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Reaction of Thioacids with Isocyanates and Isothiocyanates: A Convenient Amide Ligation Process

David Crich* and Kaname Sasaki

Centre Scientifique de Gif, Institut de Chimie des Substances Naturelles, 1 Avenue de la Terrasse, 91198 Gif-sur-Yvette, France, and Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, Michigan 48202

dcrich@icsn.cnrs-gif.fr

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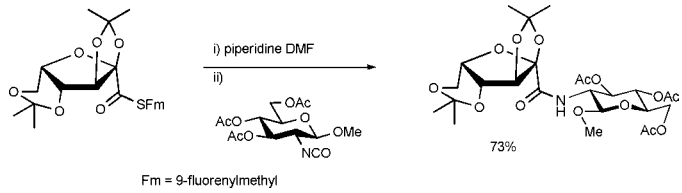
ABSTRACT



Thiocarboxylates, prepared conveniently by cleavage of 9-fluorenylmethyl or trimethoxybenzyl thioesters, react at room temperature with isocyanates and isothiocyanates to give amide bonds in good to excellent yield. A carboxylate salt is also shown to react with an electron-deficient isocyanate to give the corresponding amide in excellent yield at room temperature.

Given the widespread availability of amines and of carboxylic acids, amide bond forming reactions are necessarily some of the most widely applied transformations in parallel synthesis and combinatorial chemistry. The needs for atom ecomony, ever milder conditions, and greater selectivity combine to drive the search for new and improved methods for the formation of amide bonds.[1] The condensation of isocyanides with carboxylic acids has recently received much interest in this regard,[2] and this despite the relatively limited range of commercially available isocyanides and the somewhat forcing reaction conditions. Our attention was caught by a little known reaction[3] involving condensations of the much more widely available isocyanates and isothiocyanates with monothiocarboxylates, which result in the formation of amides with loss of a simple, volatile byproduct, carbon oxysulfide or carbon disulfide, respectively. Although this reaction was described in 1973 for use with very simple substrates, it has seen very limited application subsequently,[4] perhaps due to the relative paucity of commercially available thioacids.[5] We reasoned that the advent of convenient mild methods for thioacid synthesis[6] would combine with this reaction to afford a convenient and mild method for amide formation and report here that this is indeed the case. In addition, we report promising preliminary results of a

(1) For recent advances see: (a) Bode, J. W *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765–775. (b) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852. (c) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447–2467.

(2) (a) Li, X.; Yuan, Y.; Kan, C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13225–13227. (b) Li, X.; Yuan, Y.; Berkowitz, W. F.; Todaro, L. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13222–13224. (c) Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448. (d) Jones, G. O.; Li, X.; Hayden, A. E.; Houk, K. N.; Danishefsky, S. J. *Org. Lett.* **2008**, *10*, 4093–4096. (e) Restrop, P.; Rebek, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 11850–11851.

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

(4) Beyond the original paper,[3] which itself has only been cited 14 times to date, we are only aware of four isolated examples of the reaction of isothiocyanates with simple thioacids (three with thioacetic acid and one with indolethioacetic acid) and of none between isocyanates themselves and thioacids. The four examples of isothiocyanates and thioacids all make use of heating to 60 or 80 °C to achieve the reactions described, and none of the four papers makes reference to the original work of Kricheldorf and Leppert.[3] (a) Gonda, J.; Martinkova, M.; Walko, M.; Zavacka, E.; Budesinsky, M.; Cisarova, I. *Tetrahedron Lett.* **2001**, *42*, 4401–4404. (b) Gonda, J.; Zavacka, E.; Budesinsky, M.; Cisarova, I.; Podlaha, J. *Tetrahedron Lett.* **2000**, *41*, 525–529. (c) Gonda, J; Bednarikova, M. *Tetrahedron Lett.* **1997**, *38*, 5569–5572. (d) Schoepfer, J.; Marquis, C.; Pasquier, C.; Neier, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1001–1002.

