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Facile reaction of carboxylic acids with isonitriles in toluene

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ABSTRACT

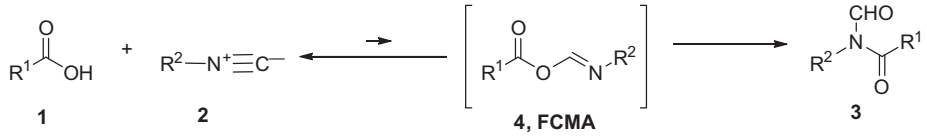
Isonitriles react with low concentrations of carboxylic acids in toluene at 110 °C to give *N*-formylamides in yields generally above 70%. These concentrations can be obtained either by syringe pump addition of a toluene solution of the acid, or by using a suspension of the acid if it has limited solubility in toluene at room temperature.

Treatment of carboxylic acids (**1**) with isonitriles (**2**) has recently been shown to produce *N*-formylamides (**3**).[1] Experiments[1,2] and calculations[3] support the mechanism in Scheme 1, in which **1** and **2** initially form a formimidate carboxylate mixed anhydride, or FCMA (**4**); a 1,3 O → N acyl transfer then gives **3**.

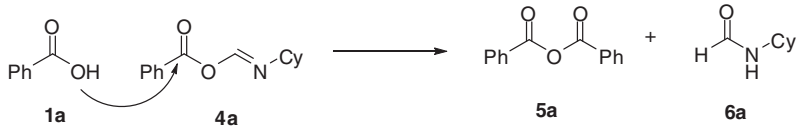
The original reports involved halogenated solvents with microwave heating, at or above 150 °C. In order to determine appropriate conditions for kinetic studies we have examined the reaction in several solvents at various temperatures, and have found that it proceeds readily in toluene at 110 °C with conventional heating. However, with benzoic acid (**1a**) and cyclohexyl isonitrile (**2a**) each 0.02 M in toluene (1:1 ratio), we obtained only a 43% yield of the *N*-formylamide and observed two major side products:[4] benzoic anhydride (**5a**) and *N*-cyclohexylformamide (**6a**). On the hypothesis[1f] that they arose from interception by **1a** of the intermediate **4a**, as depicted in Scheme 2, we used a syringe pump to add the acid slowly. A 61% yield of the *N*-formylamide **3a** was isolated when a 0.02 M stock solution of **1a** was added to 2 equiv of **2a** in 2 mL toluene over the course of 45 h at 110 °C.

The applications of RCO_2H/RNC coupling have largely been in peptide synthesis.[1a–d,5] Relatively few simple aliphatic isonitriles have been employed, and to our knowledge no aromatic ones. We have therefore tried our toluene/110 °C conditions on the combinations in Tables 1 and 2.

The results show the reaction to be remarkably tolerant of functional groups, for example, nitro (**3m** and **3n**), halo (**3i, 3n, 3o, 3u**), cyano (**3t–3x**), pyridyl (**3o**), thienyl (**3h** and **3i**), carbomethoxy (**3j**), and acetyl (**3p–3s**). It does not affect the isolated double bond in **3f**



Scheme 1. Reaction of carboxylic acids with isonitriles.



Scheme 2. Proposed mechanism of side product formation.

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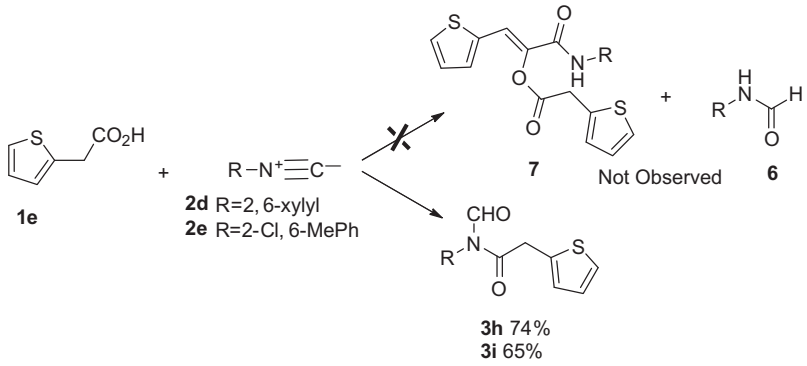
Table 1
Preparation of *N*-formylamides (**3**) by the syringe pump addition of acids (**1**) to isonitriles (**2**)

Product	Acid, R^1 =	Isonitrile, R^2 =	Yield (%)
3a	Ph (**1a**)	*cyclo*-Hex (**2a**)	61
3b	$PhCH_2CH_2$ (**1b**)	**2a**	72
3c	**1b**	*n*-C_5H_{11} (**2b**)	55
3d	**1b**	4-MeC_6H_4 (**2c**)	68
3e	**1b**	2,6-Xylyl (**2d**)	61
3f	CH_2CHCH_2 (**1c**)	**2d**	66
3g	PhCHCH (**1d**)	**2d**	75
3h	2-Thiopheneacetic (**1e**)	**2d**	74
3i	**1e**	2-Cl-6-MeC_6H_3 (**2e**)	65
3j	$MeO_2C(CH_2)_6$ (**1f**)	2,6-Xylyl (**2d**)	57
3k	$MeOCH_2CH_2OCH_2$ (**1g**)	4-$MeOC_6H_4$ (**2f**)	72

