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Tandem One-Pot Synthesis of Polysubstituted Pyridines Using the Blaise Reaction Intermediate and 1,3-Enynes

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ABSTRACT

A tandem one-pot method for the construction of a pyridine moiety with selective control of substitution patterns has been developed through the sequential reactions of nitrile with a Reformatsky reagent and 1,3-enyne involving regio- and chemoselective addition of the Blaise reaction intermediate to 1,3-enyne, followed by isomerization, cyclization, and an aromatization cascade.

The pyridine moiety is an important component of various natural products, pharmaceuticals, and functional materials.[1] Consequently, the development of a new synthetic method for the construction of pyridines is always important. Although substantial progress has been made in the derivatization of pre-existing pyridine frameworks using metal-catalyzed cross-coupling protocols,[2] *de novo* methods for the convergent construction of regiocontrolled pyridine cores would provide important complementary approaches.[3] The value of these methods would greatly increase if the reactions were run in tandem since this would minimize the synthetic steps and waste generation.[4] Due to their functional group tolerance, zinc enolate intermediates have attracted particular attention in the development of tandem reactions.[5] Here, we report an unprecedented tandem one-pot method for the modular construction of pyridine moieties through the sequential

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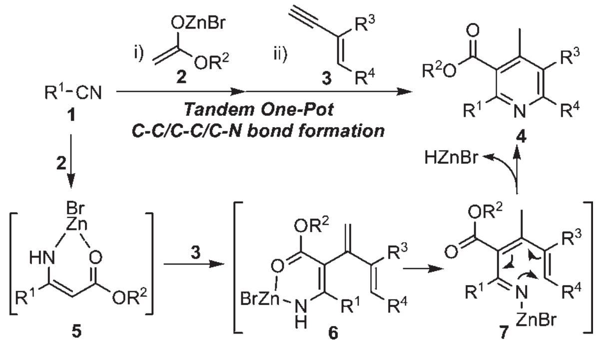
reaction of nitriles with Reformatsky reagents (the Blasie reaction) and 1,3-enynes (Scheme 1). This reaction can provide an operationally simple, scalable, and flexible method for constructing pyridine rings with controllable substitution patterns around the pyridine core. To the best of our knowledge, this represents the first use of a Reformatsky reagent in the tandem construction of the pyridine ring moiety. The direct incorporation of 1,3-enynes into the pyridine rings is also noteworthy.[6]

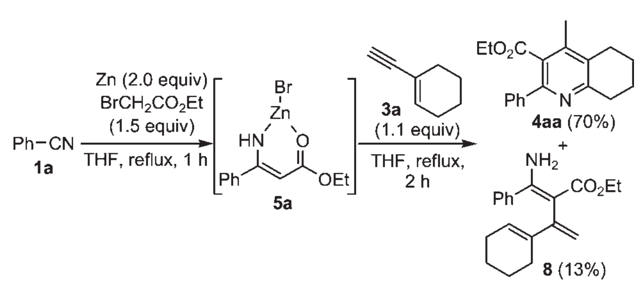
Scheme 1. Tandem One-Pot Synthetic Strategy for Construction of Pyridine Moiety



We recently became interested in the tandem use of the Blaise reaction intermediate **5** as an aza-zinc enolate with a unique ambivalent C-/N-nucleophilic nature for tandem C–C or C–C/C–N bond formations.[7] During these studies, we observed the balanced propensity of the intermediate **5** to play the dual function of a carbon nucleophile as well as a Lewis acid in activating unactivated terminal alkynes for regio- and chemoselective α-vinylation.[7c] A mechanistic study suggested that a zinc bromide complex of the α-vinylated β-enaminoester was formed first, which was then converted to the corresponding α-vinylated β-enaminoesters after workup. We reasoned that, if identical tandem reactions were conducted with a 1,3-enyene **3**, the resulting α-dienylated β-enaminozincate **6** might then be capable of undergoing an isomerization to the N-zincated 1-azatriene **7**, which could facilitate a 6π electrocyclization and/or cycloaddition to produce the pyridines **4** after elimination of HZnBr (Scheme 1).[8] Compared to the previously reported construction of a substituted pyridine moiety from the N-lithium 1-azatrienes with limited functional group compability,[9] our approach using organozinc reagents could provide the additional advantage of broad functional group tolerance.

