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A practical and inexpensive 'convertible' isonitrile for use in multicomponent reactions

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This Letter is dedicated to our dear friend and colleague, Harry H. Wasserman, in honor of his many years of service to Tetrahedron Publications and on the occasion of his 90th birthday

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ABSTRACT

N-tert-Butylamides are readily converted into the corresponding carboxylic acids by simple nitrosation. The process, which occurs under mild nonaqueous conditions, leaves carboxylic esters untouched and transforms multicomponent reaction products into useful building blocks for further synthetic elaboration.

The use of multicomponent reactions (MCRs) in generating complex small molecule arrays continues to play an important role in drug discovery and development.[1] By concurrently forming several new bonds in a one-pot procedure and with high atom economy, MCRs provide rapid access to chemically diverse structures in an operationally simple manner. Recently, the ability to perform iterative[2] as well as higher-order[3] MCRs has significantly increased the molecular complexity that can be obtained in chemical libraries.

The most versatile MCRs typically incorporate an isonitrile as one reactant,[4] which leads to a new secondary carboxamide group in the product. Mild methods for converting such amides into carboxylic acids or esters would enhance the utility of MCR products for example, as building blocks in iterative MCRs or in other synthetic transformations.

To date, several 'convertible' isonitriles have been developed, including 1-cyclohexenylisonitrile,[5] (β-isocyanoethyl)alkylcarbonates,[6] and various fragrant oxazole- and benzoxazole-derived isonitriles.[7] While these isonitriles have all demonstrated utility in the Ugi reaction, none has been shown to be 'convertible' in α-acyloxyamide (i.e., Passerini) products. Moreover isonitriles whose amides convert into esters create a new selectivity problem in Passerini reaction products, which already contain hydrolyzable ester functionality.

We recognized that *t*-butylisonitrile might serve as a useful convertible isonitrile in Passerini and related reactions. Among other advantages, *t*-butylisonitrile gives rise in MCRs to *N*-*t*-butylamides, whose characteristic NMR singlet simplifies the analysis of multicomponent reaction products. We now demonstrate that nitrosation of various *N*-*t*-butylamides affords carboxylic acids under non-hydrolytic conditions.

The nitrosation of secondary carboxamides and thermal transformations of the derived *N*-alkyl-*N*-nitrosamides, first investigated systematically by White,[8] have been the subject of extensive mechanistic study over the past half-century, including recent theoretical calculations.[9] *N*-Alkyl-*N*-nitrosamides undergo a highly solvent-dependent thermal rearrangement at 80–100 °C via diazenes to products derived either from diazoalkane or carbocation intermediates. By controlling and/or intercepting such intermediates, our laboratory several years ago developed several new synthetic transformations of amines via their derived nitrosamides to alcohols, phosphotriesters alkenes, alkynes, enol acetates, and aldehydes.[10]

Building on those earlier findings, we reasoned that the rearrangement of *N*-nitroso-*N*-*t*-butylamides should strongly favor the carbocationic pathway shown in Eq. 1, thus achieving a mild amide-to-acid conversion while releasing innocuous gaseous byproducts.

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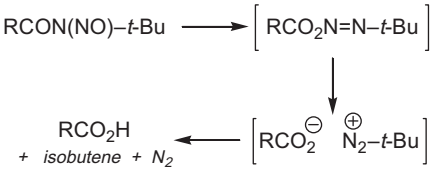


(1)

The nitrosation of *N*-cyclohexylamides has been reported in the literature to afford modest yields of carboxylic acids,[8b] but to the best of our knowledge nitrosation of secondary amides bearing tertiary alkyl substituents has not been described. The dealkylation of *N*-*t*-butylamides to acids has only been achieved non-oxidatively using strong acids.[11]

To test our hypothesis, a series of simple *N*-*t*-butylamides were nitrosated using $NaNO_2$ in 1:2 acetic acid/acetic anhydride (Method A) as first described by White. These conditions were chosen for low cost and ready availability. The results, shown in Table 1, illustrate that nitrosation and rearrangement proceed under mild conditions to afford the desired carboxylic acid in excellent yield.

