Tetrahedron Letters 54 (2013) 6129–6132

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Nucleophilic trifluoromethylation of conjugate acceptors via phenyl trifluoromethyl sulfone

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ARTICLE INFO

Article history:
Received 16 August 2013
Revised 26 August 2013
Accepted 30 August 2013
Available online 7 September 2013

Keywords:
Trifluoromethylation
Conjugate addition
Befloxatone
Phenyl trifluoromethyl sulfone

ABSTRACT

A mild procedure for the conjugate addition of the trifluoromethyl anion to activated Michael acceptors such as arylidenemalononitriles (15 examples) and arylidene Meldrum's acids (9 examples) using phenyl trifluoromethyl sulfone through a reductive magnesium metal mediated procedure is described. The new methodology is used to prepare befloxatone, a reversible and selective monoamine oxidase A inhibitor.

As a result of the increasing importance of fluorine containing molecules in the pharmaceutical, agrochemical, and materials industries considerable effort has been devoted to the development of selective fluorination methodologies.[1] Replacement of hydrogen by fluorine, the most electronegative element, changes the properties of a molecule. In particular, the CF_3 group can substantially alter electronics, chemical reactivity, lipophilicity, bioavailability, and metabolic stability of a compound. Currently, approximately 20% of pharmaceuticals and 30–40% of agrochemicals contain fluorine[2] and numerous materials including the highly utilized Teflon (polytetrafluoroethyene polymer) are perfluorinated.[3]

Incorporation of a trifluoromethyl group typically begins with a trifluoromethyl containing building block. However, utilization of pre-functionalized systems severely limits late stage incorporation. Thus, the direct introduction of a trifluoromethyl group is desirable and this is traditionally promoted via either electrophilic, radical, or nucleophilic addition (Fig. 1).[4]

Nucleophilic trifluoromethylations are attractive reactions because of the wide array of electrophilic partners and the potential to develop stereoselective variants. Due to the inherent instability of the trifluoromethyl anion (CF_3^-), a variety of methods for its in situ generation have been developed, the most common being use of the Ruppert–Prakash reagent (**4**).[5] While this reagent is highly versatile, the most utilized method of preparation involves the use of ozone-depleting CF_3Br[6] (although recently Prakash et al. have shown that fluoroform can be used as a precursor to **4**).[7] In contrast, the increasingly attractive reagent, phenyl trifluoromethyl sulfone (**5**), is readily available from methyl phenyl sulfide[8] and is a precursor in a more environmentally friendly synthesis of silane **4**.[9] Thus, the use of sulfone **5** is a more economical and green choice of reagent.

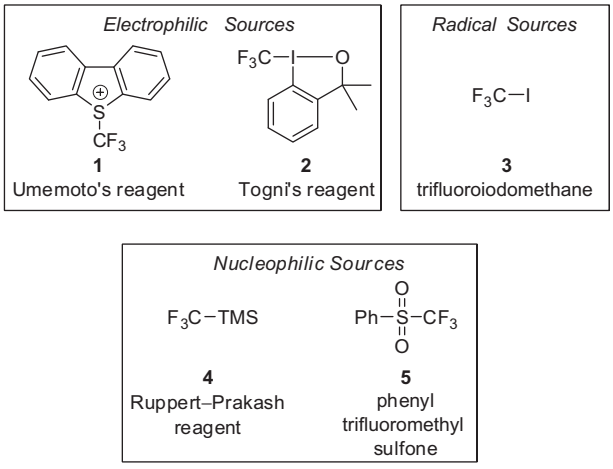

Figure 1. Sources of 'CF_3'.

Sulfone **5** has been shown to be an efficient trifluoromethyl group precursor. Reductive conditions with magnesium metal alone facilitated the reaction of the proposed trifluoromethyl anion intermediate with chlorosilane electrophiles to generate trifluoromethylsilanes.[9] Alkoxide induced generation of CF_3^- led to the generation of α-trifluoromethyl alcohols through direct addition to non-enolizable aldehydes.[10] More recently, a magnesium

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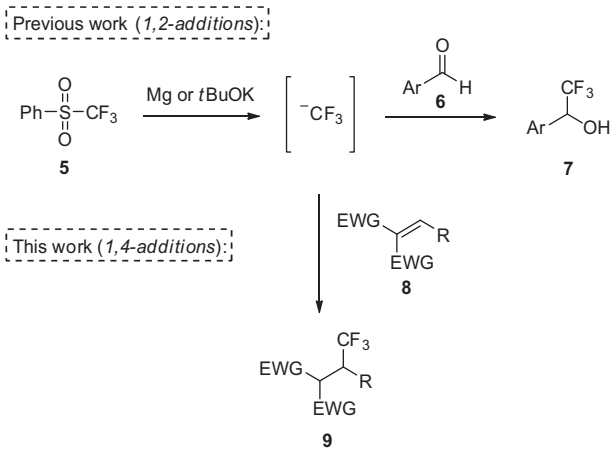
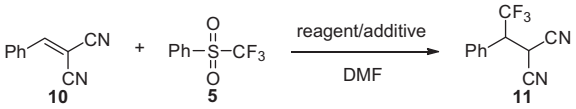
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.08.132



Scheme 1. 1,2- versus 1,4-additions.