To test our hypothesis, we commenced our investigation with the Blaise reaction intermediate **5a**, formed from the reaction of benzonitrile (**1a**) with a Reformatsky reagent **2a** generated *in situ* from ethyl bromoacetate (1.5 equiv) and zinc (2.0 equiv) in THF (over 96% of **1a** was converted to the **5a**). The tandem reaction of **5a** with commericially available 1-ethynylcyclohexene (**3a**, 1.1 equiv) was carried out in THF under reflux for 2 h to afford the tetrahydroquinoline **4aa** in 70% yield along with the α-dienylated β-enaminoester **9** (13%) (Scheme 2). This result clearly indicated that the zincated aminotriene **6** was formed as an intermediate. When the tandem reaction was carried out in 1,4-dioxane at 110 °C, the yield of **4aa** increased to 90% (entry 1, Table 1).The structure of **4aa** was unambigously determined by X-ray analysis (Figure 1).[10] Under standard conditions, various aromatic nitriles with electron-donating or -withdrawing group such as methyl, methoxy, halides, and ester groups were readily converted to the corresponding tetrahydroquinolines **4aa**–**4ka** in good to excellent yields (entries 2–11, Table 1).

Scheme 2. Initial Probe Experiment



One of the nitrile groups of the terephthalonitrile was selectively converted to a pyridine ring to produce the nitrile-functionalized **4la** in 60% yield, which could be further manipulated (entry 12, Table 1). With an excess of the Reformatsky reagent, both of the nitrile groups could be converted to the bis-enaminozincate intermediate **5lb**, which then reacted with 2.2 equiv of **3a** to afford the bipyridyl compound **4lb** in 56% yield. Based on the unique reactivity of the Blaise reaction intermediate toward propiolates affording pyridones,[7d] the sequential tandem reactions of **5lb** with 1,3-enyne **3a** and ethyl phenylpropiolate enabled divergent construction of two different heterocyclic rings, pyridine and pyridone, in one molecule **9** (39%)

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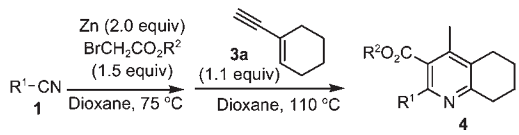
(10) The crystallographic data can be obtained from The Cambridge Crystallographic Data Centre (CCDC 847154) via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Tandem One-Pot Synthesis of Tetrahydroquinolines[a]



entry	4, yield (%)[b]	entry	4, yield (%)[b]
1	4aa (90)	10	4ja (70)
2	4ba (89)	11	4ka (77)
3	4ca (83)	12	4la (60)
4	4da (80)	13	4ma (77)
5	4ea (72)	14	4na (83)
6	4fa (80)	15	4oa (75)
7	4ga (73)	16	4pa (66)
8	4ha (80)	17	4ab (85)
9	4ia (70)	18	4ac (92)

[a] Reaction conditions: nitrile **1** (3.0 mmol), Zn (6.0 mmol), alkyl bromoacetate (4.5 mmol), **3a** (3.3 mmol) in 1,4-dioxane (1.5 mL). **3a** was added when nitrile **1** was converted to intermediate **5** in over 95% by GC, and the reaction was continued until all of **5** was consumed by GC. [b] Isolated yield.

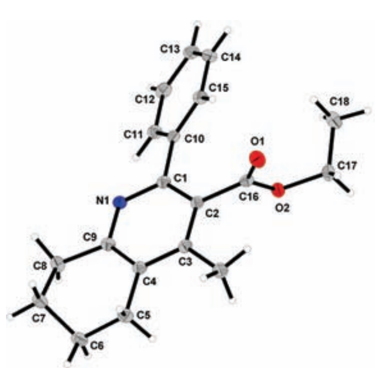
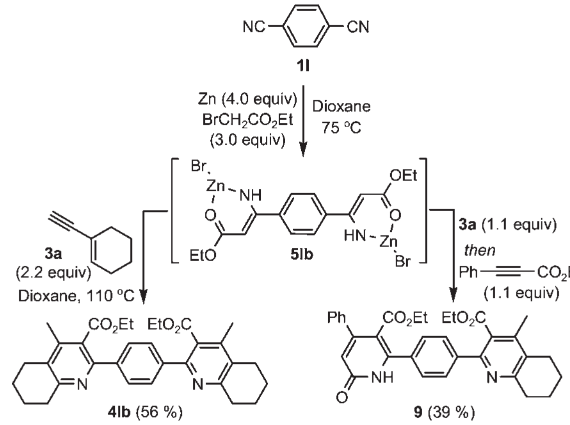


