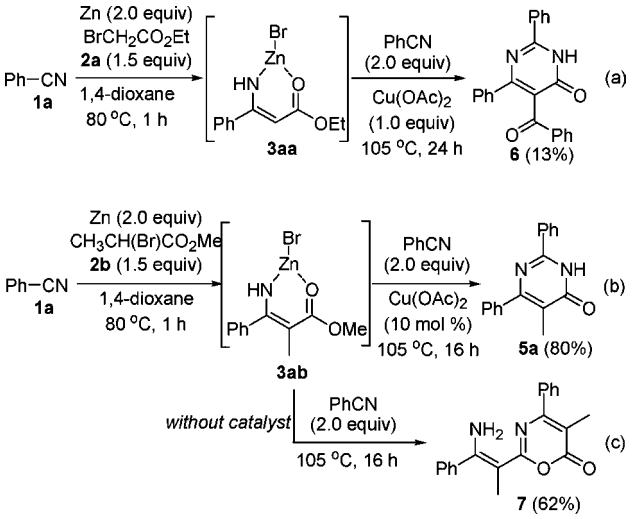
Scheme 1. Classical Stepwise and Tandem One-Pot Blaise/Pinner-Type Methods for Pyrimidin-4-ones



The Blaise reaction intermediate is a zinc bromide complex of β-enaminoesters that combines the C-/N-divalent nucleophilicity of an enamine with the electrophilicity of α,β-unsaturated ester moieties, and we considered it a potentially fruitful candidate for undergoing tandem C−C and/or N−C bond-forming reactions. Previously, we found that the α-unsubstituted Blaise reaction intermediate **3aa**, formed by reaction of the Reformatsky reagent, generated *in situ* from ethyl α-bromoacetate (**2a**) and zinc, acts as a C-nucleophile toward 1-alkynes, an isoelectronic variant of nitrile, to give α-vinylated β-enaminoesters.[6c] Moreover, in related work, Glorius and co-workers recently reported that N-arylated β-enaminoesters could be oxidatively coupled with nitriles in the presence of a stoichiometric amount of $Cu(OAc)_2$ to provide pyrazoles.[7] Therefore, the success of our tandem approach for the one-pot synthesis of pyrimidinones could be determined by the chemoselectivity of the Blaise reaction intermediate toward nitriles.

In order to investigate the intrinsic reactivity and chemoselectivity of the α-unsubstituted Blaise reaction intermediate toward nitriles, the tandem reaction of **3aa** with excess benzonitrile was carried out in THF or 1,4-dioxane reflux. However, the Blaise reaction intermediate **3aa** was not altered, even after 12 h, and only ethyl 2-amino-2-phenylacrylate, the Blaise reaction product, was isolated in 90% yield. These results suggested that the reactivity of the **3aa** toward weak nitrile electrophiles was too low for application to an efficient reaction process. Moreover, in the presence of a stoichiometric amount of $Cu(OAc)_2$, the tandem reaction became quite complex, and 5-benzoylated 2,6-diphenylpyrimidine-4-one **6** could only be isolated in 13% yield (Scheme 2a). Other Lewis acid catalysts, such as $ZnCl_2$, $Zn(OAc)_2$, $Zn(OTf)_2$, CuCl, $CuCl_2$, $In(OTf)_3$, and $InCl_3$, did not improve the reaction efficiency at all. Under all of the examined conditions, there was no sign of the formation of pyrazole, as observed in the work of Glorius *et al.*[7] Nevertheless, the formation of **6** implied that the α-unsubstituted Blaise reaction intermediate **3aa** had a propensity to be a C-nucleophile reacting with benzonitrile at the α-carbon first. The second nitrile then reacts at the β-nitrogen to form the 5-benzoylated pyrimidinone **6**.

Scheme 2. Initial Experiments for Tandem One-Pot Blaise/Pinner Synthesis of Pyrimidin-4-ones



