ORGANIC LETTERS

2013
Vol. 15, No. 22
5898–5901

A Convenient Metal-Free Reagent for the Generation and Capture of Trifluoromethanethiol

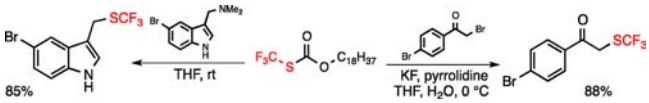
Shi-Guang Li* and Samir Z. Zard*

Laboratoire de Synthèse Organique, CNRS UMR 7652 Ecole Polytechnique, 91128 Palaiseau Cedex, France

Shiguang.li@polytechnique.edu; zard@poly.polytechnique.fr

Received October 22, 2013

ABSTRACT



***O*-Octadecyl-*S*-trifluorothiolcarbonate is a cheap and storable crystalline source of trifluoromethanethiol that can be prepared in two steps on a multigram scale from trifluoroacetic anhydride and sodium *O*-octadecyl-dithiocarbonate (xanthate). It reacts directly with gramines or with α-bromoketones and -esters in the presence of KF and pyrrolidine to give the corresponding trifluoromethyl sulfides in generally high yield.**

Following the isolation of elemental fluorine by Henri Moissan in 1886,[1] the chemistry of organofluorine compounds rapidly became of major importance.[2] However, despite much progress, the introduction of fluorinated motifs remains a significant challenge in organic synthesis. Compared to nonfluorinated counterparts, fluorine-containing substances often display better biological activities and pharmacokinetic profiles because of the change in their solubility and lipophilicity.[3] Additionally, fluorinated derivatives play a key role in agrochemicals,[4] in material and surface sciences,[5] and in organocatalysis.[6] In particular, introducing a trifluoromethyl sulfide (CF_3S-) moiety has attracted the attention of chemists in the pharmaceutical and agrochemical industries,[7] because of its strong electron-withdrawing effect and hydrophobicity parameter ($\pi_R = 1.44$).[8] Three examples of biologically active molecules bearing a CF_3S- motif are displayed in Figure 1.

Over the past few decades, a number of procedures for the indirect insertion of the CF_3S- group into organic structures have been devised.[9] More recently, various new methods for the direct introduction of the CF_3S- unit have been described. However, these methods still have severe limitations, namely the use of expensive, complex, highly toxic, or unstable CF_3S- sources, as well as expensive ligands and metal catalysts. $CuSCF_3$, $AgSCF_3$, and $Hg(SCF_3)_2$ are most commonly used as nucleophilic CF_3S-transfer reagents;[10] however, $CuSCF_3$ is very expensive (304.9 euros/gram from TCI) and is somewhat unstable to storage for extended periods, and the last two reagents have to be prepared just before use.

(1) (a) Tressaud, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6792. (b) *Nobel Lectures, Chemistry 1901−1921*; Elsevier: Amsterdam, 1966.

(2) (a) Furuya1, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 2. (c) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (d) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048. (e) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (f) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (g) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (h) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827. (i) Ojima, I. *J. Org. Chem.* **2013**, *78*, 6358. (j) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V. D.; Roy, S. *Tetrahedron* **2011**, *67*, 2161. (k) Sibi, M. P.; Landais, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 3570. (l) Kuehnel, M. F.; Lentz, D.; Braun, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 3328. (m) Tredwell, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 11426. (n) Littich, R.; Scott, P. J. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1106. (o) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (p) Manteau, B.; Pazenok, S.; Vors, J. P.; Leroux, F. R. *J. Fluorine Chem.* **2010**, *131*, 140.

(3) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.

(4) Jeschke, P. *ChemBioChem.* **2004**, *5*, 570.

(5) Hird, M. *Chem. Soc. Rev.* **2007**, *36*, 2070.

(6) Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11860.

(7) (a) Tyrra, W.; Naumann, D.; Hoge, B.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2003**, *119*, 101. (b) Boiko, V. N. *Beilstein J. Org. Chem.* **2010**, *6*, 880.

(8) (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *97*, 165. (b) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.

(9) (a) Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 9057. (b) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754. (c) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156.