Table 1
Reaction Development



Entry	Reagent/additive	*T* (°C)	Time (h)	Yield (%)
1	*t*BuOK/none	0 to rt	12	0
2	*t*BuOK/none	−50 to rt	12	0
3	Mg/none	−50 to rt	12	0
4	Mg/$ZnCl_2$	−50 to rt	24	0
5	Mg/$CuCl_2$	−50 to rt	24	0
6	Mg/$HgCl_2$	−50 to rt	3.5	64

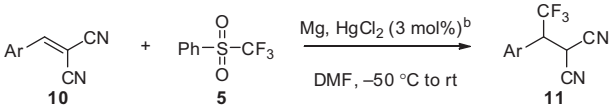
metal-mediated method for the direct trifluoromethylation of aldehydes activated by mercury(II) chloride was developed.[11]

While direct additions of the trifluoromethyl anion to a carbonyl are well studied using a variety of sources,[12] conjugate additions are rare.[13] Our interest in developing mild, inexpensive, and selective trifluoromethylation procedures led us to investigate the use of readily available sulfone **5** in conjugate addition reactions (Scheme 1).

Our initial efforts were directed toward the nucleophilic trifluoromethylation of previously examined highly electrophilic alkenes such as benzylidenemalononitrile (**10**)[13b] (Table 1). Our attempts to use Prakash, Hu, and Olah's alkoxide induced method to generate a transient trifluoromethyl anion[10] were unsuccessful with **10** and lead to recovery of the sulfone while the malononitrile was consumed (entries 1 and 2), suggesting the alkoxide reacts spontaneously with the highly electrophilic malononitrile over the sulfone. Our next attempts were focused on a reductive, magnesium metal mediated procedure (entries 3–6). Previous work by Hu and co-workers demonstrated that an additive was necessary to activate the metal for desulfonylation and generation of CF_3^-.[11] Rewardingly, our results followed previous experiments, with mercury(II) chloride (3 mol % relative to amount of magnesium) in DMF acting as an effective additive and leading to 64% of trifluoromethylated malononitrile **11**. We expect the procedure to follow the same mechanism as proposed by Hu where a single electron transfer from magnesium metal to sulfone **5** enables a reductive cleavage of the C–S bond to form the CF_3^- species, followed by addition to the highly electrophilic arylidenemalononitriles.[11]

With conditions in hand for the nucleophilic trifluoromethylation of benzylidenemalononitrile with sulfone **5**, we set out to explore the scope of the reaction (Table 2). Both electron withdrawing and electron donating substitutents on the benzene ring are tolerated and gave yields ranging from 52–82% (entries 1–12). Entries with electron withdrawing groups gave lower yield agreeing with Hu and co-workers suggestion of rapid reduction of these substrates due to the reaction condition (entries 6–10).[11] Naphthalene (entry 13) and heteroaromatic based malononitriles (entries 14 and 15) also perform well under the reaction conditions.

Table 2
Trifluoromethylation of arylidenemalononitriles[a]



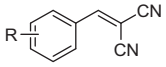
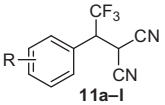
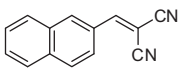
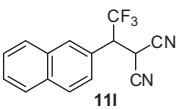
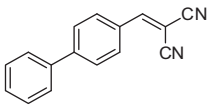
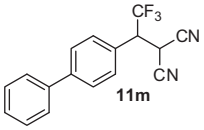
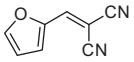
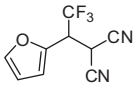
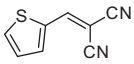
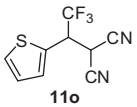
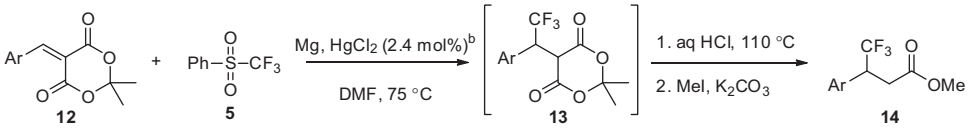
Entry	Substrate	Product		Yield[c] (%)
1			**11a** R = H	65
2			**11b** R = 4-OMe	77
3			**11c** R = 2-Me	73
4			**11d** R = 3-Me	76
5			**11e** R = 4-Me	70
6			**11f** R = 3-CF_3	60
7			**11g** R = 2-F	57
8			**11h** R = 3-F	58
9			**11i** R = 4-F	63
10			**11j** R = 4-NO_2	52
11			**11k** R = 2,6-Me_2	60
12				78
13				82

