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Tandem Blaise-Alkenylation with Unactivated Alkynes: One-Pot Synthesis of α-Vinylated β-Enaminoesters from Nitriles

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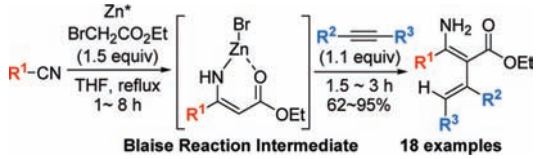
ABSTRACT



The *in situ* generated Blaise reaction intermediate, a zinc bromide complex of β-enaminoester, reacts with various unactivated terminal alkynes and an internal alkyne under mild conditions to afford α-vinylated β-enaminoesters in good to excellent yields.

Tandem and cascade reactions have attracted significant attention because of their undeniable benefits such as atom economy and one-pot operation with maximization of molecular complexicity.[1] Indeed, the device and implementation of tandem reactions is a challenging facet and has become increasingly important in organic synthesis. Recently, we were intrigued by the possible tandem use of the Blaise reaction intermediate, a zinc bromide complex of β-enaminoester,[2] as a nitrogen isostere of the zinc enolate of β-ketoester and developed a highly efficient tandem synthesis of α-acyl-β-enaminoesters.[3] Herein, we report unprecedented tandem nucleophilic addition of the Blaise reaction intermediate to unactivated terminal alkynes and an internal alkyne, which allow direct use of nitriles for effective one-pot synthesis of α-vinylated β-enaminoesters under mild conditions. Considering the importance of amine-functionalized 1,3-dienes as versatile building blocks in organic synthesis as well as in polymer chemistry, our protocol provides a highly efficient alternative method for this class of compounds.[4]

Nucleophilic 1,2-addition of metal enolates to unactivated alkynes represents the most popular method for the synthesis of α-vinylated 1,3-dicarbonyl compounds, and has received great attention in recent years. Although its early intramo-

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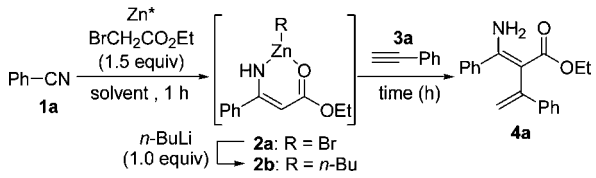
lecular version (Conia-ene reaction) was of limited use due to its high reaction temperature,[5] employment of various metal catalysts such as Au(I),[6] Ni(II)-Yb(OTf)$_3$,[7] Pd(II)-Yb(OTf)$_3$,[8] and In(III)[9] made the reaction possible under milder conditions. Recent development of In(III) or Re(I)[10e]-catalyzed intermolecular variants, mostly by Nakamura and co-workers, significantly expanded the synthetic scope of this reaction.[10] It has been also indicated that zinc enolates of 1,3-dicarbonyls and *N*-monosubstituted β-enaminoesters or β-enaminoamides could be effective nucleophiles for 1,2-addition to unactivated terminal alkynes with careful choice of Zn(II) species.[10b−d,11] For example, ethylzinc enolates of *N*-monosubstituted β-aminocrotonamides, generated *in situ* from β-aminocrotonamides and diethylzinc, reacted with unactivated terminal alkynes to afford the corresponding α-alkylidene β-carbonyl amides, whereas the combined use of a stoichiometric amount of Zn(OTf)$_2$ and Et$_3$N showed much lower reactivity.[10b] Although an alternative synthetic pathway to obtain trisubstituted alkenes via In(NTf)$_3$-catalyzed vinylation of 1,3-dicarbonyl compounds with 1-iodoalkyne followed by Pd-catalyzed cross-coupling with phenylboronic acid,[12] these reactions were not effective with unactivated internal alkynes. Moreover, there is no report on the reaction profile of *N*-unsubstituted β-aminoacrylate toward alkenylation with unactivated alkynes.