10.1021/ol403038f
Published on Web 11/05/2013

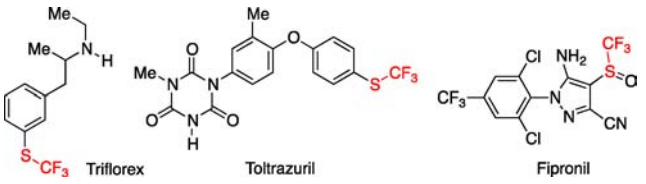
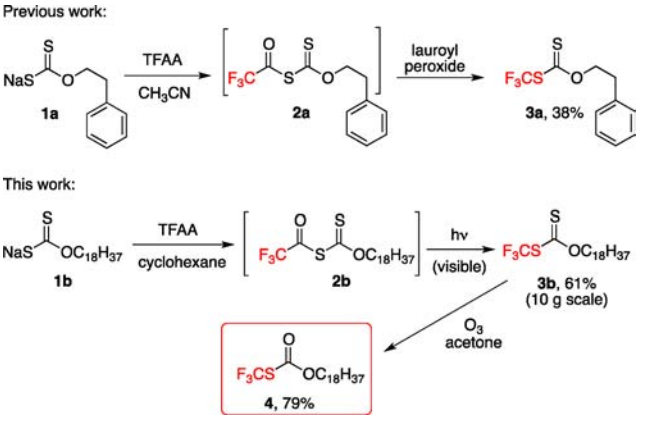


Figure 1. Examples of CF_3S-containing products.

Billard et al. prepared a family of trifluoromethanesulfanamides, which could be used as electrophilic CF_3S– sources capable of reacting efficiently with various organometallic alkenyl and alkynyl reagents.[11] The group of Daugulis described a trifluoromethylthiolation process based on copper(II) acetate and bis(trifluoromethyl) disulfide;[12] however, the latter component is highly toxic, expensive, and not easy to handle (bp 34–35 °C). Shen and Lu also prepared a hypervalent iodine reagent for the direct electrophilic trifluoromethylthiolation under mild conditions. The limitations of this reagent are that it is only stable for a few days in solution at rt and requires $AgSCF_3$ as the precursor.[13] Huang and Weng introduced a complex $CuSCF_3$ reagent, [(bpy)Cu(SCF_3)], which reacts with a wide range of aryl and heteroaryl halides to produce aryl trifluoromethylthioethers in good yield.[14] This and other related complexes have been claimed to be stable in the solid state to storage under air for several days. Recently, Shibata and his team developed a trifluoromethanesulfonyl hypervalent iodonium ylide as a novel electrophilic-type trifluoromethylthiolation reagent allowing the introduction of the CF_3S- group into various nucleophiles.[15] Most recently, Rueping and collaborators developed an enantioselective trifluoromethylsulfenylation employing *N*-trifluoromethylthiophthalimide as the electrophilic CF_3S-source; however, the preparation of this reagent involves the extremely toxic and corrosive trifluoromethylsulfenyl chloride.[16]

Scheme 1



In contrast to most of the methods adumbrated above, we now describe an efficient, cheap, air-stable, and easily available metal-free reagent allowing the generation and direct capture of the trifluoromethylthiolate anion. A few years ago, we described the preparation and use of *S*-trifluoromethyl xanthate **3a**, which proved to be a convenient source of trifluoromethyl radicals.[17] In principle, this xanthate could also act as a precursor for trifluoromethanethiol or its salts through ionic hydrolysis or aminolysis. While the synthesis of xanthate **3a** outlined in Scheme 1 and starting from xanthate salt **1a** is relatively straightforward, the yield is somewhat modest (38%). The main difficulty is the high sensitivity of the intermediate *S*-trifluoroacetyl xanthate **2a** toward water or nucleophiles in general. In fact, we have shown that *S*-acyl xanthates in general can be decomposed catalytically by an ionic chain mechanism, so even a small amount of a nucleophilic impurity can have a serious impact on the yield.[18] Hence, we considered modifying reagent **3a** by replacing the phenethyl group with a more lipophilic *n*-octadecanoyl chain. Indeed, the yield of corresponding *S*-trifluoromethyl xanthate **3b** starting from xanthate salt **1b** increased to 61%, and the reaction could be performed on multigram scale (approximately 10 g of **3b** were prepared in a single run). In this process, visible light from a tungsten incandescent lamp was used to trigger the radical chain decarbonylation sequence, in preference to a chemical initiator such as lauroyl peroxide, in order to avoid complications during purification caused by the highly

