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Exploiting the Dual Reactivity of *o*-Isocyanobenzamide: Three-Component Synthesis of 4-Imino-4*H*-3,1-benzoxazines

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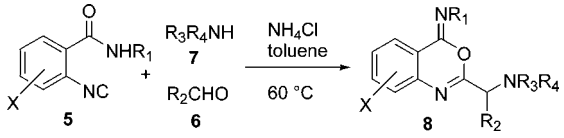
ABSTRACT



A multicomponent synthesis of 4-imino-4*H*-3,1-benzoxazines is developed. Heating a toluene solution of an aldehyde (6), an amine (7), and an isonitrile (5) in the presence of a stoichiometric amount of ammonium chloride at 60 °C for 12 h produces the title compound in good to excellent yields.

A multicomponent reaction (MCR) is a process in which three or more reactants are combined in a single reaction flask to produce a product that incorporates substantial portions of all starting materials. By saving synthetic operations while maximizing the buildup of structural and functional complexity, these highly step-economic reactions are particularly appealing in the context of diversity,[1] as well as target-oriented syntheses.[2]

The ability of isonitrile to undergo facile α-addition with a nucleophile and an electrophile under mild conditions made it a popular reactant for the development of novel MCRs. Indeed, isonitrile is one of the key components of the well-known Passerini three-component reaction (P-3CR)[3] and Ugi four-component reaction (U-4CR).[4] Although there are four diversity points in the U-4CR, the scaffolds that are accessible by the original process are limited. To enlarge the structural diversity accessible by this multicomponent reaction, the tethering principle by using bifunctional starting materials and the combination of U-4CR with another efficient post-condensation transformations have been developed.[5]

A number of isonitriles bearing additional functionalities are known. Among them, α-isocyano acetate (**1**, Figure 1)[6]

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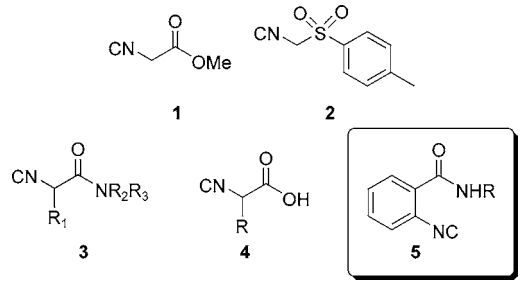
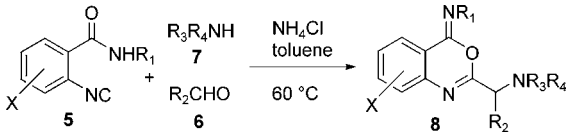


Figure 1. Functionalized isocyanides.

and toluenesulfonylmethyl isocyanide (**2**, TosMIC),[7] developed by Schöllkopf and Van Leusen, respectively, are notable examples and have found wide applications in the synthesis of diverse class of heterocycles. Reaction sequences utilizing these two synthons are in general initiated by the nucleophilic addition of the α-carbanion, rather than the divalent carbon of the isonitrile as in the P-3CR and U-4CR, onto the respective electrophiles.[8]

We have been working on the chemistry of α-isocyano acetamide (**3**)[9] and α-isocyanoacetic acid (**4**).[10] On the basis of the unique reactivities of these two synthons, a number of multicomponent reactions have since been developed for syntheses of polyheterocycles[11,12] and macrocycles[13] and for conducting the functional group transformations.[14] In all of these transformations, the reaction sequence based on **3** and **4** is triggered by the nucleophilicity of the isonitrile carbon that differentiates them from compounds **1** and **2**. As a logical extension of this work and in conjuction with our interests in the synthesis of benzofused heterocycles, we started investigating the chemical reactivity of unknown 2-isocyano benzamide (**5**)[15] and report herein a new three-component synthesis of 4-imino-4*H*-3,1-benzoxazine (**8**) involving an aldehyde **6**, an amine **7**, and isonitrile **5** (Scheme 1). 4-Imino-

