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A Direct Approach to α-Trifluoromethylamines

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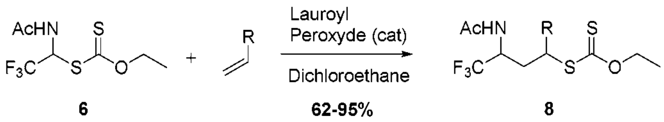
ABSTRACT



***S*-[1-(*N*-Acetylamino)-2,2,2-trifluoroethyl]-*O*-ethyl dithiocarbonate (6), a readily available xanthate, adds efficiently to various functionalized olefins to give the corresponding adducts 8 via a radical chain reaction initiated by a small amount of lauroyl peroxide.**

The introduction of fluorine atoms in a given molecule often dramatically alters its chemical properties and its pharmacological profile in the case of a biologically active compound.[1] As a consequence, much ongoing effort has been devoted to the development of practical synthetic routes to the various classes of fluorinated compounds.[2] As part of our continuing work in this area,[3] we have devised a direct, highly flexible, and efficient approach to α-trifluoromethylamines.

Several trifluoromethylated amines such as compounds **1**−**5**[4] exhibit interesting biological activity (Figure 1).

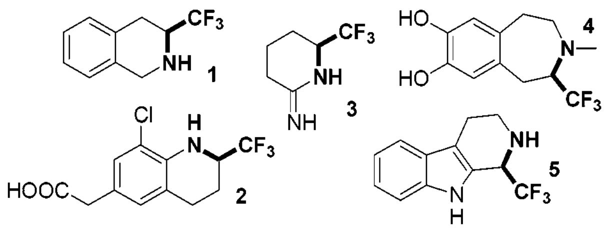


Figure 1. Some biologically active trifluoromethylamino derivatives.

Their preparation mostly hinges on the reductive[5a,b] or alkylating[5c] amination of the corresponding trifluoro methyl ketones, the reduction of trifluoromethylated enamines,[6] the addition of nucleophiles to trifluoromethyl iminium species,[7] the ring opening of trifluoromethylated aziridines,[8] and the addition of the trifluoromethyl anion to functionalized imines.[9]

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[1] (a) *Organofluorine in Medicinal Chemistry and Biochemical Applications*; Filler, R., Kobayashi, Y., Yagupolski, L. M., Eds.; Elsevier: Amsterdam, The Netherlands, 1993. (b) *Fluorine-Containing Amino Acids*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, UK, 1994. (c) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996. (d) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27.

[2] (a) *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards*; Resnati, G., Soloshonok, V. A., Eds.; Tetrahedron Symposium-in-Print No. 58. *Tetrahedron* **1996**, *52*, 1−330. (b) *Topics in Current Chemistry—Organofluorine Chemistry: Techniques and Synthons*; Chambers, R. D., Ed.; Springer: Berlin, Germany, 1997; Vol. 193.

[3] (a) Boivin, J.; Elkaim, L.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2573. (b) Boivin, J.; Elkaim, L.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2585. (c) Denieul, M. P.; Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1996**, 2511. (d) Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 9057. (e) Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 1069.

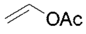
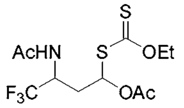
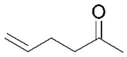
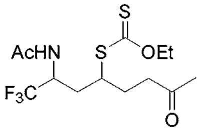
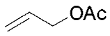
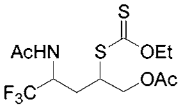
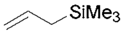
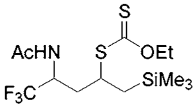
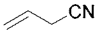
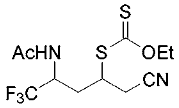
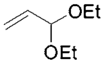
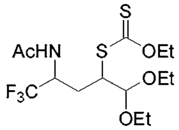
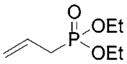
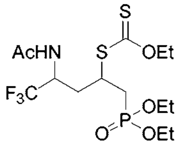
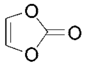
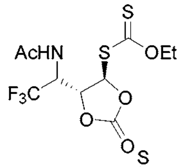
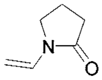
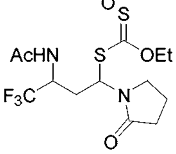
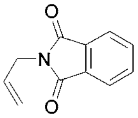
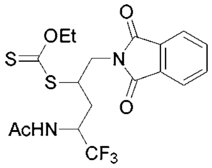
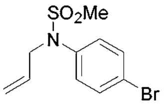
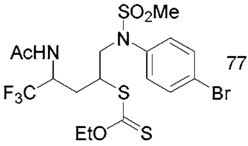
[4] (a) Grunewald, G. L.; Caldwell, T. M.; Li, Q.; Criscione, K. R. *J. Med. Chem.* **1974**, *17*, 3315. (b) Kohno, Y.; Awano, K.; Miyashita, M.; Ishizaki, T.; Kuriyama, K. *Bioorg. Med. Chem. Lett.* **1997**, *12*, 11519. Webber, K. R.; Metz, S.; Moore, W.; Connor, J. R.; Currie, M. G. *J. Med. Chem.* **1958**, *1*, 96. (c) Kawase, M.; Niwa, M.; Nozaki, M.; Motohashi, N.; *Heterocycles* **1998**, *3*, 555. (d) Bringmann, G.; Feineis, D.; Brueckner, R.; Blank, M.; Peters, K.; Peters, E. M.; Reichman, H.; Janetzky, B.; Grote, C.; Clement, H. W.; Wesemann, W. *Bioorg. Med. Chem.* **2000**, *6*, 1467.

