ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

An Expedient and Divergent Tandem One-Pot Synthesis of Pyrimidin-2,4-diones Using the Blaise Reaction Intermediate

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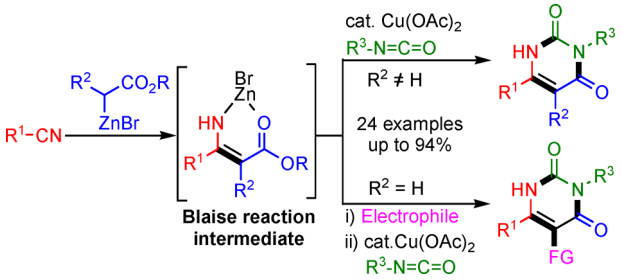
Received May 17, 2013

ABSTRACT



A novel divergent tandem one-pot method for the synthesis of 3,5,6-trisubstituted 1*H*-pyrimidin-2,4-dione derivatives is developed. In the presence of 10 mol % of $Cu(OAc)_2$, the α-substituted Blaise reaction intermediates ($R^2 \neq H$) reacted with isocyanates chemoselectively to afford pyrimidin-2,4-diones, whereas the α-unsubstituted Blaise reaction intermediate ($R^2 = H$) showed a propensity to be a C-nucleophile toward electrophiles, permitting the installation of different functionalities at the 5-position through sequential tandem reactions.

Divergent tandem synthesis provides quick access to structurally diversified compounds from the same common starting material(s) and is a highly attractive tool in the discovery of bioactive molecules and functional materials.[1] By virtue of being run in tandem, the value of these reactions are greatly enhanced not only by the rapid emergence molecular complexity but also by avoiding the isolation of intermediates, thereby alleviating waste generation.[2] The success of a divergent tandem reaction requires precise control of the chemo- and regioselectivity and a careful selection of the reaction conditions informed by understanding the reactivity of intermediates and substrates. Therefore, the development of efficient divergent tandem syntheses of biologically relevant compounds is highly desirable. In this paper, we report an expedient and divergent tandem one-pot synthesis of pyrimidin-2,4-dione derivatives using the Blaise reaction intermediate (Scheme 1).

The pyrimidin-2,4-dione unit is a fundamental scaffold in biomolecules, natural products, and pharmaceuticals and represents an excellent template in many drug discovery endeavors.[3] Recent advances in transition-metal-catalyzed cross-couplings of halogenated pyrimidindiones with metallic nucleophiles[4] or direct C−H arylations of pyrimidindions provided new approaches to aryl-substituted pyrimidindiones.[5] However, all of these

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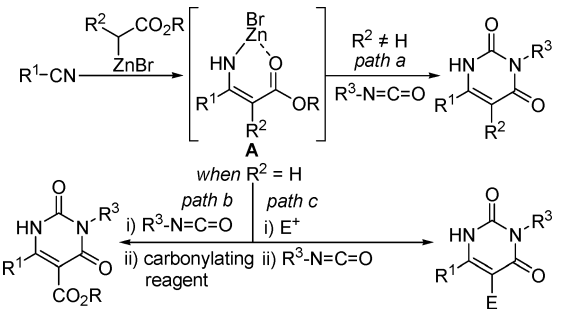
10.1021/ol401389j

Scheme 1. Strategy for the Divergent Tandem Synthesis of Pyrimidin-2,4-diones Using the Blaise Reaction Intermediate



methods are based on a pre-existing pyrimidindione moiety. Hence, the *de novo* construction of the pyrimidin-2,4-dione scaffold from a readily available starting material has continued to draw much interest. Prominent methods for the synthesis of pyrimidin-2,4-diones include the annulative condensation of β-keto esters with urea derivatives[6] or the coupling of α-seleno β-aminoester with isocyanates, followed by oxidative olefination.[7] However, these reactions generally required prolonged reaction times at elevated temperatures. Recently, Fustero and co-workers reported on the use of β-enaminoesters, which reacted with isocyanates to synthesize pyrimidin-2,4-diones through a chemoselective coupling−cyclization cascade reaction.[8] Nevertheless, the reported protocols relied on the prerequisite synthesis of β-enaminoesters by the reaction of a nitrile with lithium ester enolate, formed from LDA and alkanoates at −78 °C, and necessitated an excess of a strong base, NaH, for the coupling of the isolated β-enaminoesters with isocyanates.