(10) (a) Teverovskiy, G.; David, S.; Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7312. (b) Adams, D. J.; Clark, J. H. *J. Org. Chem.* **2000**, *65*, 1456. (c) Clark, J. H.; Jones, C. W.; Kybett, A. P.; Mcclinton, M. A. *J. Fluorine Chem.* **1990**, *48*, 249. (d) Munavalli, S.; Hassner, A.; Rossman, D. I.; Singh, S.; Rohrbaugh, D. K.; Ferguson, C. P. *J. Fluorine Chem.* **1995**, *73*, 7. (e) Munavalli, S.; Rossman, D. I.; Rohrbaugh, D. K.; Ferguson, C. P.; Durst, H. D. *J. Fluorine Chem.* **1996**, *76*, 7. (f) Remy, D. C.; Rittle, K. E.; Hunt, C. A.; Freedman, M. B. *J. Org. Chem.* **1976**, *41*, 1644. (g) Yagupolskii, L. M.; Kondratenko, N. V.; Sambur, V. P. *Synthesis* **1975**, 721. (h) Kondratenko, N. V.; Sambur, V. P.; Yagupolskii, L. M. *Synthesis* **1985**, 667. (i) Harr, J. F. *J. Org. Chem.* **1967**, *32*, 2063. (j) Man, E. H.; Coffman, D. D.; Muetterties, E. L. *J. Am. Chem. Soc.* **1959**, *81*, 3575. (k) Downse, A. J.; Ebsworth, A. V.; Emeleus, H. J. *J. Chem. Soc.* **1961**, 3187.

(11) (a) Ferry, A.; Billard, T.; Langlois, B. R.; Bacque, E. *J. Org. Chem.* **2008**, *73*, 9362. (b) Ferry, A.; Billard, T.; Langlois, B. R.; Bacque, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8551. (c) Baert, F.; Colomb, J.; Billard, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10382. (d) Alazet, S.; Zimmer, L.; Billard, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 10814.

(12) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237.

(13) (a) Shao, X. X.; Wang, X. Q.; Yang, T.; Lu, L.; Shen, Q. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 3457. (b) Wang, X. Q.; Yang, T.; Cheng, X. L.; Shen, Q. L. *Angew. Chem., Int. Ed.* **2013**, *52*, DOI: 10.1002/anie.201305075.

(14) (a) Weng, Z. Q.; He, W. M.; Chen, C. H.; Lee, R.; Tan, D.; Lai, Z. P.; Kong, D. D.; Yuan, Y. F.; Huang, K. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 1548. (b) Kong, D. D.; Jiang, Z.; Xin, S. G.; Bai, Z. S.; Yuan, Y. F.; Weng, Z. Q. *Tetrahedron* **2013**, *69*, 6046. (c) Tan, J. W.; Zhang, G. T.; Ou, Y. L.; Yuan, Y. F.; Weng, Z. Q. *Chin. J. Chem.* **2013**, *31*, 921.

(15) Yang, Y. D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782.

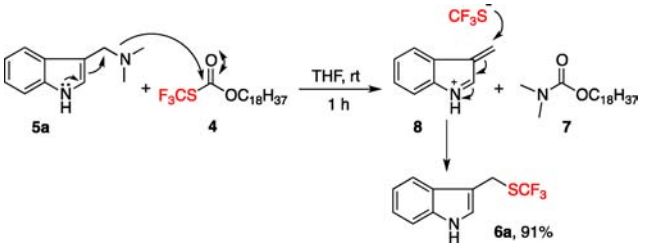
(16) (a) Munavalli, S.; Rohrbaugh, D. K.; Rossman, D. I.; Berg, F. J.; Wagner, G. W.; Durst, H. D. *Synth. Commun.* **2000**, *30*, 2847. (b) Bootwicha, Y.; Liu, X. Q.; Pluta, R.; Atodiresei, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2013**, *52*, DOI: 10.1002/anie.201304957.

(17) Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 1069.

(18) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672.

nonpolar nature of compounds. Furthermore, we converted xanthate **3b** into thiolcarbonate **4** by ozonolysis[19] to eliminate possible interference by unwanted sulfur nucleophiles arising from the thiono group. Thiolcarbonate **4** was thus obtained as a nicely crystallized indefinitely shelf-stable solid (mp 25−27 °C).

Scheme 2



We were pleased to find that gramine **5a** reacted smoothly with thiolcarbonate **4** in THF at rt to give a high yield of 3-trifluoromethylthiomethylindole **6a**. Presumably, the nucleophilic tertiary amine of gramine reacts with the activated thiolcarbonate to generate carbamate **7** and a reactive intermediate ion-pair **8**, which rapidly collapses into the observed product **6a**. The coproduct carbonate **7** was isolated in ~40% yield (Scheme 2).

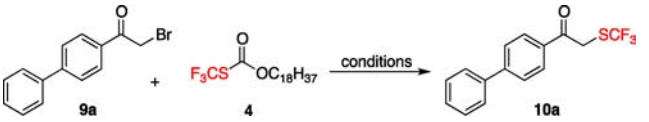
Figure 2. Examples of CF_3S-substituted gramines.