Table 2
Preparation of *N*-formylamides (**3**) from isonitriles (**2**) and acids (**1**) that are not soluble in toluene at room temperature

Product	Acid, R^1 =	Isonitrile, R^2 =	Yield (%)
3m	4-$NO_2C_6H_4$ (**1i**)	*cyclo*-Hex (**2a**)	70
3n	1i	3-BrC_6H_4 (**2g**)	67
3o	Picolinic (**1j**)	2-Cl-6-MeC_6H_3 (**2e**)	68
3p	4-Me(O)C-C_6H_4 (**1k**)	*cyclo*-Hex (**2a**)	70
3q	**1k**	4-$MeOC_6H_4$ (**2f**)	80
3r	**1k**	4-MeC_6H_4 (**2c**)	89
3s	**1k**	4-$Et_2NC_6H_4$ (**2h**)	79
3t	4-NCC_6H_4 (**1l**)	*cyclo*-Hex (**2a**)	84
3u	**1l**	3-$CF_3C_6H_4$ (**2i**)	63
3v	**1l**	Ph (**2j**)	83
3w	**1l**	4-$Et_2NC_6H_4$ (**2h**)	94
3x	**1l**	2-Naphthyl (**2k**)	65



Scheme 3.

or the conjugated one in **3g**, the ether linkage in **3k**, or the tertiary amine nitrogens in **3s** and **3w**. Addition of the acid **1e** to the isonitriles **2d** and **2e** produced only the expected products **3h** and **3i**, and no **7** (Scheme 3). (Alkenes such as **7** are the exclusive products when many arylacetic acids are treated with isonitriles under microwave conditions.[6])

Of course a syringe pump is impractical with acids that are not soluble in toluene at room temperature. With acids that dissolve completely in toluene at 110 °C, that is, 4-methoxybenzoic acid (**1h**), 4-nitrobenzoic acid (**1i**), and picolinic acid (**1j**), mixed results were obtained. Treating **1i** with **2a** or **2g** gave a good isolated yield of the *N*-formyl amide **3m** or **3n**, whereas treating **1h** with **2a** gave a substantial amount of the anhydride **5b** (about 3:1 relative to the *N*-formyl amide **3l**). Presumably the more basic **1h** is more nucleophilic and better at intercepting the FCMA. The medicinally relevant[7] acid **1j** reacts very slowly with isonitrile **2e**, requiring 3 days; we speculate that formation of the corresponding FCMA is slow.

Acids with limited solubility in toluene even at 110 °C mimic the effect of slow addition. Their concentrations remain low, which limits their ability to attack the FCMA; yields of the *N*-formyl amide are thus high. Examples are offered by the reaction of **1k** (0.05 M in toluene) with the isonitrile **2a**, **2c**, **2f**, or **2h** for 48 h, giving **3p–3s** (Table 2). Likewise, the reaction of **1l** with **2a, 2h, 2i, 2j,** or **2k** for 24 h gives **3t**–**3x** in good to excellent yields, although longer reaction times result in significant decarbonylation of the formyl groups in these products.

In summary, we have found (1) that aromatic as well as aliphatic isonitriles react with carboxylic acids in toluene at 110 °C to give good yields of *N*-formylamides, and (2) that either slow addition or limited solubility of the acid suppresses the formation of an anhydride as a byproduct.

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Supplementary data

Supplementary data (experimental details, characterization data and copies of ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.122.

References and notes

1. (a) Li, X.; Danishefsky, S. J. *Nat. Protoc.* **2008**, *3*(10), 1666; (b) Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*(16), 5446; (c) Wu, X. Y.; Li, X.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 1523; (d) Wu, X. Y.; Yuan, Y.; Li, X.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 4666; (e) Li, X.; Yuan, Y.; Berkowitz, W. F.; Todaro, L. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*(40), 13222; (f) Li, X.; Yuan, Y.; Kan, C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13225.
2. (a) Yuan, Y.; Zhu, J. L.; Li, X.; Wu, X. Y.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*(20), 2329; (b) Stockdill, J. L.; Wu, X. Y.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*(36), 5152.
3. (a) Jones, G. O.; Li, X.; Hayden, A. E.; Houk, K. N.; Danishefsky, S. J. *Org. Lett.* **2008**, *10*(18), 4093; (b) Marcelli, T.; Himo, F. *Eur. J. Org. Chem.* **2008**(28), 4751.
4. (a) Gautier, A. *Ann. Chim. (Paris)* **1869**, *17*, 103 (This article has often been cited incorrectly. Although the chemistry of interest does not begin until page 223, the article begins on page 103); (b) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1.
5. Wu, X. Y.; Stockdill, J. L.; Wang, P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 4098.
6. Basso, A.; Banfi, L.; Galatini, A.; Guanti, G.; Rastrelli, F.; Riva, R. *Org. Lett.* **2009**, *11*, 4068.
7. Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 8082.