The addition of a Reformatsky reagent to nitriles (Blaise reaction) is known to proceed *via* the zinc bromide complex of β-enaminoester intermediate **A** that combines the C-/N- ambident nucleophilicity of enamines with electrophilic β-unsaturated ester moieties (Scheme 1). During the course of our recent research program on the use of intermediate **A** in tandem schemes,[9] it was observed that the C-/N-chemoselectivity of intermediate **A** was largely determined by the α-substituent; i.e., α-unsubstituted **A** (R^2 = H) generally showed a propensity to be a C-nucleophile, whereas α-substituted **A** ($R^2 \neq$ H) acts as a N-nucelophile.[9i,j] On the basis of these observations, we envisioned that a chemoselective tandem coupling reaction of **A** with isocyanates could provide a novel one-pot method for the synthesis of pyrimidin-2,4-diones that does not require the isolation of β-enaminoesters. When the addition of α-substituted **A** ($R^2 \neq$ H) to isocyanates proceeds chemoselectively at the nitrogen atom, 3,5,6-trisubstituted pyrimidin-2,4-diones are obtained in a one-pot manner (*path a* in Scheme 1). In addition, the C-nucleophilic character of α-unsubstituted **A** allows us to design the sequential tandem reaction with an isocyanate and a carbonylating agent such as triphosgene (*path b* in Scheme 1), or with an appropriate electrophile and an isocyanate (*path c* in Scheme 1), enhancing the divergency of accessible pyrimidin-2,4-diones.

We first investigated the effects of α-substituents on the reactivity and C-/N-chemoselectivity of **A** toward isocyanate electrophiles. The tandem reaction of α-unsubstituted **Aaa** (R^1 = Ph, R^2 = H, R = Et), formed by the reaction of benzonitrile (**1a**) and a Reformatsky reagent generated *in situ* from ethyl α-bromoacetate (**2a**), with 1.1 equiv of phenyl isocyanate **3a** at 40 °C afforded the α-carboamoylated β-enaminoester **5** in 92% yield. This result clearly indicates that the α-unsubstituted intermediate **Aaa** has a propensity to act as a C-nucleophile toward isocyanate electrophiles. In contrast, the α-methyl substituted intermediate **Aab** (R^1 = Ph, R^2 = Me, R = Me), formed with **2b**, showed its N-nucleophilic nature, and thus reacted with **3a** to afford the pyrimidin-2,4-dione **4a**. However, its reactivity is not sufficiently high yielding only 58% of **4a** (Scheme 2b). The reaction efficiency was not significantly improved by either increasing the reaction temperature or the addition of an equivalent of base such as NaH or NaHMDS. Under these reaction conditions, the phenyl methyl carbamate was formed as a major side product, which implied that methoxyzinc bromide, generated during pyrimidindione ring formation, could also react with phenyl isocyanate, decreasing the yield of product. To address this problem, we attempted to increase the electrophilicity of the isocyanate using a Lewis acid. To our delight, we found that, in the presence of 10 mol % $Cu(OAc)_2$, the first coupling reaction of **Aab** with 1.5 equiv of **3a** proceeded very cleanly at room temperature

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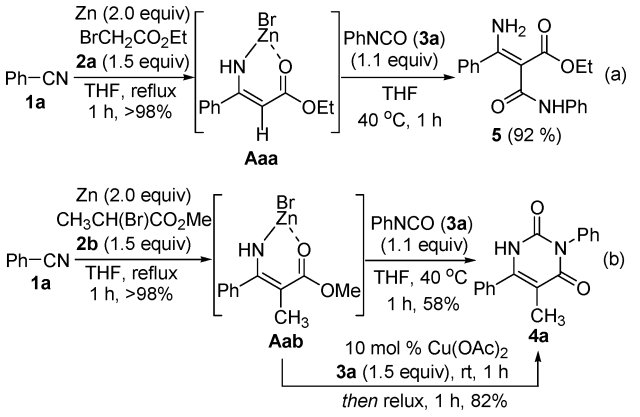
(full consumption of **Aab** evidenced by TLC). Subsequent intramolecular cyclization in THF at reflux afforded the desired **4a** in 82% yield.

Scheme 2. Intrinsic Reactivity and C-/N-Chemoselectivity of the Blaise Reaction Intermediates toward Isocyanates