Under identical conditions, substituted gramines reacted in a similar way with thiolcarbonate **4**. 5-Bromo-, 2-methyl-, and 2-phenyl-substituted gramines furnished good to excellent yields of the corresponding indoles **6b**−**6d** (Figure 2). In contrast, the less nucleophilic 6-nitro-substituted gramine reacted sluggishly and gave rise to a poor yield of the desired CF_3S− substituted product **6e**. 3-Trifluoromethylthiomethylindoles **6a**−**e** represent a hitherto unknown class of compounds with perhaps some potential in medicinal chemistry.

We next turned our attention to the trifluoromethylthiolation of α-bromoketones. This substitution, which is trivial with normal thiolates, proved quite problematic with the far less nucleophilic and unstable trifluoromethylthiolate anion. At first, we treated 2-bromo-4′-phenylacetophenone **9a** with 2 equiv of thiolcarbonate **4** and 2 equiv of KF

(19) Quiclet-Sire, B.; Zard, S. Z. *Bull. Korean Chem. Soc.* **2010**, *31*, 543.

Table 1. Conditions for Substitution of *p*-Phenylphenacyl Bromide with the Trifluoromethanethiolate Anion



entry	4 (equiv)	solvent (0.1 M)	KF (equiv)	base	*t*/°C	rxn time	yield % (NMR)[a]
1	2.0	THF	2.0	–	reflux	72 h	<10
2	2.0	THF	4.0	pyrrolidine 2 equiv	reflux	24 h	<7
3	2.0	THF	4.0	$PhNMe_2$ 2 equiv	reflux	18 h	18
4	2.0	THF	4.0	pyrrolidine 2 equiv	rt	4 h	20
5	2.0 + 2.0	THF	4.0	pyrrolidine 2 + 2 + 2 equiv	rt	92 h	68
6	4.0	THF/H_2O 20:1	10.0	pyrrolidine 6 equiv	rt	1 h	70
7	4.0	THF/H_2O 20:1	10.0	pyrrolidine 3.8 equiv	rt	0.5 h	87 (80)
8	**4.0**	**THF/H_2O 20:1**	**10.0**	**pyrrolidine 3.8 equiv**	**0**	**1.5 h**	**96 (88)**
9	2.0	THF/H_2O 20:1	5.0	pyrrolidine 1.9 equiv	rt	8 h	39

[a] Yields in parentheses correspond to isolated yields.

under reflux for 72 h. Unfortunately, we obtained the desired CF_3S− substituted ketone **10a** in less than 10% yield, as estimated by NMR. The major product (~70%) turned out to be 4-acetylbiphenyl, formed by reduction of the starting bromide (Table 1, entry 1). The addition of KF is to stabilize the CF_3S− anion, which has a tendency to form difluorothiophosgene by extrusion of a fluoride anion. We attempted adding 2 equiv of pyrrolidine to promote the generation of the CF_3S anion, but after reflux for 24 h, the conversion and yield of the desired product were still low; however, only 6% of the debrominated 4-acetylbiphenyl was found (Table 1, entry 2). The use of *N*,*N*-dimethylaniline as the accelerator instead of pyrrolidine gave 18% (by NMR) of the desired product and also ~75% of 4-acetylbiphenyl (Table 1, entry 3). Operating with 2 equiv of pyrrolidine at rt for 4 h resulted in the formation of 20% of product **10a**, but significantly, no 4-acetylbiphenyl was detected (Table 1, entry 4). Increasing the reaction time and adding a further 2 equiv of thiolcarbonate **4** and 4 equiv of pyrrolidine afforded 2-trifluoromethylthio-4′-phenylacetophenone **10a** in 68% yield after 92 h of reaction time (Table 1, entry 5). Incorporation of a little water to augment the solubility of the KF, the amount of which was also increased to 10 equiv, furnished the desired product in 70% NMR yield (Table 1, entry 6). Reducing the amount of pyrrolidine to 3.8 equiv further improved the yield (87% conversion and 80% isolated yield, Table 1, entry 7). Finally, lowering the temperature to 0 °C lengthened the reaction time to 1.5 h, but resulted in a 96% conversion and 88% isolated yield (Table 1, entry 8). Unfortunately, diminishing the excess of