In this context, we initially anticipated that the ligating group to the zinc of the Blaise reaction intermediate would exert significant influence on the reactivity, and thus, investigated the reactivity profiles of the intact zinc bromide intermediate **2a** and the butylzinc complex **2b** toward unactivated alkyne in their α-vinylation reaction (Table 1). To began our investigations, a Blaise reaction intermediate **2a** was prepared *in situ* by addition of ethyl bromoacetate (1.5 equiv) to a solution of benzonitrile (**1a**, R^1 = Ph) (1.0 equiv) and zinc powder (2.0 equiv preactivated by using 5.0 mol % of CF_3SO_3H)[13] in THF at reflux temperature or in dioxane at 80 °C for 1 h (>97% conversion of nitrile by GC). For the preparation of the butylzinc complex **2b**, an equivalent amount of *n*-BuLi was added to the formed Blaise reaction intermediate **2a** at 0 °C. The alkenylations were carried out by addition of the phenyl acetylene **3a** to the zinc complex solution all at once at either reflux in THF or 80 °C in dioxane (entries 7−9, Table 1).

Table 1. Optimization Study for Tandem Reaction of the Blaise Intermediate with Phenylacetylene[a]



entry	**2**	**3** (equiv)	solvent	time (h)	additive[b]	yield (%)[c]
1	**2a**	1.1	THF	1.5	−	91
2[d]	**2a**	1.1	THF	24	−	90
3	**2b**	1.1	THF	12	−	20
4	**2b**	2.0	THF	12	−	24
5	**2b**	4.0	THF	12	−	57
6	**2b**	5.0	THF	12	−	70
7[e]	**2b**	5.0	Dioxane/CH_2Cl_2	12	Sc(OTf)$_3$	79
8[e]	**2b**	5.0	Dioxane/CH_2Cl_2	12	Yb(OTf)$_3$	70
9[e]	**2b**	5.0	Dioxane/CH_2Cl_2	12	In(OTf)$_3$	89

[a] Reaction was carried out on a 7.6 mmol scale of **1a** at reflux in THF (4 mL) under the conditions described in the text unless otherwise noted. [b] Additive (20 mol %) was used. [c] After silica column chromatography. [d] Reaction was carried out at room temperature. [e] Reaction was conducted at 80 °C (bath temperature) in a mixture of 1.4-dioxane/CH_2Cl_2 (1/1, v/v).

As shown in Table 1, the intact zinc bromide complex **2a** showed superb reactivity. Thus, the tandem reaction of **2a** with phenylacetylene has been completed within 1.5 h to provide, after workup with aqueous sat. NH_4Cl solution, the α-vinylated β-enaminoester **4a** in 91% yield (entry 1, Table 1).[14] The reaction also proceeded smoothly at room temperature with almost the same yield after 24 h (entry 2, Table 1). In contrast, the alkenylation of the butylzinc complex **2b** required an excess amount of **3a** and prolonged reaction time to achieve reasonable yield (entries 3−6, Table 1).[15] The yields were increased slightly by the addition of 20 mol % of Lewis acids such as Sc(OTf)$_3$ (79%, entry 7, Table 1), Yb(OTf)$_3$ (70%, entry 8, Table 1), and In(OTf)$_3$ (89%, entry 9, Table 1), where a mixture of 1,4-dioxane and CH_2Cl_2 (1/1, v/v) was used since the reaction was sluggish in THF or in dioxane only. However, excess of alkyne was still necessary for good yield.[16] These results suggested that the zinc bromide complex **2a** may have balanced propensity to play dual functions of a nucleophile as well as a Lewis acid activating alkyne. In contrast, the reaction was significantly retarded when the more electron-donating butyl group is

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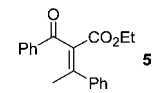
(14) When the reaction was workup with 3N aqueous HCl solution, the α-alkylidene β-ketoester **5** was isolated in 85% yield (see Supporting Information).



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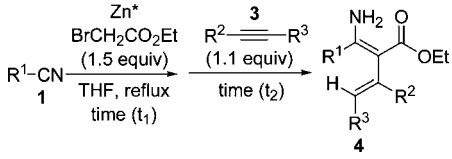
(15) Similar results were obtained with ethylzinc complex of β-enaminoester, which was prepared *in situ* from the isolated β-enaminoester and diethylzinc.

ligated in **2b** lowering Lewis acidity, but the reactivity of which can be restored marginally through the activation of alkyne by using additional Lewis acid catalyst.