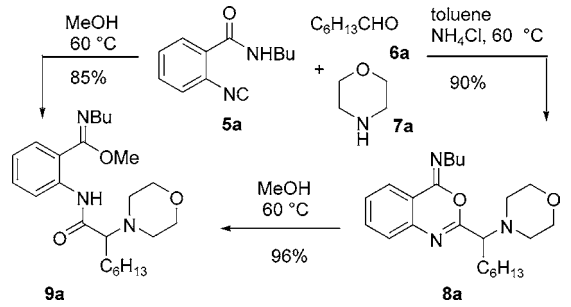
Scheme 1



4*H*-3,1-benzoxazines have previously been prepared by dehydrative cyclization of *N*-acylanthranilamides[16] and are readily rearranged to the quinazolin-4-one, a privileged structure in medicinal chemistry.[17−21] Although little is know about the biological activity of iminobenzoxazine, a recent patent dealing with the application of 4-imino-4*H*-3,1-benzoxazine (**8**) in crop science to control invertebrate pests is noteworthy.[22]

Using isonitrile **5a** (X = H, R_1 = *n*-Bu), heptanal **6a**, and morphiline **7a** as test substrates (Scheme 2), we performed

Scheme 2



a survey of the reaction conditions. In the event, stirring a toluene solution of **5a**, **6a**, and **7a** in the presence of ammonium chloride at room temperature for 8 h resulted in the formation of iminobenzoxazine **8a** (R_1 = *n*-Bu, R_2 = *n*-C_6H_{13}, NR_3R_4 = morpholinyl) in 78% yield. Heating the reaction to 60 °C increased the reaction rate and conversion

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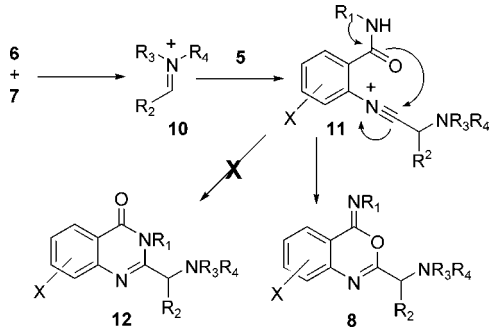
Scheme 3



to afford **8a** in 90%. It is worth noting that this three-component reaction took place even in the absence of ammonium chloride albeit with slight decreased yield. When the same reaction was performed in MeOH, a classic solvent for Ugi-type reaction, imidate (**9a**) was produced (12%) together with **8a** (62%). Prolonged heating in methanol led to the exclusive formation of **9a** (85%) at the expense of **8a**. Control experiment indicated that **9a** was produced from **8a**, most probably by nucleophilic addition of methanol onto the C-4 carbon of **8a** followed by fragmentation. Compound **8a** is stable in basic or neutral conditions and can be easily purified by flash chromatography on alumina support.

A plausible reaction scenario that accounts for the formation of **8** is shown in Scheme 3. Thus, condenstion of an aldehyde **6** and an amine **7** would give the iminium **10**, which would react with isonitrile **5** to afford the nitrilium intermediate **11**. Trapping of the latter by the internal amide oxygen would produce the 4-iminobenzoxazine **8**. Formation of quinazolin-4-one (**12**), which could result from the nucleophilic addition of amide nitrogen to the nitrilium intermediate was not observed.

The following conditions, toluene (0.2 M), NH_4Cl, 60 °C, 12 h, were used to evaluate the scope of this novel three-

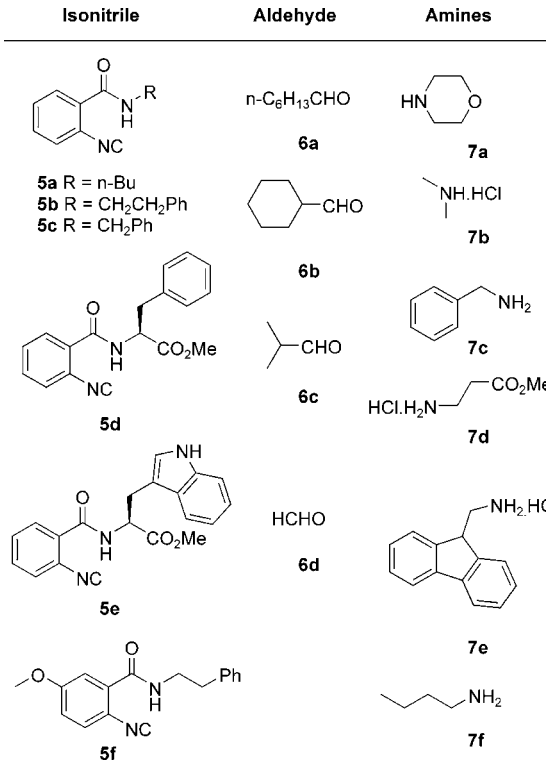


Figure 2. Structures of amines, aldehydes, and isonitriles.