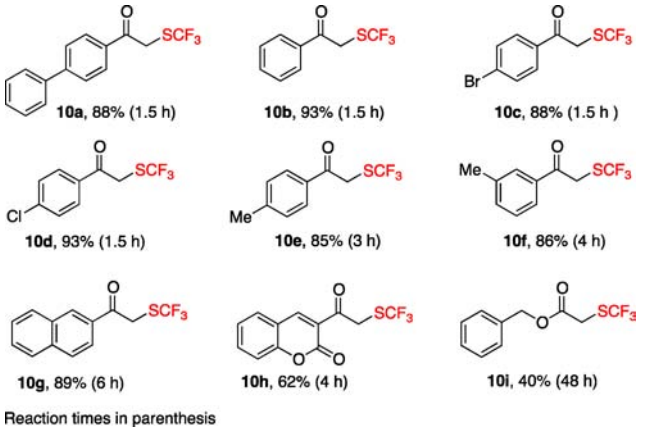


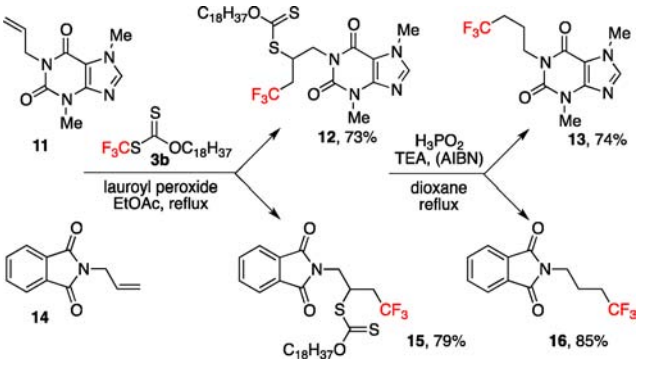
Figure 3. Examples of CF_3S-substituted ketones and esters.

reagents caused a significant drop in the yield to only 39% (Table 1, entry 9). It is interesting that, in these experiments, the pyrrolidine is clearly reacting faster with trifluorothiolcarbonate **4** than with bromoketone **9a**.

Having optimized the reaction conditions, we extended this procedure to various α-bromoketones. Both electron-poor and -neutral substituted derivatives gave high yields under the same conditions (**10a**–**10d**, Figure 3). Substrates with electron-rich substituents also provided a good yield of product but needed longer reaction times (**10e**–**10f**, Figure 3). For 2-bromoacetylnaphthalene, we used additionally 2 equiv of thiolcarbonate **4** and pyrrolidine, and after 6 h of reaction, we obtained the desired product in 89% yield (Figure 3, **10g**). 3-(Bromoacetyl)coumarin also proved suitable for this reaction furnishing a 62% yield of the corresponding trifluoromethylsulfide **10h**. In the case of benzyl-2-bromoacetate the reaction was less efficient and sluggish, giving sulfide **10i** in 40% yield after 48 h at rt.

In summary, we have developed a convenient, practical, and storable source of trifluoromethanethiol for *in situ* generation and capture. Our preliminary results indicate that highly reactive electrophiles are necessary, but the scope still needs to be better delineated. It is worth mentioning that this procedure is readily scalable. For example, trifluoromethylsulfide **10c** was prepared on a 1.24 g scale in comparable yield (83% versus 88%; see Supporting Information). In principle, thiolcarbonate **4** could also be used to prepare more traditional reagents such as the disulfide (CF_3SSCF_3) or the copper salt $CuSCF_3$ and its various complexes.

Scheme 3



Finally, it is worth noting that xanthate **3b**, the precursor to thiolcarbonate **4**, represents an efficient reagent for accomplishing the addition of trifluoromethyl radicals to alkenes. It is in fact somewhat more effective than the initially described xanthate **3a**, because it is easier to obtain pure, and the presence of the long aliphatic chain does not hinder the radical chain process, as demonstrated by the two examples displayed in Scheme 3. Thus, lauroyl peroxide mediated addition to alkenes **11** and **14** furnishes adducts **12** and **15** in 73% and 79% yield, respectively; the xanthate group in the products is easily reduced off with hypophosphorus acid[20] to give sulfur-free compounds **13** and **16**, also in good yield.

Because of their ease of access, storability and safety in handling, and cheapness, both reagents **3b** and **4** should prove useful for introducing the CF_3– and CF_3S– motifs through radical and ionic mechanisms, respectively. In contrast to all previous methods, the ultimate source of the trifluoromethyl group is the inexpensive and readily available trifluoroacetic anhydride.

Acknowledgment. We thank the China Scholarship Council for a grant to S.-G.L. This paper is dedicated with respect to Professor Bernard R. Langlois (Université de Lyon 1, Lyon, France).

Supporting Information Available. Experimental procedures, full spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, V. T. *Org. Lett.* **2003**, *5*, 1645.

The authors declare no competing financial interest.