[5] For recent contributions, see: (a) Ohkura, H.; Handa, M.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2002**, *67*, 2692. (b) Fustero, S.; Navarro, A.; Pina, B.; Soler, J. G.; Bartolome, A.; Asensio, A.; Simon, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621. (c) Osipov, S.; Artyushin, O.; Kolomiets, A.; Bruneau, C.; Picquet, M.; Dixneuf, P. H. *Eur. J. Org. Chem.* **2001**, *20*, 3891.

[6] Begue, J. P.; Bonnet-Delpon, D.; Mesureur, D.; Née, G.; Wu, S. W. *J. Org. Chem.* **1992**, *57*, 3807.

10.1021/ol034812m CCC: $25.00

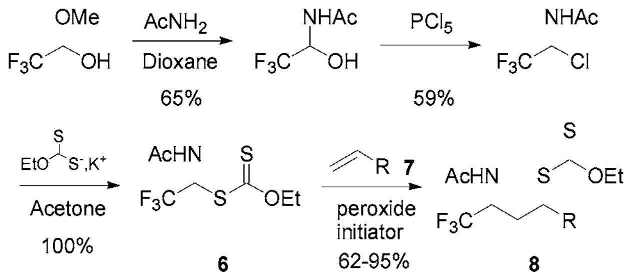
Table 1. Results of Radical Addition of Xanthate **6** to Olefin **7**

	olefin	reaction time		adduct	yield %	isomeric ratio
7a		1.5h	**8a**		95%	6/4
7b		1.5h	**8b**		88%	1/1
7c		1.5h	**8c**		84%	1/1
7d		1h	**8d**		95%	6/4
7e		4.5h	**8e**		87%	6/4
7f		1.5h	**8f**		95%	6/4
7g		1.5h	**8g**		86%	6/4
7h		6h	**8h**		72%	1/1
7i		3h	**8i**		62%	6/4
7j		3h	**8j**		77%	6/4
7k		7h	**8k**		77%	1/1

Our synthetic design, depicted in Scheme 1, relies on the rich chemistry of xanthates.[10] Thus, radical addition of xanthate **6** to olefin **7** leads directly to a variety of α-trifluoromethyl amides **8**. The large-scale preparation of reagent **6**, a nicely crystalline solid, was straightforward starting from the readily available hemiacetal of trifluoroacetaldehyde via the known *N*-(2,2,2-trifluoro-1-chloroethyl)-acetamide.[11]

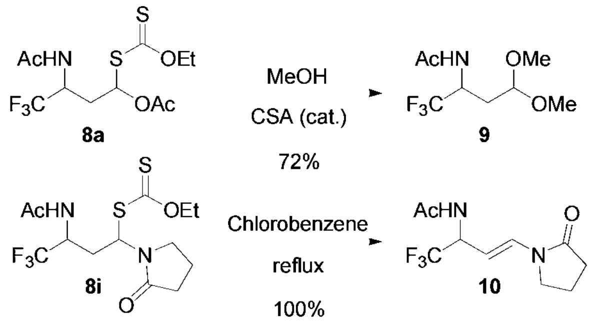
Indeed, when a solution of **6** and vinyl acetate **7a** (1.1 equiv) in 1,2-dichloroethane (1 M) was heated to reflux in the presence of 2 mol % of lauroyl peroxide, a 95% yield of the expected adduct **8a** was obtained. Xanthate **6** turned out to be quite an effective reagent for the introduction of the α-trifluoromethylamine motif, as demonstrated by the examples compiled in Table 1. Many of the common functional groups are tolerated in the olefinic partner, allowing the synthesis of a wide variety of fluorinated derivatives in generally good yield.