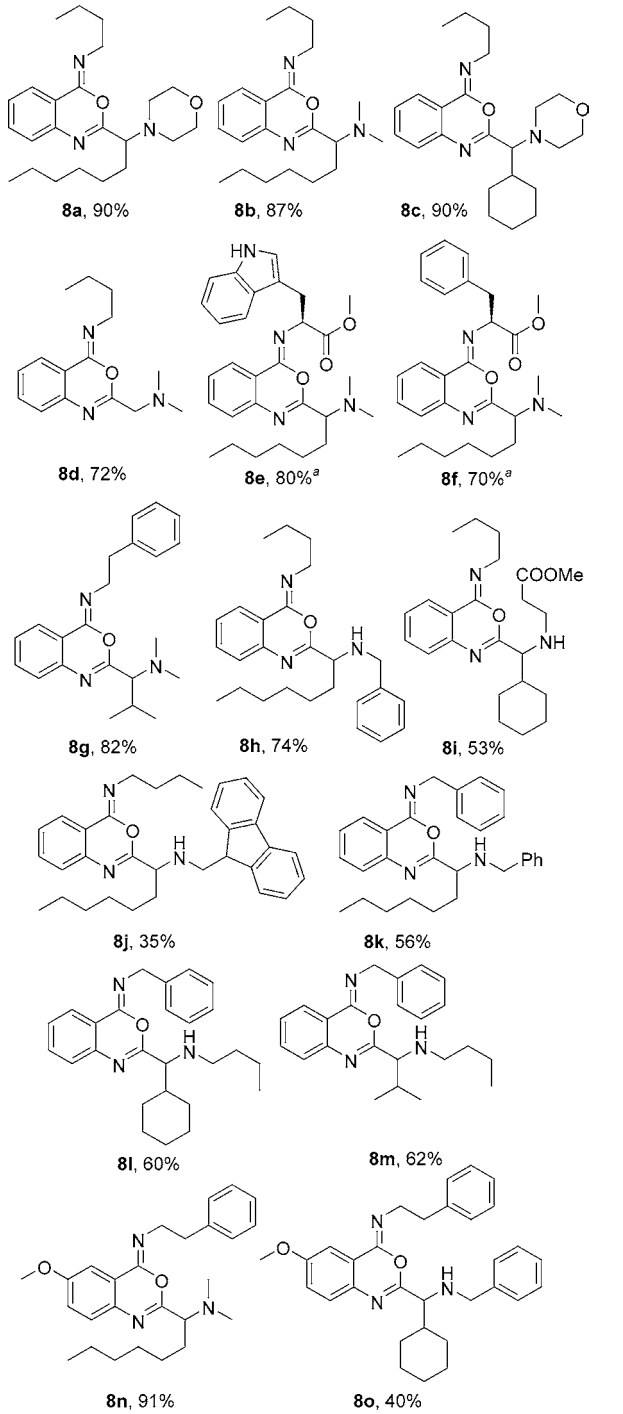
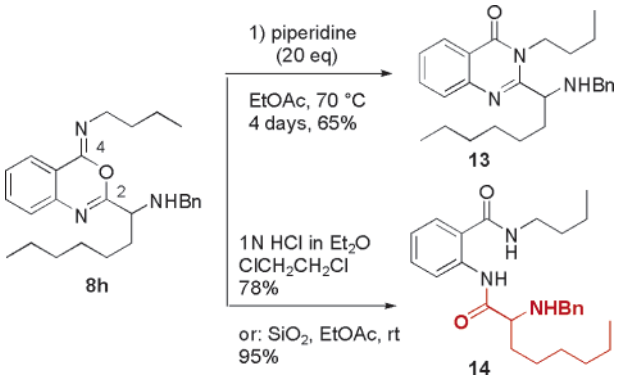