As we expected, the reactivity and chemoselectivity were dramatically increased with the α-methyl substituted Blaise reaction intermediate **3ab**, which was formed by reaction of benzonitrile and the Reformatsky reagent obtained from methyl α-bromopropionate **2b**. The tandem coupling reaction of **3ab** with benzonitrile (2.0 equiv) at 105 °C in 1,4-dioxane for 16 h, in the presence of only 10 mol % of $Cu(OAc)_2$, afforded the 5-methyl-2,6-diphenylpyrimidin-4-one **5a** in an 80% yield (Scheme 2b). Later we found that methanesulfonic acid was also an efficient catalyst for this tandem coupling reaction. Thus, the tandem reaction of **3ab** with benzonitrile at 90 °C in the presence of 30 mol % methanesulfonic acid afforded **5a** in a 78% yield after 24 h (entry 2, Table 1). When the same reaction was carried out in the absence of the catalyst, only less than 5% of pyrimidin-4-one **5a** was formed, and the dimerized 2-(β-enamino)-1,3-oxazine-6-one **7** could be isolated in 62% yield as a major product (Scheme 2c).[8] The structure of **7** was determined by X-ray analysis (see Supporting Information).[9] These results clearly indicated that the α-substituted Blaise reaction intermediate acts as an *N*-nucleophile.[10] However, its reactivity is not sufficiently high to react with a weak nitrile electrophile.

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(9) The CIF deposition number: CCDC 908745.

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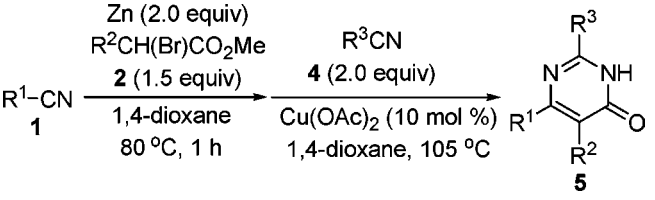
To accomplish the chemoselective tandem reaction of the Blaise reaction intermediate with a nitrile to afford 2,5,6-trisubstituted pyrimidin-4-ones, activation of the nitrile using a catalytic amount of $Cu(OAc)_2$ or methanesulfonic acid is necessary.

We next explored the substrate scope of this reaction by using 10 mol % $Cu(OAc)_2$ (Table 1). The Blaise reaction intermediates **3**, formed by reaction of a Reformatsky reagent, generated *in situ* from **2b**, with various aromatic nitriles having electron-donating methyl (**1b**) and methoxy (**1c**) substituents and electron-withdrawing bromide (**1d**) and ester (**1e**) substituents, and benzylnitrile (**1f**), were reacted with benzonitrile to afford the corresponding pyrimidin-4-ones **5a**–**5f** in good yields (entries 1–7, Table 1). The second nitrile **4** could also be varied. Thus, the Blaise reaction intermediate **3ab** reacted with aromatic nitriles bearing electron-donating methyl (**4b**) (entry 8, Table 1) and methoxy groups (**4c**) (entry 9, Table 1) as well as a withdrawing ester group **4d** (entry 10, Table 1) to afford the corresponding pyrimidin-4-ones **5g**–**5i** in good yields. The heteroaromatic 2-furylnitrile could also be employed as a second nitrile to afford the corresponding 2-furyl substituted pyrimidin-4-one **5j** in a 68% yield (entry 11, Table 1). A tandem reaction of **3ab** with benzyl nitrile also proceeded successfully to afford 2-benzyl substituted pyrimidin-4-one **5k** in a 77% yield (entry 12, Table 1). 2,6-Diaryl **5l** and difuryl-substituted pyrimidin-4-ones **5m** could also be synthesized efficiently (entries 13 and 14, Table 1). However, the Blaise reaction intermediates, prepared from aliphatic nitriles **1i**–**1j**, were not effective under standard conditions. For example, the tandem reaction of intermediate **3ia**, prepared from butyronitrile **1i**, with 3-phenylpropionitrile using 10 mol % $Cu(OAc)_2$ was quite messy, and only an 18% yield of pyrimidin-4-one **5n** was isolated (entry 15, Table 1). Fortunately, we found that methanesulfonic acid was effective for this reaction, and thus, the tandem reaction at 90 °C for 24 h in the presence of 30 mol % methanesulfonic acid afforded **5n** in a 60% yield (entry 16, Table 1). At a higher reaction temperature (*ca.* 105 °C), the Blaise reaction intermediate decomposed. Under the same reaction conditions, sterically bulky 2,6-diisobutyl substituted pyrimidin-4-one **5o** can be synthesized in a 45% yield (entry 17). Variation of the Reformatsky reagents, generated from ethyl α-bromophenylacetate **2c** and ethyl 2-bromopentanoate **2d**, allowed us to introduce different substituent (R^2) groups at the 5-position to afford pyrimidin-4-ones **5p**–**5r** (entries 18–20, Table 1).