Scheme 1. Synthetic Route to α-Trifluoromethylamines



The adducts lead themselves to a number of useful transformations (Scheme 2). For example, heating the addition product **8a** in methanol with catalytic amounts of camphorsulfonic acid resulted in the formation of dimethyl acetal **9** in good yield (72%). With a conveniently masked aldehyde function, this compound represents a useful springboard for accessing more complex trifluoromethylated

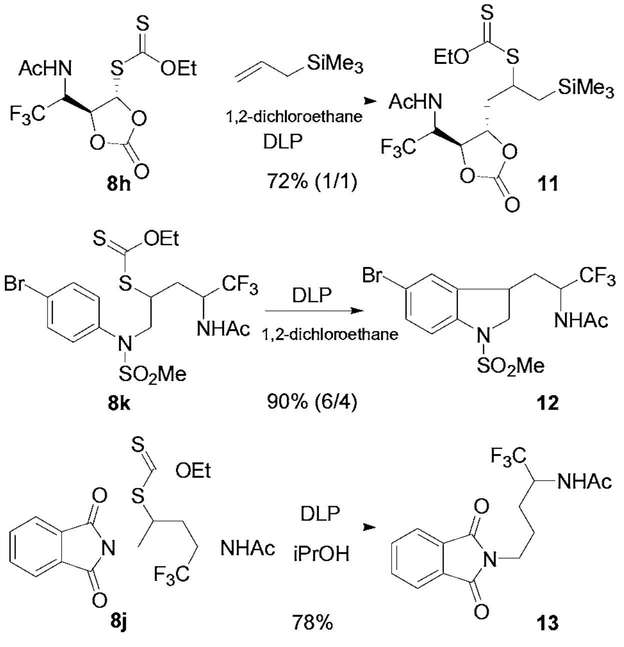
Scheme 2. Transformation of Adducts **8a** and **8i**



structures. In the case of **8i**, derived from *N*-vinyl pyrrolidone, refluxing in chlorobenzene caused the elimination of the xanthate group to give olefin **10** in quantitative yield.

Alternatively, the xanthate group in the adduct may be used to implement another radical addition (Scheme 3). This is illustrated by the conversion of one the isomers of **8h** into the densely functionalized **11** in 72% yield by heating it with allyl trimethylsilane (2 equiv) in 1,2-dichloroethane in the presence of a small amount of lauroyl peroxide (5 mol %). As expected, the addition of the olefin occurred from the least hindered face of the carbonate ring to give the trans-adduct.

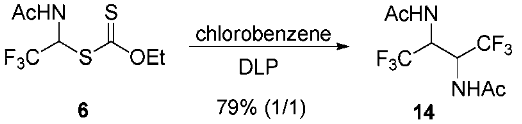
Scheme 3. Radical Transformations of Adducts **8h**, **8j**, and **8k**



In the case of adduct **8k**, refluxing in the same solvent with a gradual addition of a stoichiometric amount of peroxide induced ring-closure onto the aromatic ring to give the corresponding indoline **12** in 90% yield as a 6/4 mixture of diastereoisomers.[12]The xanthate group may simply be reductively cleaved by using a tin-free procedure we developed a few years ago,[13] as shown by the transformation of **8j** into compound **13**. Interestingly, this substance contains two differently protected amino groups.

Finally, we found that exposure of reagent **6** alone to a stoichiometric amount of lauroyl peroxide furnished a surprisingly good yield of dimer **14** as a 1/1 mixture of the *meso* and *dl* isomers (Scheme 4). The hitherto undescribed free diamine corresponding to **14** would be an interesting building block for novel ligands for transition metals.

Scheme 4 Dimerization of Xanthate **6**



In summary, we have presented very promising preliminary results concerning the use of reagent **6** for the expedient synthesis of α-trifluoromethylamines. The reaction is quite general, proceeds under mild conditions, is easily scaled up, and tolerates a wide variety of functional groups. A large diversity of hitherto inaccessible trifluoromethylated compounds can now be readily prepared.

Acknowledgment. This paper is dedicated with respect and admiration to Professor Heinz Viehe. We thank Rhodia Chimie Fine for generous financial support to one of us (F.G.) and Drs Jean-Marc Paris and François Metz of Rhodia for friendly discussions.

Supporting Information Available: Detailed experimental procedures and spectra data for xanthate **6**, radical adducts **8a−k,** and compounds **9−14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For recent contributions, see: (a) Fuchigami, T.; Ichikawa, S. *J. Org. Chem.* **1994**, *59*, 607. (b) Takaya, J.; Kagoshima, H.; Akiyama, T. *Org. Lett.* **2000**, *2*, 1577. (c) Xu, Y.; Dolbier, W. R. *J. Org. Chem.* **2000**, *65*, 2134. (d) Billard, T.; Langlois, B. R. *J. Org. Chem.* **2002**, *67*, 997.

(8) Crousse, B.; Narizuka, S.; Bonnet-Delpon, D.; Begue, J. P. *Synlett* **2001**, 679.

(9) For a recent contribution, see: Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847.

(10) (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur, Silicon* **1999**, 137.

(11) (a) Weygand, F.; Steglich, W.; Lengyel, I.; Fraunberger, F.; Maierhofer, A.; Oettmeier, W. *Chem. Ber.* **1966**, *99*, 1944. (b) Tanaka, K.; Ishiguro, Y.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 661.

(12) Ly, TM.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2529.

(13) Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5877.