The first chemoselective tandem acylation of the Blaise reaction intermediate: a novel method for the synthesis of α-acyl-β-enamino esters, key intermediate for pyrazoles†

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The Blaise reaction intermediate, a zinc bromide complex of β-enamino ester, could be activated *in situ* by addition of a stoichiometric or catalytic amount of *n*-BuLi to allow chemoselective tandem C2-acylation providing α-acyl-β-enamino esters, which are valuable intermediates for the syntheses of tri- and tetrasubstituted pyrazoles.

Due to their excellent reactivity and high functional group tolerance, organozinc compounds play critical roles in various kinds of organic reactions.[1] The reaction of Reformatsky reagent with nitrile, the so-called Blaise reaction,[2] is known to proceed *via* a zinc bromide complex of a β-enamino ester. Hydrolytic work-up 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.[3] During our ongoing studies on the synthesis of β-amino acids[4] and on a new process for the synthesis of bioactive compounds by using the Blaise reaction,[5] we envisioned that the Blaise reaction intermediate can be considered as a functionalized organozinc nucleophile possessing potentially two reactive atoms, *i.e.* nitrogen and C2-carbon. However, the latent potential of the Blaise reaction intermediate as a functionalized organozinc nucleophile has not been fully recognized to date.

To our best knowledge, there is only one report describing *in situ* utilization of the Blaise reaction intermediate. Kouklovsky and co-workers found that the zinc bromide complex generated from the reaction of *N*-benzyl-*N*-Cbz protected chiral α-aminonitrile with a Reformatsky reagent acts as a nitrogen nucleophile: its nitrogen atom reacted with the protected Cbz group intramolecularly to form imidazolidinones.[6] In contrast, as a work closely related to the Blaise reaction intermediate, Nakamura *et al.* reported that ethylzinc complex of *N*-monosubstituted β-aminocrotonamides, *in situ* generated with diethylzinc, showed carbon nucleophile character, and underwent sequential C2-alkynylation/isomerization to produce, upon hydrolysis, the corresponding α-alkylidine-β-dicarbonyl compounds.[7] A similar trend was observed with free β-enamino esters towards acylation: direct acylations of free β-enamino esters with anhydrides or acyl chlorides led to the formation of *N*-acylated product dominantly,[8] whereas the reaction profile was shifted towards C2-acylation exclusively as a substituent was loaded at the nitrogen atom of β-enamino ester.[9] Based on these observations, we anticipated that chemoselective C2-acylation of the Blaise reaction intermediate would serve as a convenient method for α-acyl-β-enamino esters **2**, which could be a useful intermediate for the synthesis of bioactive heterocyclic molecules such as pyrazoles. So far, the most popular route to **2** is Knoevenagel condensation of β-ketoesters, commonly prepared by Blaise reaction, with nitrile by using a stoichiometric amount of tin(IV) chloride.[10] Therefore, in view of atom economic and environmental concern, the development of a direct synthetic method for α-acyl-β-enamino esters **2** from the Blaise reaction intermediate would be highly desirable. Herein we report the first chemoselective tandem acylation of Blaise reaction intermediate providing α-acyl-β-enamino esters **2** and their conversion to tri- and tetrasubstituted pyrazoles.

Our initial efforts were directed at an examination of the intrinsic reactivity of the Blaise reaction intermediate generated *in situ* from the reaction of benzonitrile (**1a**) with the Reformatsky reagent towards acylation.

Reaction of the Blaise reaction intermediate with various acylating agents, such as acetyl chloride, isopropenyl acetate and acetic anhydride, led to very sensitive outcomes depending on acylating agents. For example, tandem reaction of the Blaise intermediate **A**·ZnBr with acetyl chloride resulted in an intractable mixture and no reaction was observed with isoprenyl acetate. In contrast, when the reaction was conducted with acetic anhydride, both C2-acetylated product **2a** and *N*-acetylated product were formed in 18 and 27% yield, respectively, after prolonged reaction time of 3 d at room temperature (entry 1, Table 1). This result clearly delineated the ambivalent intrinsic reactivity profile of the Blaise intermediate A·ZnBr which is similar to that of the free β-enamino ester. To improve the poor chemoselectivity towards N *vs.* C-2, we tested various additives which would modify its intrinsic reactivity. First, we added 1.0 equiv. of *n*-BuLi on a simple assumption that it would displace the bromide by an electron donating butyl group to change the intrinsic reactivity as well as chemoselectivity of acylation of the Blaise intermediate. To our delight, reaction of benzonitrile (**1a**) with Reformatsky reagent followed by the sequential

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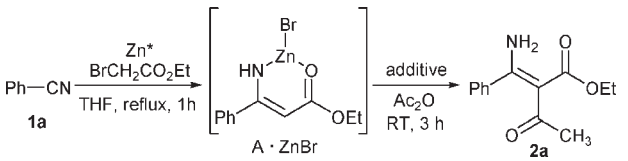
† Electronic supplementary information (ESI) available: Details of synthetic procedure for **2**, **3**, **4** and **5**, and ^{1}H and ^{13}C NMR spectral data. See DOI: 10.1039/b813369g