In our previous mechanistic study of the tandem reaction of α-unsubstituted Blaise reaction intermediate **3aa** with terminal alkyne,[6c] we proposed that the zinc bromide complex **8** could be formed as a second intermediate, which led us to consider the possibility for a chemoselective double tandem reaction with 1-alkyne and nitrile affording 5-vinylated pyrimidin-4-ones (Scheme 3). Thus, the α-unsubstituted Blaise reaction intermediate **3aa** (R^1 = Ph) reacted first with 1.1 equiv of phenylacetylene in 1,4-dioxane at 80 °C to form the second intermediate **8**. The tandem reaction of **8** with 2.0 equiv of benzonitrile as a second nitrile, in the presence of the $Cu(OAc)_2$ catalyst, provided the 5-vinylated pyrimidin-4-one **5s** in a 78% yield. The structure of **5s** was unambiguously determined by NMR analysis as well as X-ray analysis. Figure 1 shows the X-ray crystal structure of **5s**.[11] Variation of the 1-alkyne was also possible as exemplified by the synthesis of **5t** in a 75% yield. Under the same reaction conditions, the sequential tandem reaction of the Blaise reaction intermediate **3ha** (formed from furylnitrile **1h**) with phenylacetylene and benzonitrile afforded pyrimidinone **5u** in a 61% yield.

It was found that the tandem reaction of a Blaise reaction intermediate, derived from an aliphatic nitrile, also proceeded with phenylacetylene to form intermediate **8**, but the coupling with the second nitrile was less efficient, even in the presence of 30 mol % methanesulfonic acid, resulting in 1-alkyl-5-vinylated pyrimidin-4-one **5v** in a 44% yield. Nevertheless, it is noteworthy that in this

Table 1. Tandem One-Pot Blaise/Pinner Synthesis of Pyrimidin-4-ones[a]

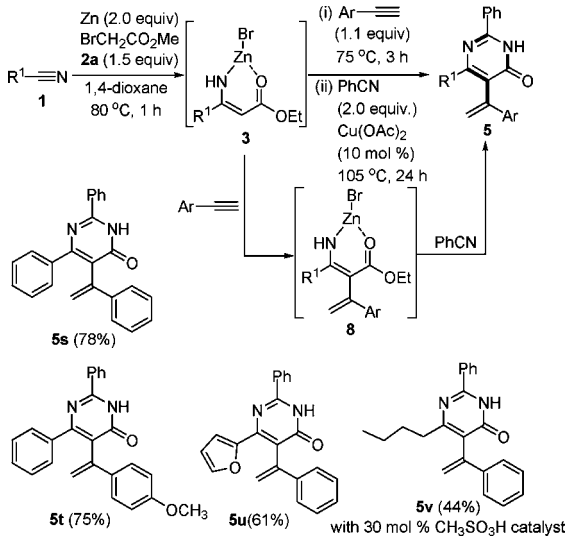


entry	**1**, R^1	**2**, R^2	**4**, R^3	**5** (%)[b]
1	Ph (**a**)	Me (**b**)	Ph (**a**)	**5a** (80)
2[c]	Ph (**a**)	Me (**b**)	Ph (**a**)	**5a** (78)
3	2-MeC_6H_4 (**b**)	Me (**b**)	Ph (**a**)	**5b** (71)
4	4-$MeOC_6H_4$ (**c**)	Me (**b**)	Ph (**a**)	**5c** (71)
5	4-BrC_6H_4 (**d**)	Me (**b**)	Ph (**a**)	**5d** (71)
6	4-$MeO_2CC_6H_4$ (**e**)	Me (**b**)	Ph (**a**)	**5e** (71)
7	Bn (**f**)	Me (**b**)	Ph (**a**)	**5f** (74)
8	Ph (**a**)	Me (**b**)	3-Me-C_6H_4 (**b**)	**5g** (72)
9	Ph (**a**)	Me (**b**)	4-$MeOC_6H_4$ (**c**)	**5h** (60)
10	Ph (**a**)	Me (**b**)	4-$MeO_2CC_6H_4$ (**d**)	**5i** (68)
11	Ph (**a**)	Me (**b**)	2-furyl (**e**)	**5j** (68)
12	Ph (**a**)	Me (**b**)	Bn (**f**)	**5k** (77)
13	4-MeC_6H_4 (**g**)	Me (**b**)	4-MeC_6H_4 (**g**)	**5l** (72)
14	2-furyl (**h**)	Me (**b**)	2-furyl (**e**)	**5m** (70)
15	*n*butyl (**i**)	Me (**b**)	$PhCH_2CH_2$ (**h**)	**5n** (18)
16[c]	*n*butyl (**i**)	Me (**b**)	$PhCH_2CH_2$ (**h**)	**5n** (60)
17[c]	Me_2CHCH_2 (**j**)	Me (**b**)	Me_2CHCH_2 (**i**)	**5o** (45)
18[c]	*n*butyl (**i**)	Ph (**c**)	Ph (**a**)	**5p** (67)
19	Ph (**a**)	*n*Propyl (**d**)	Ph (**a**)	**5q** (60)
20	Ph (**a**)	Ph (**c**)	Ph (**a**)	**5r** (54)