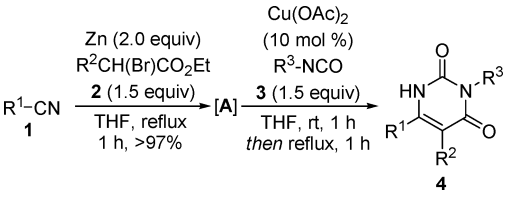


With the optimized reaction conditions in hand, we next explored the scope and limitation of this reaction. We were pleased to find that α-methyl substituted intermediates **A** ($R^2 = CH_3$), formed from α-bromopropionate **2b** and aryl nitriles having different substituents on the aryl moiety, could be reacted with phenyl isocyanate (**3a**) to afford the corresponding pyrimidin-2,4-diones **4a**–**4e** in high yields (entries 1–5, Table 1). In particular, the intermediate **A** derived from pentafluorobenzonitrile afforded pyrimidin-2,4-dione **4f** in an excellent yield of 94% (entry 6, Table 1). Additionally, the reaction with a heteroaromatic 2-furonitrile afforded the corresponding 6-furylated pyrimidin-2,4-dione **4g** in 63% yield (entry 7, Table 1). The alkyl nitrile-derived intermediates **A** ($R^1 = PhCH_2CH_2$ and Bn) were also reacted with phenyl isocyanate (**3a**) to give the corresponding pyrimidin-2,4-diones **4h** and **4i**, albeit with somewhat lower yields (entries 8 and 9, Table 1).

Next, we investigated the scope and limitations of this reaction with various isocyanates, while using the intermediate **A** derived from benzonitrile (**1a**) and α-bromopropionate **2b**. Aryl isocyanates having varied substituents successfully participated in the reaction to afford the corresponding products **4j**–**4l** in good yields (entries 10–12, Table 1). The tandem reaction with an alkyl isocyanate also proceeded to furnish the 3,5-dialkyl substituted pyrimidin-2,4-diones **4m**, albeit at the expense of a decreased yield of 46% (entry 13, Table 1). Structural variation in the Reformatsky reagent was also well tolerated, as both intermediates **Aac** (R^1 = Ph, R^2 = *n*-Pr, R = Me) and **Aad** (R^1 = Ph, R^2 = Ph, R = Me) gave the desired products **4p** and **4q** in high yields (entries 16 and 17, Table 1). The structures of all products were unambigously determined by spectroscopic analyses and further confirmed with an X-ray diffraction study for **4c** (Figure 1).[10]

(10) CCDC 938319. For X-ray crystal data, see Supporting Information.

Table 1. Tandem One-Pot Synthesis of Pyrimidin-2,4-diones[a]



entry	**1**, R^1	**2**, R^2	**3**, R^3	**4**, yield (%)[b]	
1	Ph	Me	Ph	**4a**	82
2	3-Me-C_6H_4	Me	Ph	**4b**	75
3	4-Me-C_6H_4	Me	Ph	**4c**	82
4	4-MeO-C_6H_4	Me	Ph	**4d**	81
5	4-Br-C_6H_4	Me	Ph	**4e**	79
6	C_6F_5	Me	Ph	**4f**	94
7	2-furyl	Me	Ph	**4g**	63
8	$PhCH_2$	Me	Ph	**4h**	52
9	$PhCH_2CH_2$	Me	Ph	**4i**	51
10	Ph	Me	4-Me-C_6H_4	**4j**	84
11	Ph	Me	4-MeO-C_6H_4	**4k**	66
12	Ph	Me	4-F-C_6H_4	**4l**	79
13	Ph	Me	*n*Bu	**4m**	46
14	3-Me-C_6H_4	Me	4-Me-C_6H_4	**4n**	67
15	4-Me-C_6H_4	Me	4-Me-C_6H_4	**4o**	82
16	Ph	*n*Pr	Ph	**4p**	90
17	Ph	Ph	Ph	**4q**	89

[a] Reaction conditions: nitrile **1** (3.0 mmol), Zn (6.0 mmol), ethyl α-bromoalkanoate (**2**, 4.5 mmol) in THF (1.5 mL). A solution of **3** (4.5 mmol) in THF (1.0 mL) and $Cu(OAc)_2$ (0.3 mmol) were added when nitrile **1** was converted to the intermediate **A** 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.

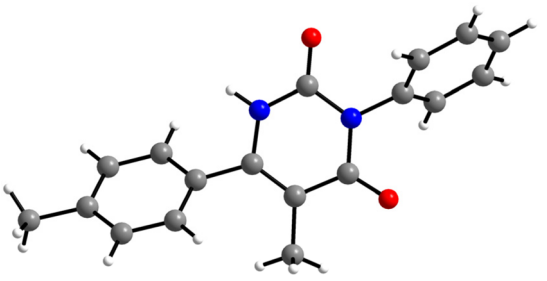
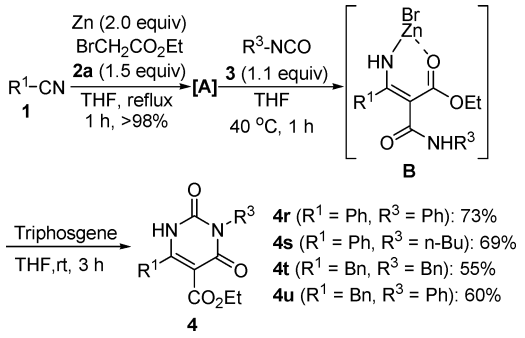


Figure 1. X-ray crystal structure of **4c**.