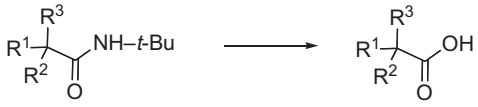
Next a representative group of α-acyloxyamides **1a–e** (Scheme 1) was prepared using the Passerini three-component reaction following standard procedures for reacting the appropriate carbonyl compound, carboxylic acid, and *t*-butylisonitrile.

Initially nitrosation of **1a–e** was performed using Method A, which afforded variable results. The more sterically hindered Passerini compounds **1c–e** reacted sluggishly, but cleanly, using Method A, with recovered starting material being the only other product. Superior results were obtained using the more reactive nitrosating reagent N_2O_4 with sodium acetate in CCl_4 (Method B). Much higher yields and complete conversion were achieved with amides **1c–e** (Table 2).

Of particular interest was the fact that the *t*-butylamides in **1a–e** were transformed into the corresponding carboxylic acids without affecting the carboxylic esters present in each substrate. Notably **1d**, which incorporates two ester groups (one of which is sterically uncongested) was transformed into acid-diester **2d** in excellent yield (Method B), thus highlighting the non-hydrolytic nature of this transformation.

Next a series of α-hydroxy-*N*-*t*-butylamides **1f–h** (Table 3) were prepared by a recently reported variation of the Passerini two-component reaction using boric acid as the Bronsted acid.[12] Method A was not compatible with these substrates. When **1f** was nitrosated under those conditions, acetylation of the free alcohol group afforded acetoxyacid **2e** as the major product. However, Method B furnished the desired hydroxyacids in excellent yield (Table 3).

t-Butylisonitrile has been widely used in Ugi four-component condensations, thus it was of interest to learn whether the derived



1 **2**

(a) R^1= Ph, R^2= H, R^3= OAc
(b) R^1= $PhCH_2CH_2$, R^2= H; R^3= OAc
(c) R^1= $PhCH_2CH_2$, R^2= H; R^3= OBz
(d) R^1= $PhCH_2CH_2$, R^2= H; R^3= $OCO(CH_2)_3CO_2CH_3$
(e) R^1,R^2= $(CH_2)_5$; R^3= OAc

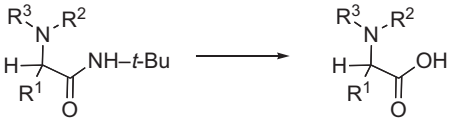
Scheme 1.

Table 2
Conversion of Passerini compounds **1** to carboxylic acids

Reactant	Carboxylic acid	% Yield (Method)
1a	**2a**	79 (A)
1b	**2b**	95 (A)
1c	**2c**	52 (A)
		81 (B)
1d	**2d**	63 (A)
		95 (B)
1e	**2e**	33 (A)
		89 (B)

Table 3
Conversion of hydroxy-*t*-butylamides to carboxylic acids

Hydroxy-*t*-butylamide	Carboxylic acid	% Yield
1f R^1,R^2 = $(CH_2)_5$; R^3 = OH	**2f**	87 (B)
1g R^1 = $PhCH_2CH_2$, R^2 = H; R^3 = OH	**2g**	99 (B)
1h R^1 = $CH_3(CH_2)_6$, R^2 = H; R^3 = OH	**2h**	98 (B)



3 4

(a) R^1= $PhCH_2CH_2$, R^2= Bz, R^3= Bn
(b) R^1= $PhCH_2CH_2$, R^2= Ac, R^3= Bn
(c) R^1= $PhCH_2CH_2$, R^2= Ac, R^3= CH_3
(d) R^1= $PhCH_2CH_2$, R^2= Bz, R^3= *n*-Bu
(e) R^1= Ph, R^2= Bz, R^3= Bn

Scheme 2.