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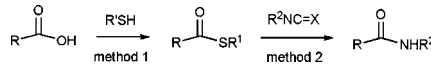
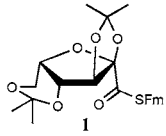
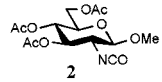
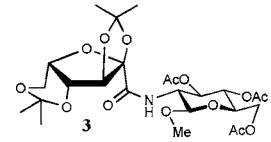
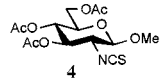
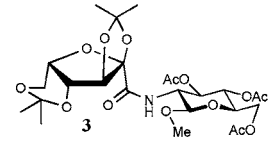
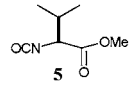
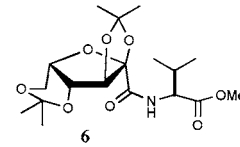
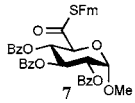
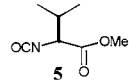
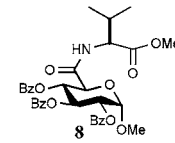
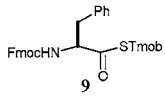
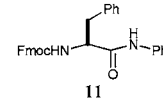
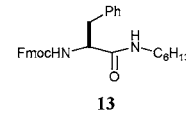
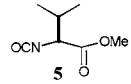
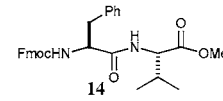
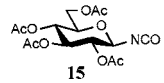
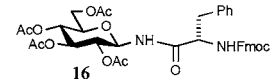
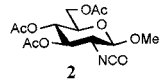
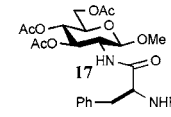
Table 1. Preparation of Thioesters and Their Reaction with Isocyanates and Isothiocyanates[a]



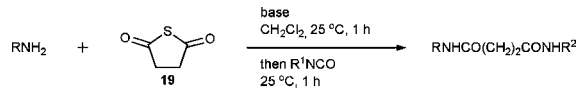
	preparation of $RCOSR^1$			$R^2NC=X$	preparation of $RCONHR^2$		
	method 1	thioester	yield		method 2	amide	yield
1	$NaH, (COCl)_2$ FmSH, pyr	 **1**	79%	 **2**	i) $RCOSR^1$, piperidine in DMF, 15 min, rt ii) R^2NCO, CH_2Cl_2, 6 h, rt	 **3**	73%
2		**1**		 **4**	i) $RCOSR^1$, piperidine in DMF, 15 min, rt ii) R^2NCS, CH_2Cl_2, 6 h, rt	 **3**	70%
3		**1**		 **5**	i) $RCOSR^1$, piperidine in DMF, 15 min, rt ii) R^2NCO, CH_2Cl_2, 6 h, rt	 **6**	76%
4	FmSH, EDCI, DMAP	 **7**	83%	 **5**	i) $RCOSR^1$, piperidine in DMF, 15 min, rt R^2NCO, CH_2Cl_2, 6 h, rt	 **8**	52%
5	TmobSH, EDCI, DMAP	 **9**	85%	PhNCO, **10**	i) $RCOSR^1$, TFA, Et_3SiH, CH_2Cl_2, 4 h, rt ii) R^2NCO, *i*-Pr_2NEt, CH_2Cl_2, 6 h, rt	 **11**	66%
6		**9**		$C_6H_{13}NCO$, **12**	i) $RCOSR^1$, TFA, Et_3SiH, CH_2Cl_2, 4 h, rt ii) R^2NCO, *i*-Pr_2NEt, CH_2Cl_2, 6 h, rt	 **13**	73%
7		**9**		 **5**	i) $RCOSR^1$, TFA, Et_3SiH, CH_2Cl_2, 4 h, rt ii) R^2NCO, *i*-Pr_2NEt, CH_2Cl_2, 6 h, rt	 **14**	68%
8		**9**		 **15**	i) $RCOSR^1$, TFA, Et_3SiH, CH_2Cl_2, 4 h, rt ii) R^2NCO, *i*-Pr_2NEt, CH_2Cl_2, 6 h, rt	 **16**	36%
9		**9**		 **2**	i) $RCOSR^1$, TFA, Et_3SiH, CH_2Cl_2, 4 h, rt ii) R^2NCO, *i*-Pr_2NEt, CH_2Cl_2, 6 h, rt	 **17**	30%