[a] Reaction conditions: nitrile **1** (3.0 mmol), Zn (6.0 mmol), and ethyl α-bromoalkanoate (**2**, 4.5 mmol) in 1,4-dioxane (1.5 mL). **4** and $Cu(OAc)_2$ (0.3 mmol) were added when nitrile **1** was converted to the intermediate **3** in >97% by GC, and the reaction was continued until all of **3** was consumed by TLC and GC. [b] Isolated yield of average two runs. [c] Reaction was carried out at 90 °C in the presence of 30 mol % methanesulfonic acid instead of $Cu(OAc)_2$.

(11) The CIF deposition number: CCDC 908746.

Scheme 3. Tandem One-Pot Synthesis of 5-Vinylated Pyrimidin-4-ones



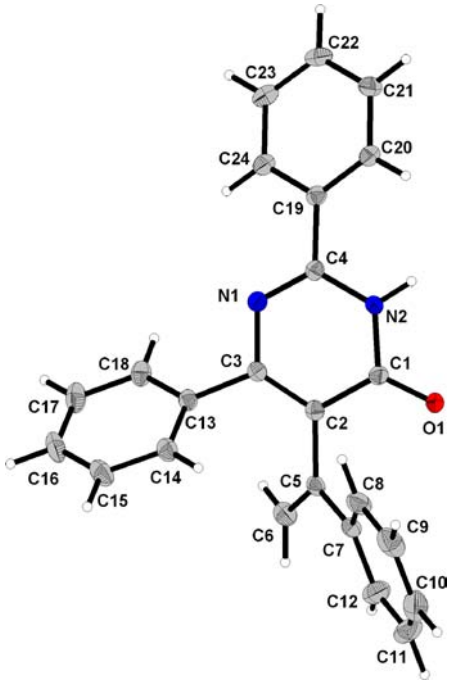
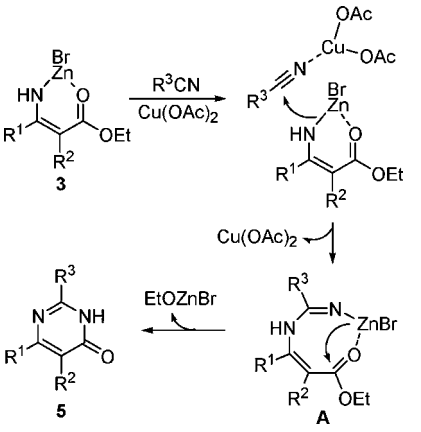


Figure 1. X-ray crystal structure of **5s**.

tandem procedure, four different C–C/C–C/N–C/N–C bonds can be sequentially formed in one pot.

The following mechanism can be proposed (Scheme 4). The weakly electrophilic nitrile could be activated by the Lewis acidic $Cu(OAc)_2$, allowing the chemoselective nucleophilic addition of the Blaise reaction intermediate *via* its nitrogen atom. The intramolecular cyclization of **A** then eliminates EtOZnBr to furnish the pyrimidin-4-one **5**.

Scheme 4. Proposed Reaction Mechanism



In summary, we have developed a novel tandem one-pot method for the synthesis of 2,5,6-trisubstituted pyrimidin-4-ones from Reformatsky reagents and two nitriles *via* the $Cu(OAc)_2$-catalyzed chemoselective coupling of a Blaise reaction intermediate with a nitrile. The sequential chemoselective tandem reaction of the Blaise reaction intermediate with terminal alkynes and nitriles has allowed for the synthesis of 5-vinylated pyrimidin-4-ones. Considering the ready availability of the starting materials and the one-pot operation, the presented tandem protocol could be a useful method for diversity-oriented synthesis of pyrimidinones.

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Supporting Information Available. Experimental details and spectral data of **5a**–**5v**, **6**, and **7** and the copies of their ^1H, ^{13}C NMR, and HRMS spectra. X-ray data of **5s** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.