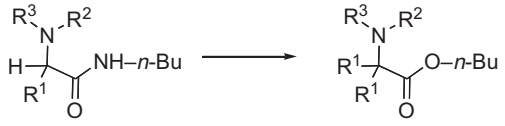
Table 1
Nitrosation/rearrangement of *t*-butylamides leading to carboxylic acids[a]

N-*t*-Butylamide	Carboxylic acid	% Yield[b]
N-*t*-Butyl-*p*-bromobenzamide	*p*-Bromobenzoic acid	92
N-*t*-Butyl-*p*-methoxybenzamide	*p*-Methoxybenzoic acid	99
N-*t*-Butyl-hydrocinnamide	$PhCH_2CH_2CO_2H$	92
N-*t*-Butyl-octanamide	Octanoic acid	65[c]
Cyclohexanecarboxylic acid *N*-*t*-butylamide	Cyclohexanecarboxylic acid	66[c]

[a] Conditions: 2 × 10 equiv $NaNO_2$; 1:2 acetic acid/acetic anhydride, 0 °C, 3 h; then stirring 16 h at rt followed by concentration and partitioning between ether and aq $NaHCO_3$.
[b] Reported yields are corrected for small quantities (usually 2–8%) of recovered starting material.
[c] Control workups established that ca. 25% of this volatile product was lost by rotary evaporation during workup.

secondary/tertiary diamides could be 'converted' into the corresponding amidoacids. A test series of diamides were prepared (Scheme 2) using *t*-butylisonitrile following the standard Ugi protocol in methanol. Somewhat surprisingly, we observed no nitrosation of diamide **3a** using Method A conditions. To test whether steric effects at the tertiary amide group were a factor, diamides **3b** and **3c** were also subjected to Method A conditions, and in each case starting material was recovered nearly quantitatively. Diamides **3d–e** behaved similarly.

Nitrosations of **3a–e** using the more potent nitrosating agent N_2O_4 (Method B) were also unpromising, affording at best trace quantities of acids **4a–e** along with (mostly) unreacted diamide and several uncharacterized byproducts. Difficulties in nitrosating *N*-cyclohexyl- and other sterically hindered amides have previously been reported.[13]



5 6

(a) R^1= Ph, R^2= Bz, R^3= Bn
(b) R^1= Ph, R^2= Ac, R^3= Bn

Scheme 3.

The resistance of Ugi amides **3a–e** to nitrosation made it possible to selectively deprotect a Passerini *t*-butylamide in the presence of an Ugi *t*-butylamide. Nitrosation of a 1:1 mixture of **1b** and **3e** using Method A afforded **2b** in 54% yield (96% based on recovered **1b**) compound **3e** was recovered quantitatively.

It was of interest to determine whether *n*-butylisonitrile might serve as a convertible isonitrile for Ugi reactions by enabling an amide-to-ester conversion of the corresponding *N*-(*n*-butyl)amide product.[14] Ugi compounds **5a–b** (Scheme 3) incorporating *n*-butylisonitrile underwent smooth nitrosation using Method A to afford the corresponding *N*-nitrosoamides (not shown) following the standard workup. Upon heating to reflux in hexane, the desired *n*-butylesters **6a** and **6b** were produced in 80% and 83% overall yield, respectively.

In summary, the studies presented herein demonstrate that *t*-butylisonitrile can serve as an inexpensive, efficient, and readily available 'convertible isonitrile' in Passerini and related multicomponent reactions. To the best of our knowledge, *t*-butylisonitrile is the first isonitrile whose amide-to-acid 'conversion' is compatible with preexisting ester functionality in MCR products. We further show that *n*-butylisonitrile may provide a viable alternative to other convertible isonitriles for amide-to-ester transformations in Ugi MCR products.

Acknowledgments

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Supplementary data

Supplementary data (representative experimental procedures and complete spectroscopic data for new reactants and products shown in Tables 1–3) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.156.

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