We next explored the substrate scope of the reaction, and the results are summarized in Table 2.[17] A wide range of

Table 2. Tandem Blaise-Alkenylation with Terminal and Internal Alkynes[a]



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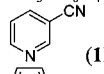
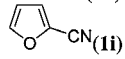
entry	R^1(1)	R^2/R^3 (3)	t_1/t_2 (h)[b]	4, yield (%)[c]
1	Ph (**1a**)	Ph/H (**3a**)	1/1.5	**4a**(91)
2	*o*-$CH_3C_6H_4$ (**1b**)	Ph/H (**3a**)	5/1.5	**4b**(89)
3	*m*-$CH_3C_6H_4$ (**1c**)	Ph/H (**3a**)	1/1.5	**4c**(90)
4	*p*-$CH_3C_6H_4$ (**1d**)	Ph/H (**3a**)	1/1.5	**4d**(88)
5	*p*-FC_6H_4 (**1e**)	Ph/H (**3a**)	1/1.5	**4e**(93)
6	*p*-$CF_3C_6H_4$ (**1f**)	Ph/H (**3a**)	1/1.5	**4f**(85)
7	*p*-$CH_3OC_6H_4$ (**1g**)	Ph/H (**3a**)	1/1.5	**4g**(91)
8	 (**1h**)	Ph/H (**3a**)	1.5/5	**4h**(87)
9	 (**1i**)	Ph/H (**3a**)	1/1.5	**4i**(88)
10	$PhCH_2$ (**1j**)	Ph/H (**3a**)	1/1	**4j**(92)
11	CH_3CH_2 (**1k**)	Ph/H (**3a**)	1/1	**4k**(94)
12[d]	$(CH_3)_2CH$ (**1l**)	Ph/H (**3a**)	8/2	**4l**(62)
13	$(CH_3)_2CHCH_2$ (**1m**)	Ph/H (**3a**)	1/1	**4m**(88)
14	Ph (**1a**)	*p*-FC_6H_4/H (**3b**)	1/3	**4n**(95)
15	Ph (**1a**)	*p*-$CH_3OC_6H_4$/H (**3c**)	1/1	**4o**(92)
16	Ph (**1a**)	CH_3OCH_2/H (**3d**)	1/1	**4p**(80)
17	Ph (**1a**)	$CH_3(CH_2)_3$/H (**3e**)	1/1	**4q**(91)
18	Ph (**1a**)	Ph/CH_3 (**3f**)	1/48	**4r**(63)
19	Ph (**1a**)	Ph/C_3H_7(**3g**)	1/48	-
20	Ph (**1a**)	Ph/Ph (**3h**)	1/48	-

[a] For reaction conditions, see ref 17. [b] t_1: time for >97% conversion of nitrile to the Blaise intermediate, t_2: time for the disappreance of the Blaise intermediate. [c] After silica column chromatography. [d] **3a** was added after 80% conversion of nitrile.

aromatic (**1a**−**1g**), heteroaromatic (**1h** and **1i**), and aliphatic (**1j**−**1m**) nitriles could be transformed efficiently to the corresponding α-vinylated *β*-enaminoesters **4a**−**4m** with good to excellent yields through the tandem alkenylation of the Blaise reaction intermediate with phenylacetylene **1a** (entries 1−13, Table 1). The sterically more demanded isobutyronitrile **1l** showed diminished reactivity in both Blaise (*ca*. 80% conversion of nitrile) and alkenylation (*ca*. 78%) reactions, resulted in a slightly lower yield of α-vinylated *β*-enaminoester **3l** (entry 12, Table 1). The nature of terminal alkyne did not affect the efficiency of the reaction as well, and thus the tandem reaction with aromatic and aliphatic terminal alkynes proceeded efficiently, as clearly shown in entries 14−17 in Table 2. Importantly, the Blaise reaction intermediate **2a** reacts with an internal alkyne, methyl phenyl acetylene **3f**, to afford the corresponding trisubstituted alkene **4r**, but required prolonged reaction time (63% yield, entry 18 in Table 2). This is the first intermolecular alkenylation of metal enolate with unactivated internal alkyne. However, other internal alkynes **3g** and **3h** did not react at all with **2a** (entries 19 and 20 in Table 2).

Finally, to acquire an insight into the reaction mechanism, the tandem Blaise reaction of **1a** with 1.1 equiv of deuterium labeled **3a**-*d* was carried out to afford a mixture of isotopically discriminated **4a**-DD, **4a**-DH, **4a**-HD, and **4a**-HH with a 3:2:2:5 ratio in 90% yield. The scrambling of proton and deuterium atoms at the terminal vinyl group clearly indicated the generation of unlabeled **3a**, and its incorporation into the reaction as shown in the proposed pathways (Figure 1).

