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Versatile, Fragrant, Convertible Isonitriles

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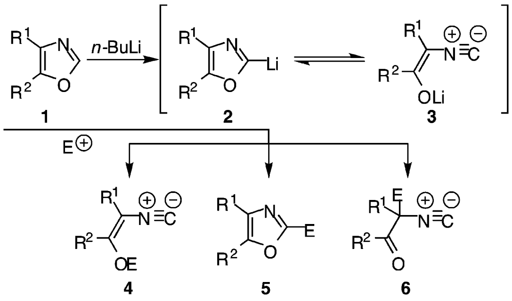
Isonitriles are versatile functionalities in organic synthesis. They are active participants in radical reactions, and as such have played crucial roles in several total and combinatorial syntheses.[1] They can substitute for the gaseous and poisonous carbon monoxide in organometallic transformations,[2] they are polymerized to helical polymers,[3] and they are key to several multicomponent processes, such as the Passerini and Ugi reactions, of high interest in combinatorial chemistry.[4] Despite these attractions, isonitriles are relatively unavailable commercially and can be challenging to prepare. The most common method of isonitrile preparation is by dehydration of formamides. Reagents often used for this reaction (e.g., $COCl_2$)[5] are hazardous and reactive. Only a few routes to isonitriles not involving formamide dehydration are known.[6]

Another hindrance to the use of isonitriles is their piercing odor. Ugi states[5] "The development of the chemistry of isonitriles has probably suffered ... through the characteristic odor of volatile isonitriles, which has been described by Hofmann and Gautier as 'highly specific, almost overpowering', 'horrible', and 'extremely distressing'. It is true that many potential workers in this field have been turned away by the odor." The potent odor of isonitriles is the basis of a classic qualitative test for primary amines via conversion to the "carbylamine" by KOH/$CHCl_3$ (the Hofmann isonitrile synthesis)[7] and makes them useful for the characterization of odorant receptors.[8] They are sufficiently obnoxious to have been included in nonlethal weapons.[9] As a consequence of these properties, only the simplest, unfunctionalized isonitriles, which chemists can purchase and which need minimal handling, are used routinely. We have provided a solution to these problems with the family of isonitriles described herein.

Oxazoles **1** are readily metalated at the 2-position (Scheme 1). The resulting anion **2** equilibrates (by α-elimination/ring-opening) with α-isocyano enolate **3**. With benzoxazole and oxazole, the latter form dominates and has been observed by NMR.[10] Reactions of this equilibrating anion are dependent on the electrophile. Most carbonyl electrophiles give products such as **5**.[11] *O*-Acylation gives products such as **4**.[12] *O*-Silylation can occur, but the enol silane can close back to the 2-silyloxazole (like **5**).[11b] Iodine is one of the few electrophiles to react with **3** on carbon. Following *C*-iodination to give an intermediate like **6** (R^1 = H), cyclization produces 4-iodooxazole.[13]

Scheme 1. Reaction Pathways for Metalated Oxazoles



Scheme 2. Synthesis of Unsaturated Isonitriles from Oxazoles

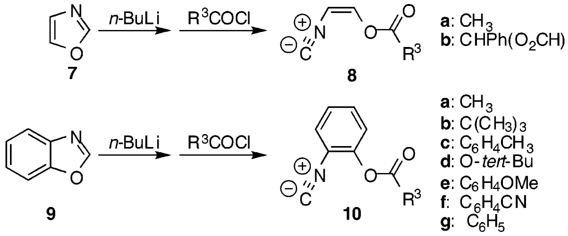


Table 1. Synthesis of Unsaturated Isonitrile-esters

	reactant	yield	IR (cm^{-1})	odor
8a	AcCl	75%	2128	mild isonitrile
8b	*O*-formylmandeloyl-Cl	95%	2126	soy
10a	AcCl	85%	2125	malt
10b	PivCl	92%	2125	natural rubber
10c	MeC_6H_4COCl	96%	2126	creosote
10d	BocCl	83%	2124	taffy
10e	$MeOC_6H_4COCl$	96%	2128	mild cherry
10f	NCC_6H_4COCl	90%	2128	old wood
10g	C_6H_5COCl	93%	2131	mild petroleum

Our initial investigations centered on commercial oxazoles **7** and **9** (Scheme 2). These compounds are readily metalated by treatment at −78 °C in THF with *n*-BuLi and allowed to react with an acyl chloride. Following warming to room temperature and stirring for 2 h, the desired (*Z*)-isocyanovinyl (**8**) and 2-isocyanophenyl (**10**) esters are obtained in good to excellent yields. Results are summarized in Table 1. All of these compounds exhibit isonitrile IR stretches in the normal range of 2124−31 cm^{-1}. That these derivatives include the ester functionality, widely regarded as giving pleasant organoleptic properties to organic compounds, stimulated our curiosity concerning their odor. Included in the table is a subjective assessment of the olfactory properties of isonitriles **8** and **10**.