Figure 1. X-ray structure of **4aa**.

along with **4lb** (15%) (Scheme 3). Heteroaromatic and aliphatic nitriles were also readily converted to the corresponding tetrahydroquinoline derivatives **4ma**–**4pa** in high yield (entries 13–16, Table 1). The use of Reformatsky reagents with different R^2 groups did not diminish the yield of the tandem reaction, allowing 3-methylester **4ab** (entry 17, Table 1) and 3-isopropyl ester tetrahydroquinolines **4ac** (entry 18, Table 1) to be prepared in high yield.

Scheme 3. Double Tandem Reactions with Bisnitrile for One-Pot Construction of Two Heterocycles in One Molecule



The generality of types of 1,3-enyene **3** that could be employed was investigated using the Blaise reaction intermediate **5a** (Table 2). Both seven- and eight-membered carbocyclic 1,3-enyenes were successfully incorporated into the pyridine moieties to afford the corresponding carbocycle-fused pyridines **4ad** (82% yield, entry 1,

Table 2. Tandem One-Pot Synthesis of Pyridines with Various 1,3-Enynes[a]

entry	4, yield (%)[b]	entry	4, yield (%)[b]
1	4ad (82) (4ad: n = 1)	5	4ah (40)
2	4ae (70) (4ae: n = 2)		
3	4af (62)	6	4ai (53)[c] (51)[d]
4	4ag (53)	7	4aj (49)

[a] Reaction conditions: nitrile **1a** (3.0 mmol), Zn (6.0 mmol), ethyl bromoacetate (4.5 mmol), 1,3-enyne **3** (3.3 mmol) in 1,4-dioxane (1.5 mL). Enyne **3** was added when **1a** was converted to intermediate **5a** in over 95% by GC, and the reaction was continued until all of **5a** was consumed by GC. [b] Isolated yield (average of two experiments). [c] Yield from the reaction with (*E*)-**3i**. [d] Yield from the reaction with (*Z*)-**3i**.

Table 2) and **4ae** (70% yield, entry 2, Table 2), respectively. Benzofused **4af** was also synthesized in good yield (entry 3, Table 2). Although these yields were lower than those obtained from cyclic 1,3-enynes, likely due to the entropic effects, a series of acyclic 1,3-enyenes with phenyl/methyl (entry 4, Table 2), phenyl/phenyl and phenyl/H (entries 5 and 6, Table 2), and propyl/propyl (entry 7, Table 2) substituents was also smoothly reacted with **5a** in a tandem manner to produce the corresponding polysubstituted pyridines **4ag**–**4aj**. Noteworthy is that the stereochemistry of the enyne did not affect the reactivity of the reactions. Thus, tandem reactions with the enynes (*E*)- and (*Z*)-**3i** afforded the same pyridine **4ai** with almost the same yield (entry 6, Table 2). However, it was found that the 1,3-enynes with internal alkynes such as 1-prop-1-ynylcyclohexene and cyclohex-1-enylethynylbenzene were not suitable substrates for this tandem reaction.

In summary, an efficient tandem one-pot method was developed for the synthesis of polysubstituted pyridines with complete control of substitution patterns from readily available nitriles, Reformatsky reagents, and 1,3-enynes. The tandem reaction proceeded via the regio- and chemoselective addition of the Blaise reaction intermediate to 1,3-enyne followed by an isomerization/cyclization/aromatization cascade. Extrapolation to divergent tandem reactions allowed the construction of two different heterocycles, pyridine and pyridone rings, in one molecule.

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Supporting Information Available. Experimental details; characterization data of **4aa**–**4pa**, **4ab**–**4aj**, **8**, **9** and their ^{1}H, ^{13}C NMR and HRMS spectra; and CIF for **4aa**. This material is available free of charge via the Internet at http://pubs.acs.org.