Table 1 Additive effects on tandem Blaise-acylation reaction‡



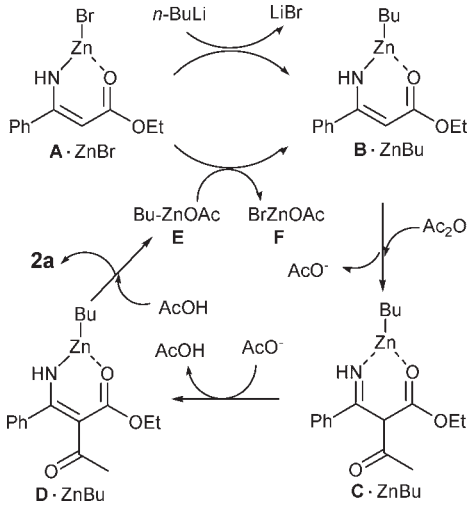
Entry	Additive	Equivalent	Yield **2a** (%)
1[a]	None	—	18
2	*n*-BuLi	1.0	82
3	CH_3Li	1.0	81
4	LiHMDS	1.0	61
5	NaHMDS	1.0	69
6	*tert*-BuOK	1.0	57
7	$(CH_3)_2CHMgBr$	1.0	20
8[b]	*n*-BuLi	1.0	81
9	*n*-BuLi	0.5	78
10	*n*-BuLi	0.1	67

[a] Reaction carried out for three days. [b] The acylation was conducted with the THF solution of the Blaise reaction intermediate kept for one week at room temperature.

addition of 1.0 equiv. of *n*-BuLi and 1.2 equiv. of acetic anhydride resulted in exclusive formation of C2-acetylated product **2a** in 82% yield (entry 2, Table 1). No trace of *N*-acylated product was detected. A similar result can be obtained by addition of CH_3Li (entry 3, Table 1). Other additives such as LiHMDS (entry 4, Table 1), NaHMDS (entry 5, Table 1), and *tert*-BuOK (entry 6, Table 1) also promoted exclusive generation of the C2-acylated product **2a**, but the yields are lower than when *n*-BuLi is used. However, the Grignard reagent did not activate the reaction efficiently affording **2a** in only 20% yield (entry 7, Table 1). We also found that the Blaise intermediate **A**·ZnBr has extraordinary stability in THF. Thus, acylation reaction of a THF solution of the intermediate, stored for a week at room temperature, leads to the same result as is obtained from reaction of directly formed intermediate (entry 8, Table 1). Very interestingly, lowering the equivalency of *n*-BuLi to 0.5 showed similar selectivity to lead to **2a** with only slightly decreased yield of 78% (entry 9 in Table 1). Even in the presence of 10 mol% of *n*-BuLi, the reaction profile did not change except slightly diminishing the yield (67%) (entry 10 in Table 1).

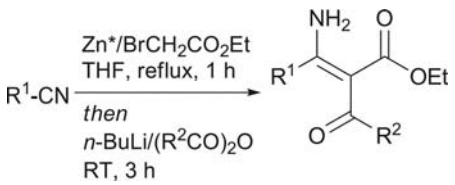
These observation suggest that a second catalytic butylzinc species is generated *in situ*, which causes bromide-to-butyl exchange. The catalytic role of *n*-BuLi can be explained by using the pathway outlined in Scheme 1. Ligand exchange of **A**·ZnBr intermediate with *n*-BuLi affords the corresponding **B**·ZnBu complex, which reacts with acetic anhydride to form C2-acylated iminobutylzinc complex **C**·ZnBu and acetate anion. Owing to the increased acidity of C2-proton, acetate promoted rapid isomerization of **C**·ZnBu to the more stable **D**·ZnBu then leads to production of the C2-acylated **2a** and buthylzinc acetate **E**, which acts as a second catalytic species for bromide exchange regenerating **B**·ZnBu and unreactive (or less reactive) acetoxyzinc bromide **F**.

Based on the initial observation, we next investigated the substrate scope of this transformation and the results are summarized in Table 2. Aromatic nitriles (entries 1–4, Table 2)



Scheme 1 Proposed mechanism for the chemoselective acylation of the Blaise intermediate **A**·ZnBr with catalytic *n*-BuLi

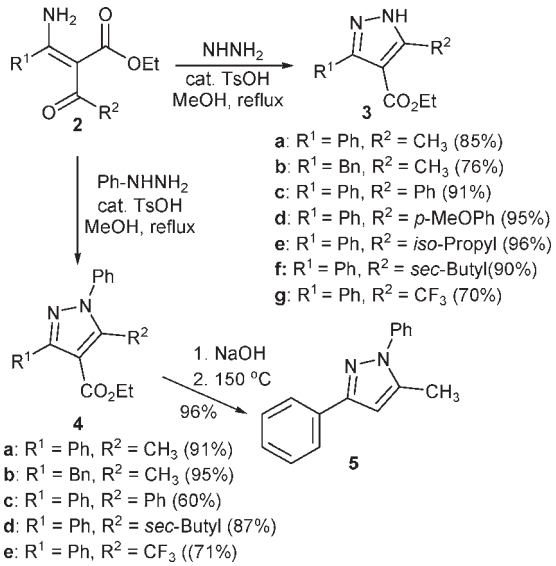
Table 2 Chemoselective tandem Blaise-acylation for the formation of α-acyl-β-enamino esters **2**‡