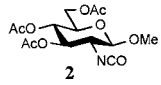
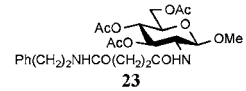
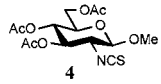
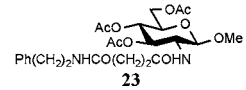
[a] The isocyanates used in this study were either commercial or prepared by reaction of the corresponding amine with phosgene in the presence of aqueous sodium bicarbonate in excellent yield. The isothiocyanate **4** was similarly prepared in quantitative yield by reaction of the amine with thiophosgene under phase transfer conditions.

comparable reaction between simple carboxylic acids and electron-deficient isocyanates, with loss of carbon dioxide, also leading to the formation of amide bonds.

The 9-fluorenylmethyl (Fm) thioesters are a readily prepared class of self-stable thioesters whose treatment with piperidine provides a convenient in situ means of entry into

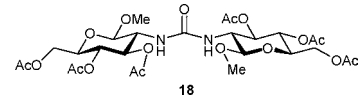
Table 2. Three-Component Coupling Reactions of Amines with Succinic Thioanhydride and Isocyanates or Isothiocyanates



	RNH_2	$R^1NC{=}X$	base	product	yield
1	$Ph(CH_2)_2NH_2$	PhNC=O	*i*-Pr_2NEt	$Ph(CH_2)_2NHCO(CH_2)_2CONHPh$, **20**	90%
2	$Ph(CH_2)_2NH_2$	$C_6H_{13}NC{=}O$	*i*-Pr_2NEt	$Ph(CH_2)_2NHCO(CH_2)_2CONHC_6H_{13}$, **21**	96%
3	$PhNH_2$	$C_6H_{13}NC{=}O$	*sym*-collidine	$PhNHCO(CH_2)_2CONHC_6H_{13}$, **22**	66%
4	$PhNH_2$	 **2**	*i*-Pr_2NEt	 **23**	30%
5	$PhNH_2$	 **4**	*i*-Pr_2NEt	 **23**	27%

thiocarboxylates.[6b] Their complement, the equally readily available 2,4,6-trimethoxybenzyl (Tmob) thioesters, release thioacids on exposure to trifluoroacetic acid.[6a] Accordingly, the Fm and Tmob thioesters were selected as the precursors of choice for thioacids in this study, and several were prepared as outlined in Table 1. The thiocarboxylates were released with piperidine or trifluoroacetic acid and triethylsilane, according to the thioester employed, and then exposed to either isocyanates or an isothiocyanate at room temperature, leading to the results set out in Table 1.

Entry 1 of Table 1 establishes the viability of the method and nicely illustrates the potential for application to a hindered tertiary thioacid. The release of the thioacid from the 9-fluorenylmethyl thioester by simple treatment with piperidine in DMF at room temperature is an important feature of this reaction and one that ensures compatibility with the two acetonide groups of the substrate. A comparison of entries 1 and 2 of Table 1 indicates that isocyanates and isothiocyanates behave more or less analogously in this chemistry; this observation led us to favor the more readily available isocyanates in the subsequent studies. Examples 3 and 4 of Table 1 illustrate the coupling of 9-fluorenylmethyl thioester derived thiocarboxylates with an α-isocyanato ester and hint at the potential for the application of this chemistry in the formation of neoglycopeptides.[7] Entries 5−9 of Table 1 use the 2,4,6-trimethoxybenzylthioester technology, with release of the thioacid by treatment with trifluoroacetic acid and triethylsilane, thereby enabling the generation of the thioacid in the presence of the 9-fluorenylmethoxy carbamate protecting group favored in solid-phase peptide synthesis. Entries 5 and 6 (Table 1) indicate that both aromatic and aliphatic isocyanates function correctly in this chemistry. Entry 7 of Table 1 is directed at the formation of a peptide bond, while entries 8 and 9 are again directed at the neoglycopeptide area. Only modest yields were obtained in entries 8 and 9, and in the latter case the symmetrical urea **18** was isolated as the major byproduct in 45% yield.