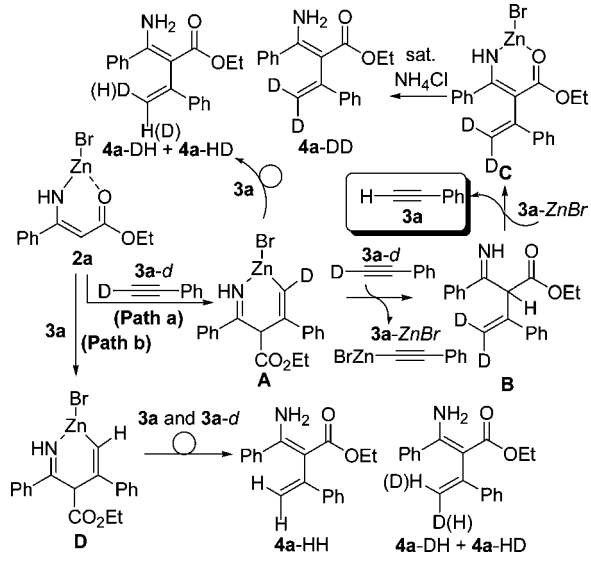


Figure 1. Possible reaction pathways.

In path a, the Blaise reaction intermediate **2a** reacted with **3a**-*d* to form vinylzinc bromide **A**, which abstracted the deuterium from the second **3a**-*d* resulting in zinc acetylide **3a**-*ZnBr*. The inter- and/or intramolecular deprotonation of the acidic proton by **3a**-*ZnBr* could generate **3a** and the zinc bromide complex **C**, which hydrolyzed to form **4a**-DD. Proton transfer from the generated **3a** to the vinylzinc

(16) The reaction of the isolated *β*-enaminoester with phenylacetylene in the presence of 20 mol % of $In(OTf)_3$ only or a stoichiometric mixture of $In(OTf)_3$ and Et_3N did not proceeded efficiently, and less than 10% of **4a** was obtained after 24 h.

(17) A typical procedure for the tandem alkenylation of the Blaise reaction intermediate: To a stirred suspension of commercial zinc dust (1.0 g, 15.3 mmol) was added methansulfonic acid (3.7 mg) in anhydrous THF (4.0 mL). After 10 min reflux, benzonitrile (**1a**, 0.8 mL, 7.6 mmol) was added. While maintaining the reflux temperature, ethyl bromoacetate (1.26 mL, 11.4 mmol) was added over 1 h by using a syringe pump, and the reaction mixture was further refluxed for 1 h. To this reaction mixture, phenylacetylene (**3a**, 0.92 mL, 8.4 mmol) was added, and the reaction mixture was refluxed for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl at room temperature. After evaporation of THF, the residue was extracted with ethyl acetate (20 mL × 3), and the combined organic layer was dried with anhydrous $MgSO_4$ and filtered then concentrated under reduced pressure. The residue was purified by silica chromatography (eluent: *n*-hexane/EtOAc = 5:1) to afford viscous yellowish liquid **4a** (2.03 g, 91%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.90 (t, J = 7.1 Hz, 3H), 4.00 (q, J = 7.1 Hz, 2H), 4.76 (d, J = 1.5 Hz, 1H), 5.36 (d, J = 1.5 Hz, 1H), 7.20∼7.33 (m, 8H), 7.39∼7.43 (m, 2H) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.0, 59.2, 98.4, 118.2, 126.1, 126.8, 127.4, 128.0, 128.2, 128.8, 138.8, 143.0, 144.5, 160.8, 170.2 ppm; HRMS calcd for $[M + H]^+$: $C_{19}H_{20}NO_2$: 294.1494. Found: 294.1500.

complex **A** afforded **4a**-DH + **4a**-HD. The generated **3a** in path a reacts with the Blaise intermediate **2a** to form the vinylzinc **D**, which was then converted to **4a**-HH and **4a**-HD + **4a**-DH via proton and deuterium transfer from **3a** and **3a**-*d*, respectively (path b).

In conclusion, we have developed unprecedented tandem alkenylation of the Blaise reaction intermediate with unactivated terminal and internal alkynes in a one-pot operation under mild conditions. This discovery opens a new direct method for the synthesis of various α-vinylated β-enaminoesters from nitrile. These results underscore the potential of the Blaise reaction intermediate as an organozinc nucleophile as well as a Lewis acid for the formation of carbon−carbon bonds. Studies extending the range of tandem Blaise reactions by modulating the Blaise reaction intermediate are currently underway in our laboratory.

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Supporting Information Available: Experimental details and spectral data of **4a**−**4r** and their ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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