Entry		R^1	R^2	Yield (%)
1	**a**	Ph	CH_3	82
2	**b**	1-$CH_3C_6H_4$	CH_3	72
3	**c**	4-FC_6H_4	CH_3	53
4	**d**	3-Pyridyl	CH_3	57
5	**e**	4-$CH_3OC_6H_4CH_2$	CH_3	60
6	**f**	$C_6H_4CH_2$	CH_3	95
7	**g**	CH_3	CH_3	83
8	**h**	CH_3CH_2	CH_3	86
9	**i**	$(CH_3)_2CH$	CH_3	57
10[a]	**j**	Ph	Ph	80
11[a]	**k**	Ph	4-$CH_3OC_6H_4CH_2$	89
12[b]	**l**	Ph	$(CH_3)_2CH$	45
13	**m**	Ph	$(CH_3)_2CHCH_2$	94
14	**n**	Ph	CF_3	81

[a] Yield of *E* : *Z* (*ca.* 2 : 1) mixture. [b] Yield of *E* : *Z* (*ca.* 3 : 1) mixture.

as well as aliphatic nitriles such as acetonitrile, propionitrile and isobutyronitrile (entries 5–9, Table 2) were converted to their corresponding α-acetyl-β-aminoacrylates **2a–2i** in moderate to excellent yield. In addition to acetic anhydride, benzoic (entry 10, Table 2), *p*-methoxybenzoic (entry 11, Table 2), isovaleric (entry 13, Table 2) and trifluoroacetic anhydrides (entry 14, Table 2) also lead to the formation of the corresponding C2-acylated products **2j**, **2k**, **2m** and **2n** in high yields (up to 95%). In the case of sterically demanding isobutyric anhydride, the yield was decreased to 45% (entry 11, Table 2). Nevertheless, these results clearly demonstrated that the Blaise reaction intermediate serves as a useful functionalized organozinc nucleophile for chemoselective C2-acylation reactions.



Scheme 2 Transformation of **2** to tri- and tetrasubstituted pyrazoles **3–5**.

Finally, as a proof of synthetic potential of the C2-selective acylation of the Blaise reaction intermediate, the resulting α-acyl-β-enamino esters **2** were transformed to pyrazoles, which are important pharmacophores in various biologically active compounds.[11] As shown in Scheme 2, reactions of **2** with hydrazine and phenylhydrazine in the presence of catalytic amounts of *p*-TsOH afforded the corresponding 3,4,5-trisubstituted **3a–g** (70–96%) and 1,3,4,5-tetrasubstituted pyrazoles **4a–e** (71–95%) in good to excellent yields. The tetrasubstituted **4a** could also be transformed efficiently to 1,3,5-trisubstituted pyrazole **5** in 96% yield through the hydrolysis of the ester followed by decarboxylation.

In summary, we have been investigated for the first time the intrinsic reactivity of the Blaise reaction intermediate, a zinc bromide complex of β-enamino ester, for acylation, which showed low levels of chemoselectivity (N *vs.* C2) with a low efficiency. A modification of the reaction conditions, involving the addition of a stoichiometric or catalytic amount of *n*-BuLi, leads to highly regioselective C2-acylation to provide α-acyl-β-enamino esters in moderate to excellent yields. Transformation of a α-acyl-β-enamino ester to pyrazoles in high yields showcases the overall methodology. This investigation has provided a platform for future studies probing applications of the Blaise intermediate as a functionalized organozinc complex. Further applications of the Blaise reaction intermediate to other conceivable reactions are underway and will be reported in due course.

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Notes and references

‡ A representative procedure for the synthesis of **2**: To a stirred suspension of commercial zinc dust (10 μm, 0.65 g, 10.0 mmol) was added 5.0 mol% of methanesulfonic acid in THF (2.5 mL), and the mixture was refluxed for 10 min. While maintaining reflux, benzonitrile (0.52 mL, 5.0 mmol) was added all at once, followed by ethyl bromoacetate (0.83 mL, 7.5 mmol) over 1 h with syringe pump. After 1 h at reflux, the reaction temperature was cooled to 0 °C. To the reaction mixture was added *n*-BuLi (2.0 M in cyclohexane, 2.5 mL, 5.0 mmol) and acetic anhydride (0.62 mL, 6.5 mmol) in sequence. After stirring for 3 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl, and the product was extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica chromatography to afford **2a** (0.96 g, 82%).

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