In order to increase the divergency of accessible products, we next turned our attention to the reaction of the α-unsubstituted intermediate **A** (R^2 = H) showing a propensity to be a C-nucleophile (paths b and c in Scheme 1). As anticipated, the sequential tandem reaction of **Aaa** (R^1 = Ph, R^2 = H, R = Et) with phenyl isocyanate **3a**, producing a zinc bromide complex of α-carbamoylated *β*-enaminoester **B** as a second intermediate, followed by a reaction with a carbonylating agent, triphosgene, afforded the corresponding 5-ester-functionalized pyrimidin-2,4-dione **4r** in 73% yield (Scheme 3). Variation of either

Scheme 3. Sequential Tandem Reactions of α-Unsubstituted Blaise Reaction Intermediates with Isocyanates and Triphosgene

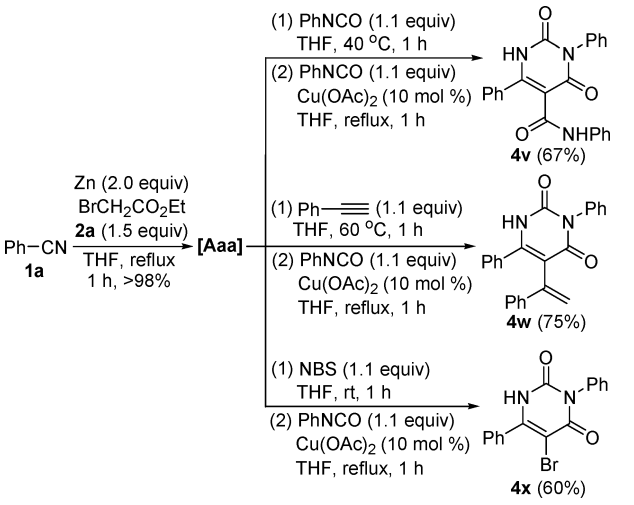


nitrile or isocyanate exerted little influence in this reaction and allowed the synthesis of pyrimidin-2,4-diones **4s**–**4u** in moderate to good yields in a tandem one-pot manner.

The divergency of products could further be increased by the sequential reaction of the intermediate **B** with another isocyanate in the presence of $Cu(OAc)_2$ catalyst. Thus the tandem reaction of α-unsubstituted intermediate **Aaa** (R^1 = Ph, R^2 = H, R = Et) first with 1.1 equiv of phenyl isocyanate, giving intermediate **B**, and then with phenyl isocyante in the presence of 10 mol % $Cu(OAc)_2$ gave the pyrimidin-2,4-dione **4v** in 67% yield (Scheme 4). This strategy could also extended by substituting as the initial electrophile phenyl isocyanate for 1-alkynes[9c] and *N*-bromosuccinimide (NBS). For example, the reaction of **Aaa** with phenylacetylene, followed by phenyl isocyanate **3a**, in the presence of 10 mol % $Cu(OAc)_2$ afforded the 5-vinyl substituted pyrimidin-2,4-dione **4w** in 75% yield. When *N*-bromosuccinimide (NBS) was employed as the electrophile, the 5-bromo-substituted product **4x** was isolated in 60% yield.

In summary, we have developed a novel tandem one-pot divergent method for the synthesis of 3,5,6-trisubstituted pyrimidin-2,4-ones using the Blaise reaction intermediate. In the presence of 10 mol % of $Cu(OAc)_2$, the α-substituted Blaise reaction intermediates ($R^2 \neq H$), which are formed by the reaction of Reformatsky reagents with nitriles, reacted with isocyanates chemoselectively to afford pyrimidin-2,4-diones, whereas the α-unsubstituted

Scheme 4. Sequential Tandem Reactions of α-Unsubstituted Blaise Reaction Intermediate with Various Electrophiles and Phenyl Isocyanate



Blaise reaction intermediate (R^2 = H) showed a propensity to be a C-nucleophile allowing for sequential tandem reactions that enabled the installation of varied functionalities such as ester, vinyl, bromide, and amide at the C5-position. The presented tandem protocol could find utility in the preparation of a focused chemical library of pyrimidin-2,4-diones.

Acknowledgment. This work was supported by the Korea Research Foundation (KRF-2013035117). Y.S.C. thanks Ewha Womans University for RP-support. We thank Dr. Y. M. Kim and Prof. J. Bouffard at Ewha Womans University for X-ray analysis and helpful discussions, respectively. We thank the Korea Basic Science Institute for HR-MS analysis.

Supporting Information Available. Experimental details and spectral data of **4a**–**4x**, **5** and copies of their ^1H and ^{13}C NMR spectra. X-ray data of **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.