Ugi reactions with isonitriles **8** and **10** should give enamide products similar to those derived from the "convertible" isonitrile 1-isocyanocyclohexene reported by Armstrong.[14] He showed that isocyanocyclohexene-derived Ugi products **11** could undergo acyl substitution to yield esters **13**. When R^1 = Ph, they may also cyclize to münchnones **12** that undergo 1,3-dipolar cycloaddition with alkynes to give pyrroles. The convertibility of an Ugi reaction product derived from **8a** was first examined (Scheme 3). Treatment of **14** under Armstrong's conditions (anhydrous HCl, MeOH, 55 °C, 3 h) provides **15** quantitatively. Two further reactions provide information concerning the mechanism of this conversion. The related Ugi product **16** was prepared from **10c** so that the portion of the amide derived from the isonitrile would be nonvolatile and easily traceable. When treated with HCl/MeOH, **16** is converted quantitatively to **15** and benzoxazole **17** (Scheme 4). Whether Ugi reaction products derived from **10** can form a münchnone was

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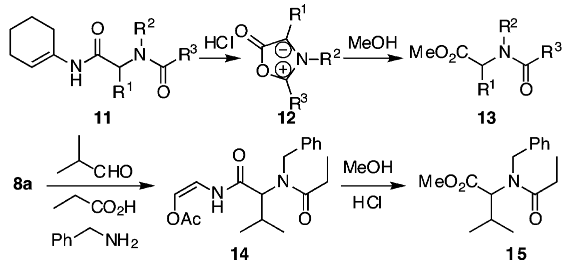
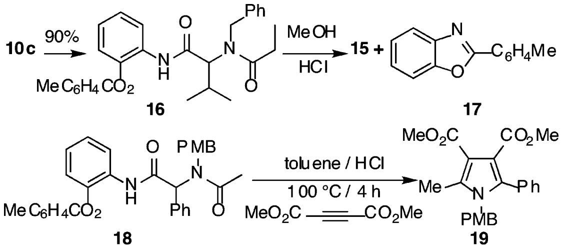
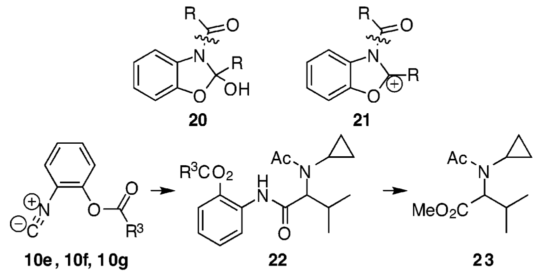
Scheme 3. Convertible Isonitriles



Scheme 4. A Conversion Reaction and Evidence about Its Mechanism



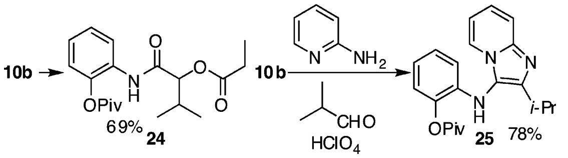
Scheme 5. Test for Possible Intermediates in the Conversion Reaction



investigated by treatment of **18** with DMAD. Pyrrole **19** is obtained in 58% yield, and **17** is obtained in 72% yield. For comparison, Armstrong prepared **19** from the corresponding Ugi product of 1-isocyanocyclohexene in 63% yield. It is possible that the formation of **17** occurs via simple methanolysis to 2-aminophenyl toluate, which then cyclizes. Also possible is the intermediacy of **20** or **21**, which could be strong acylating agents. To address their potential involvement in the conversion reaction, three derivatives of **10** with diverse para substituents were prepared (**10e**−**g**). An electron-withdrawing group should accelerate the formation of **20** and an electron-donating group should accelerate the formation of **21**, and thereby their conversion reactions (Scheme 5). Ugi products **22** were derived from **10e**−**g**, and their conversions to **23** were examined. When treated with HCl/MeOH at room temperature, conversion of **22e** to **23** requires 0.5 h, while **22g** requires 1 h and **22f** requires 2.5 h. These results suggest the possible involvement of **21** in the conversion reaction.

Isonitriles **10** are suitable for other multicomponent reactions, such as the Passerini reaction and the Gröbcke reaction of 2-aminopyridines with aldehydes,[15] as exemplified in the products **24** and **25** (Scheme 6).

Scheme 6. Other Multicomponent Reactions of Convertible Isonitriles



Despite the significantly modified odor properties of **8** and **10**, their reactivity does not seem to be compromised; they undergo the classical multicomponent reactions of isonitriles. As convertible isonitriles, they are far superior to isocyanocyclohexene, which we have found difficult to prepare in quantities larger than a few hundred milligrams, unstable on storage, and of vile odor. Conversion of Ugi products derived from isocyanocyclohexene to esters also requires more demanding reaction conditions than Ugi products derived from **10**. Studies of **10e** have so far shown it stable at room temperature under nitrogen. We have had no difficulty preparing **10e** in batches as large as 5 g.

Owing to their combination of two different functionalities having distinctive odors, molecules **8** and **10** may also pose interesting questions for theories of olfaction.

Supporting Information Available: Experimental descriptions and characterization for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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