Figure 3. Structure of 4-imino-4*H*-3,1-benzoxazines. (*a*) Two separable diastereoisomers were obtained.

component reaction. From six amines, four aldehydes, and six 2-isocyano benzamides (Figure 2), the 4-imino-4*H*-3,1-benzoxazines listed in Figure 3 were synthesized. As is seen, most of these heterocycles (**4**) were isolated with good to excellent yields. Both primary and secondary amines can be used, although primary amines usually gave lower yields. When hydrochloride salts of amines were used in the presence of triethylamine, the reaction took place smoothly in the absence of ammonium chloride.[23] The stoichiometric amount of $Et_3N{\cdot}HCl$ generated in situ seems to be able to promote the 3CR as did the ammonium chloride. No reaction occurred when aniline (structure not shown) was used as the amine input. For the aldehyde part, aliphatic aldehydes including formaldehyde participated well in this transformation; however, aromatic aldehyde failed to react under these conditions. As far as 2-isocyano benzamides were concerned, amide derived from a variety of primary amines including butylamine, benzylamine, phenethylamine, methyl phenylalanate, and tryptophane methyl ester are well tolerated. When chiral nonracemic isonitriles **5d** and **5e** were used, two enantiomerically pure diastereoisomers were isolated. As it may be expected, no asymmetric induction was observed in this multicomponent reaction.

The rearrangement of 4-imino-4*H*-3,1-benzoxazines to quinazolin-4-one has been studied in detail since Mazurkiewicz's initial report.[15] Under basic conditions developed by Ganesan[16] and Snider,[17] compound **8h** did rearrange to **13** (Scheme 3). However, we found that, in accord with previous studies, this rearrangement is quite substrate-dependent.[16,19] In fact, 4-imino-4*H*-3,1-benzoxazines derived from secondary amine did not undergo rearrangement under a variety of conditions varying the nucleophilic amines (pyrrolodine, piperidine, proline, DBU with or without silica gel), the temperatures, and the solvents. We suspected that the steric hindrance around the C-2 of **8** may hamper the nucleophilic addition of amine and hence the rearrangement. On the other hand, treatment of **8h** under acidic conditions (EtOAc, silical gel, or 1 N HCl) led to the formation of *N*-acylanthranilamide resulting from the nucleophilic addition of water onto the C-4 carbon (**14**, Scheme 4). This two-step sequence (3CR followed by acidic hydrolysis) was an effective alternative route for the construction of **14** when the amino acid to be incorporated is not easily available. In fact, the amino acid unit to be attached to the amino function of anilamide was generated in the course of the three-component reaction.

Scheme 4



In summary, we have developed a three-component synthesis of 4-imino-4*H*-3,1-benzoxazine heterocycles based on the dual reactivity of 2-isocyano benzamide (**5**). Complimentary to the dehydrative cyclization of *N*-acylanthranilamide, the present methodology has an added advantage in that it de novo creates the amino acid unit in the course of the reaction.

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Supporting Information Available: Experimental details and physical data for compounds **8a**−**o**, **9a**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Synthesis of **8b** is typical. Dimethylamine hydrochloride (14.7 mg, 0.18 mmol, 1.2 equiv) was added to a solution of heptanal (25.0 μL, 0.18 mmol, 1.2 equiv) in dry toluene (1.0 mL). Triethylamine (25 μL, 0.18 mmol, 1.2 equiv) was added to the mixture, which was allowed to stir for 15 min at room temperature. *N*-Butyl-2-isocyanobenzamide **5a** (30.3 mg, 0.15 mmol) was added, and the reaction was stirred for 12 h at 60 °C. The reaction was then evaporated to dryness. Purification by flash column chromatography on Al_2O_3 (eluent, 30% diethyl ether in heptane) gave pure 1-(4-(butylimino)-4*H*-benzo[1,3]oxazin-2-yl)-*N*,*N*-dimethylheptan-1-amine **8b** as a colourless oil (45 mg, 87%).