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Facile Amide Bond Formation from Carboxylic Acids and Isocyanates

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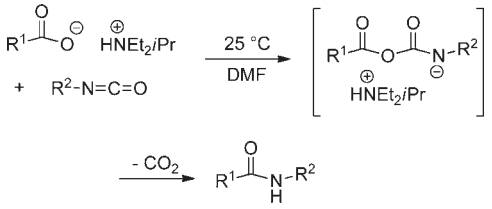
ABSTRACT



A wide variety of carboxylic acids in the form of their salts condense with aryl isocyanates at room temperature with loss of carbon dioxide to give the corresponding amides in high yield. Application of the reaction to acyl isocyanates gives unsymmetric imides. The reaction is compatible with hydroxyl groups and both Fmoc and Boc protecting groups for amines and is applicable to aliphatic, aromatic, and heteroaromatic acids.

Amide bond formation is, in principle, one of the simplest chemical transformations requiring only the condensation of an amine with a carboxylic acid with the extrusion of a molecule of water. Yet, it is also one of the most important of reactions, as amides are important constituents of many fine chemicals, drugs, chemical intermediates, biopolymers, and polymers. Indeed, amide bond formation is one of the most common chemical transformations in the pharmaceutical industry and in scaled up reactions.[1] As such, it is difficult to underestimate the importance of amides in both the bulk, specialty and polymer fields. Such condensations are achieved through activation of the acid, either by conversion to an acyl chloride or anhydride or, for fine chemicals, by means of a coupling reagent. Such protocols are inherently inefficient generating stoichiometric quantities of byproduct that can be both difficult and expensive to remove, resulting in the frequent identification of amide-forming reactions as an area in need of improvement from a chemical perspective.[1] Accordingly, much attention has been devoted to the design of improved coupling reagents[2] and the development of alternative methods such as, for example, the reaction of carboxylic[3] or thiocarboxylic acids[4] with isonitriles and other reagents, of thiocarboxylic acids with azides,[5] and the recent oxidative coupling of bromonitroalkanes with amines.[6] For our part, we have described the facile condensation of thiocarboxylic acids with readily available isocyanates and isothiocyanates leading directly to amide bonds with the formation of only carbon oxysulfide or carbon disulfide as stoichiometric byproduct.[7] Here, we outline a method for amide bond formation that responds to many of the principles of atom economy;[8] the room-temperature condensation of widely available carboxylic acids with aryl and other electron-deficient isocyanates that leads to the high-yield formation of anilides with only carbon dioxide as byproduct.

(1) (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347. (b) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J., J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaksh, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411–420. (c) Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Process Res. Dev.* **2005**, *9*, 253–258.

(2) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606–631.

(3) Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448.

(4) (a) Stockdill, J. L.; Wua, X.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 5152–5155. (b) Wang, P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 17045.

(5) (a) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754–7755. (b) Kolakowski, R. V.; Shangguan, N.; Sauers, R. R.; Williams, L. J. *J. Am. Chem. Soc.* **2006**, *128*, 5695–5702. (c) Merkx, R.; Brouwer, A. R.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005**, *7*, 1125–1128.

(6) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027–1033.

(7) Crich, D.; Sasaki, K. *Org. Lett.* **2009**, *11*, 3514–3517.

(8) (a) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686–694. (b) Trost, B. M. *Science* **1991**, *254*, 1471–1477. (c) Sheldon, R. A. *Chem. Commun.* **2008**, 3352–3365.

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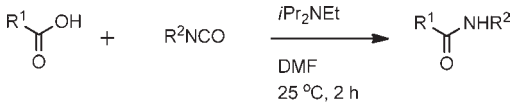
Table 1. Amide Bond Formation from Carboxylate Salts and Isocyanates