18

To further extend the scope of this reaction, we have also applied it to thioacids generated in situ through the nucleophilic ring-opening of succinic monothioanhydride (Table 2). Here too, generally good yields were obtained with the exception of the use of the sugar-based isocyanate **2** and isothiocyanate **4** (Table 2, entries 4 and 5). Entries 4 and 5 of Table 2 serve as a second comparison between the isocyanates and the isothiocyanates and support the earlier conclusion that the two have comparable reactivity in this chemistry.

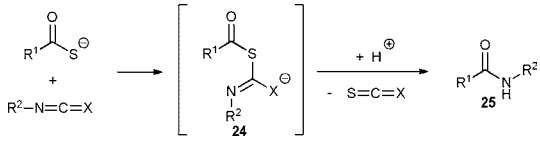
The general mechanism of the reaction of thiocarboxylates with isocyanates and isothiocyanates likely involves attack

(5) For other amide bond forming reactions employing thioacids, see: (a) Blake, J. *Int. Pept. Protein Res.* **1981**, *17*, 273–274. (b) Yamashiro, D.; Blake, J. F. *Int. J. Pept. Protein Chem.* **1981**, *18*, 383–392. (c) Blake, J.; Yamashiro, D.; Ramasharma, K.; Li, C. H. *Int. J. Pept. Protein Res.* **1986**, *28*, 468–476. (d) Yamashiro, D.; Li, C. H. *Int. J. Pept. Protein Res.* **1988**, *31*, 322–334. (e) Mitin, Y. V.; Zapevalova, N. P. *Int. J. Pept. Protein Chem.* **1990**, *35*, 352–356. (f) Høeg-Jensen, T.; Olsen, C. E.; Holm, A. *J. Org. Chem.* **1994**, *59*, 1257–1263. (g) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. H. *Science* **1994**, *266*, 776–779. (h) Tam, J. P.; Lu, Y.-A.; Liu, C.-F.; Shao, J. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12485–12489. (i) Messeri, T.; Sternbach, D. D.; Tomkinson, N. C. O. *Tetrahedron Lett.* **1998**, *39*, 1673–1676. (j) Messeri, T.; Sternbach, D. D.; Tomkinson, N. C. O. *Tetrahedron Lett.* **1998**, *39*, 1669–1672. (k) Crich, D.; Sharma, I. *Angew. Chem., Int. Ed.* **2009**, *48*, 2355–2358. (l) Hakimelahi, G. H.; Just, G. *Tetrahedron Lett.* **1980**, *21*, 2119–2122. (m) Rosen, T.; Lico, I. M.; Chu, D. T. W. *J. Org. Chem.* **1988**, *53*, 1580–1582. (n) Rakotomanomana, N.; Lacombe, J.-M.; Pavia, A. *Carbohydr. Res.* **1990**, *197*, 318–323. (o) McKervey, M. A.; O'Sullivan, M. B.; Myers, P. L.; Green, R. H. *J. Chem. Soc., Chem. Commun.* **1993**, 94–96. (p) Dudkin, V. Y.; Crich, D. *Tetrahedron Lett.* **2003**, *44*, 1787–1789. (q) Kolakowski, R. V.; Shangguan, N.; Sauers, R. R.; Williams, L. J. *J. Am. Chem. Soc.* **2006**, *128*, 5695–5702. (r) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754–7755. (s) Fazio, F.; Wong, C. H. *Tetrahedron Lett.* **2003**, *44*, 9083–9085. (t) Barlett, K. N.; Kolakowski, R. V.; Katukojvala, S.; Williams, L. J. *Org. Lett.* **2006**, *8*, 823–826. (u) Merkx, R.; van Haren, M. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *J. Org. Chem.* **2007**, *72*, 4574–4577. (v) Zhu, X. M.; Pachamuthu, K.; Schmidt, R. R. *Org. Lett.* **2004**, *6*, 1083–1085. (w) Merkx, R.; Brouwer, A. R.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005**, *7*, 1125–1128.