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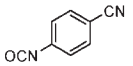
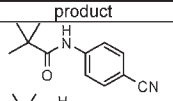
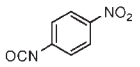
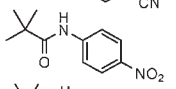
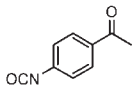
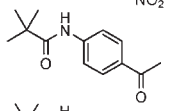
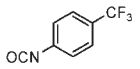
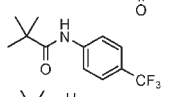
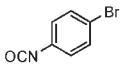
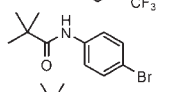
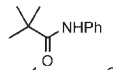
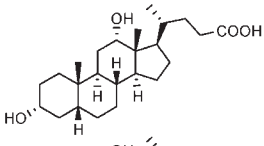
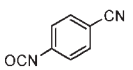
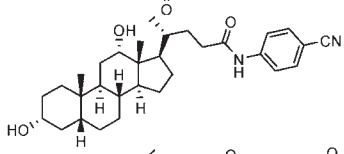
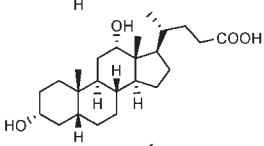
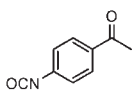
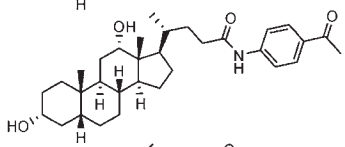
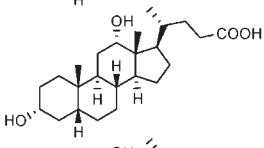
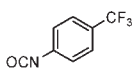
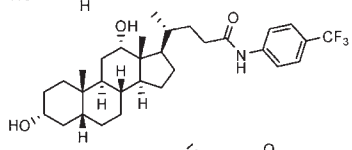
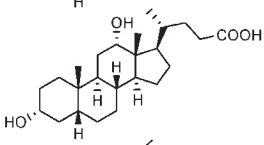
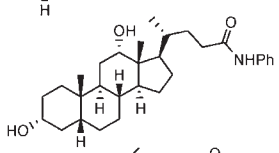
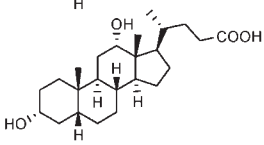
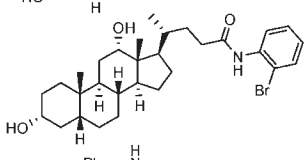
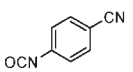
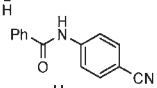
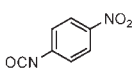
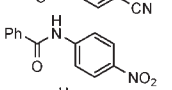
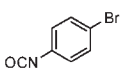
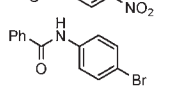
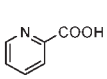
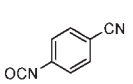
1				90
2				93
3				88
4				82
5				85
6		PhNCO		77[a]
7				85
8				86
9				81
10[a]		PhNCO		40
11				16
12	PhCOOH			83
13	PhCOOH			79
14	PhCOOH			75
15				90
16[a]		PhNCO		54
17[b]				59[b]
18				80

Table 1. Continued

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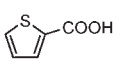
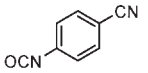
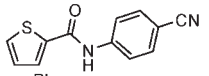
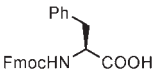
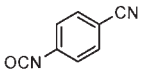
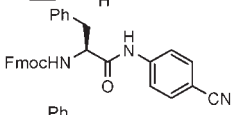
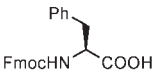
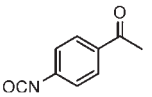
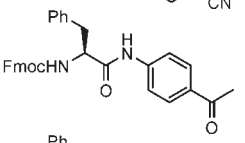
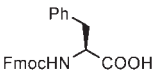
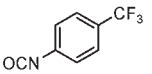
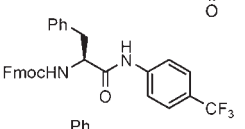
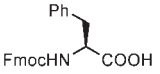
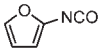
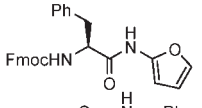
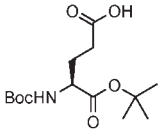
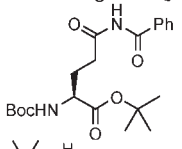
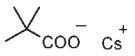
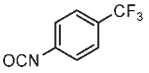
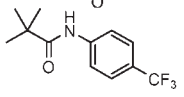
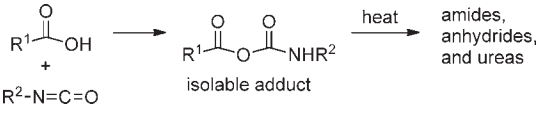
19				82
20				82[c]
21				80[c]
22				71[c]
23[b]				45[c]
24				84[c]
25[c]				88[d]

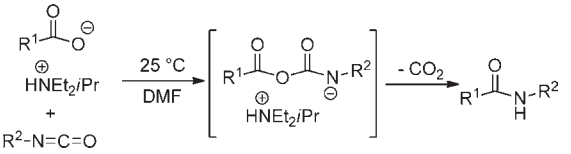
[a] 16 h reaction time. [b] Reaction conducted under strictly anhydrous conditions. [c] The ee of the amino acid based products has not been determined. [d] This reaction was conducted without the inclusion of $i\text{Pr}_2\text{EtN}$.

The condensation of carboxylic acids with isocyanates[9] has been known for almost 120 years[10] and has been shown to afford an adduct whose stability is a function of the two substituents (Scheme 1).[11] The thermal decomposition of this adduct was variously promoted as being a source of symmetrically *N*,*N*′-disubstituted ureas, of symmetric carboxylic anhydrides, and of amide and even peptide bonds.[12] With respect to the formation of amide bonds, Kricheldorf and Leppert later reported the more facile condensation of thioacids with isocyanates and the generally lower decomposition temperatures of the intermediate adducts.[13] The development of improved methods for the synthesis of thiocarboxylic acids[5a,14] in conjunction with the use of their highly nucleophilic cesium salts enabled us transform this latter reaction into a broadly useful synthetic method,[7] but nevertheless, the much broader commercial availability of the carboxylic acids themselves prompted us to investigate their condensation with isocyanates more closely. In particular, and in contrast to the historical precedent which employed the conjugate acids, we were attracted to the condensation of carboxylate salts with isocyanates in the expectation that the intermediate adduct, in its

Scheme 1. Adduct Formation from Carboxylic Acids and Isocyanates



Scheme 2. Amide Bond Formation from Carboxylate Salts and Isocyanates



(9) As isocyanates are typically produced from amines and phosgene, which itself is available industrially in a very clean process from carbon monoxide and chlorine, the production of isocyanates can be viewed as an efficient and clean process. Zhang, T.; Troll, C.; Rieger, B.; Kintrup, J.; Schlueter, O. F.-K.; Weber, R. *Appl. Catal. A, Gen.* **2009**, *365*, 20–27 and references cited therein.

(10) (a) Haller, A. *C. R. Acad. Sci.* **1895**, *120*, 1326–1329. (b) Haller, A. *C. R. Acad. Sci.* **1895**, *121*, 189–193.

(11) (a) Dieckmann, W.; Breest, F. *Ber. Deutsch. Chem. Ges.* **1906**, *39*, 3052–3055. (b) Naegeli, C.; Tyabji, A. *Helv. Chim. Acta* **1934**, *17*, 931–957. (c) Naegeli, C.; Tyabji, A. *Helv. Chim. Acta* **1935**, *18*, 142–160. (d) Petersen, S. *Liebigs Ann. Chem.* **1949**, *562*, 205–229. (e) Motoki, S.; Saito, T.; Kagami, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 775–776.

(12) (a) Goldschmidt, S.; Wick, M. *Liebigs Ann. Chem.* **1952**, *575*, 217–231. (b) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 569–583. (c) Schuemacher, A. C.; Hoffmann, R. W. *Synthesis* **2001**, 243–246.

(13) Kricheldorf, H. R.; Leppert, E. *Makromol. Chem.* **1973**, *167*, 47–68.

(14) (a) Crich, D.; Sana, K.; Guo, S. *Org. Lett.* **2007**, *9*, 4423–4426. (b) Crich, D.; Sana, K. *J. Org. Chem.* **2009**, *74*, 7383–7388.

deprotonated form, would readily extrude carbon dioxide to give amides (Scheme 2), for which limited precedent was found in a report on the accelerated decomposition in pyridine as solvent.[12]

In the event, our expectations were borne out, and the simple stirring of a wide variety of carboxylic acids with aryl and other electron-deficient isocyanates in the presence of a hindered amine in dimethylformamide solution at room temperature provided good to excellent yields of anilides and other substituted amides in a matter of hours (Table 1).

Inspection of Table 1 reveals that the reaction is compatible with a wide range of electron-deficient aryl isocyanates and both aliphatic and aromatic acids and tolerates the presence of free hydroxyl groups. The reaction is also compatible with both Fmoc- and Boc-protected amino acids and when applied to an *N*-acyl isocyanate (entry 24) results in the high-yield formation of an unsymmetrical imide. With phenyl isocyanate itself, the condensation is somewhat slower (entries 6, 10, and 16) but still affords very respectable yields on stirring for a longer time at room temperature. The sterically bulky *o*-bromophenyl isocyanate on the other hand proved to be somewhat recalcitrant (entry 11). Heteroaromatic isocyanates also react with simple carboxylate salts to give heteroaromatic amides as illustrated by the examples of Table 1, entries 17 and 23. A final example (Table 1, entry 25) illustrates the successful use of a cesium carboxylate salt in place of the ammonium carboxylates that we have employed predominantly. Overall, while not a panacea to all problems, the reaction is broadly comparable in scope to the condensation of thioacids with electron-deficient azides but clearly is of broader application as it does not suffer from the need for prior synthesis of thioacids.[5]

In summary, the room-temperature condensation of carboxylate salts with aryl and other electron-deficient isocyanates to the corresponding amides and carbon dioxides is an operationally simple, effective, and atom-economical protocol. In view of the wide commercial availability of the substrates, and the general importance of amide bonds, we anticipate that it should find extensive use in organic and medicinal chemistry.

Supporting Information Available. Full experimental details and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. References 12b and c were added in the version reposted March 28, 2011.