(6) (a) Vetter, S. *Synth. Commun.* **1998**, *28*, 3219–3223. (b) Crich, D.; Sana, K.; Guo, S. *Org. Lett.* **2007**, *9*, 4423–4426. (c) Crich, D.; Bowers, A. A. *Org. Lett.* **2007**, *9*, 5323–5325. (d) Crich, D.; Sasaki, K.; Rahaman, Md.; Bowers, Y. *J. Org. Chem.* **2009**, *74*, 3886–3893.

by the thiocarboxylate at the sp carbon to give an intermediate adduct **24** that undergoes rearrangement with loss of COS or CS_2 to give the final product **25** (Scheme 1).

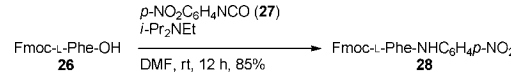
Scheme 1. Anticipated Reaction Mechanism



In view of this mechanism the somewhat poorer yields obtained with the carbohydrate-based isocyanates **2** and **15** (Table 1, entries 8 and 9; Table 2, entry 4) and the related isothiocyanate **4** (Table 2, entry 5) must be viewed in the light of the intermediate adduct, particularly in view of the good yield obtained with one of these isocyanates and a different thioacid (Table 1, entry 1). We speculate the reduced yields in these cases are due to the decomposition of the intermediate adduct **24** to the product with loss of COX being retarded by the multiplicity of electron-withdrawing β-C-O (acetoxy groups and/or acetals), which serves to reduce the nucleophilicity of the nitrogen atom in the adduct. A slower decomposition enables competing processes to intervene, such as the attack of a further equivalent of thiocarboxylate at the thiocarboxyl center in the adduct leading to the generation of a thioanhydride and liberation of the amine (Scheme 1). The symmetric urea byproducts (e.g., **18**) are then formed by attack of the liberated amine on the initial isocyanate. The good yield obtained with the more hindered thioacid **1** (Table 1, entry 1) is the result of the steric hindrance about the thiocarboxylate that retards attack of external nucleophiles on the intermediate adduct, thereby providing the time for the desired rearrangement to take place.[8]

We have also attempted the reaction of simple carboxylate esters with isocyanates, with a view to eliminating the dependency on thiocarboxylates. In accord with the earlier findings of Kricheldorf and Leppert, however, we find this to be an unproductive avenue for most isocyanates (and isothiocyanates) surveyed owing to the much reduced nucleophilicity of the carboxylates. However, in the case of suitably electron-deficient isocyanates, such reactions proceed in a satisfactory manner over a period of several hours at room temperature as illustrated in Scheme 2.

Scheme 2. Reaction of a Carboxylate with an Electron-Deficient Isocyanate



The reaction that we describe overall is closely related to the reaction of thiocarboxylic acids with azides[5l−w] but is potentially of broader scope for combinatorial and parallel synthesis applications owing to the much wider commercial availability of isocyanates. Although we have not investigated the possibility, we anticipate that, as in the case of the azide reaction, selenocarboxylates will also perform as suitable nucleophiles in this chemistry.

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

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(8) In an attempt to accelerate the decomposition of the intermediate and improve the yield of **2** and **9**, a number of Lewis acids ($^nBu_2BOTf$, $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, $Sn(OTf)_2$, $Yb(OTf)_3$, $TiCl_4$, $CuBr_2$, $Fe(acac)_3$, $Cu(acac)_2$, $Ti(O^iPr)_4$, $Zr(O^iPr)_4$, and Sn(2-ethylhexanoate)$_2$) were screened both with and without the addition of Hunig's base, unfortunately to no avail.