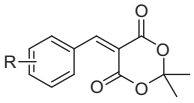
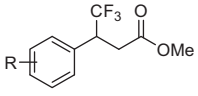
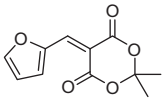
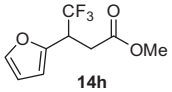
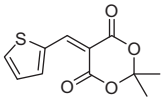
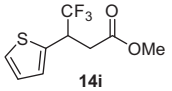
Table 2 (*continued*)

Entry	Substrate	Product	Yield[c] (%)
		 **11m**	
14		 **11n**	59
15		 **11o**	60

[a] Reactions carried out using **5** (2 mmol), **10** (1 mmol), Mg (2 mmol) and $HgCl_2$ (0.06 mmol) in DMF (3 mL).
[b] Relative to the amount of Mg metal used.
[c] Isolated yield.

Table 3
Trifluoromethylation of arylidene Meldrum's acids[a]

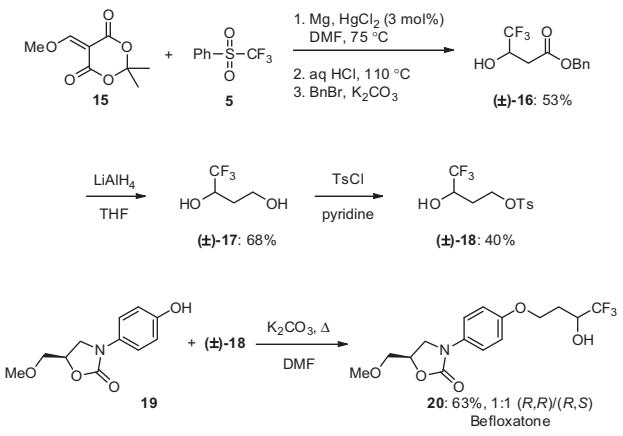


Entry	Substrate	Product		Yield[c] (%)
1		 **14a–g**	**14a** R = H	63
2			**14b** R = 4-OMe	69
3			**14c** R = 2-Me	65
4			**14d** R = 4-Me	68
5			**14e** R = 4-NO_2	32
6			**14f** R = 4-F	45
7			**14g** R = 2,6-Me_2	53
8		 **14h**		52
9		 **14i**		54

[a] Reactions carried out **5** (2.5 mmol), **12** (1 mmol), Mg (2.5 mmol) and $HgCl_2$ (0.06 mmol) in DMF (3 mL).
[b] Relative to the amount of Mg metal used.
[c] Isolated yield.

Following the successful trifluoromethylation of various arylidenemalononitriles, we sought to determine if other Michael acceptors would be suitable as electrophiles. Arylidene derivatives of Meldrum's acid **12** are highly electrophilic and have previously undergone nucleophilic trifluoromethylation with trifluoromethyltrimethylsilane (**4**).[13a] Modification of the above procedure to include elevated temperatures (75 °C) led to intermediate trifluoromethylated compounds **13** which were immediately hydrolyzed and decarboxylated to avoid decomposition and esterified for ease of handling (Table 3). Overall yields of transformation of Meldrum's acid derivatives **12** to β-trifluoromethyl esters **14** were between 32% (R = 4-NO_2, entry 5) and 69% (R = 4-OMe, entry 2). Heteroaromatic derivatives of Meldrum's acid (entries 8 and 9) were also viable substrates in the process.

Befloxatone ((*R*,*R*)-**20**) is a reversible and selective monoamine oxidase A (MAO-A) inhibitor containing a trifluoromethyl group at a chiral center (Scheme 2).[14] Previous syntheses of befloxatone have involved the etherification of phenol **19** with trifluoromethyl



Scheme 2. Synthesis of Befloxatone.

containing tosylate **18**.[14c,15] We have developed a synthesis of tosylate **18** using the described conjugate addition of a trifluoromethyl group to Meldrum's acid derivatives. Trifluoromethylation of compound **15** using our standard trifluoromethylation conditions was followed by hydrolyzation and decarboxylation and esterification to give product (±)-**16** in 53% overall yield. Reduction of the benzyl ester followed by tosylation of the primary alcohol gave (±)-**18**. Finally, etherification of (*R*)-**19**[15] with (±)-**18** yielded desired compound **20** in a 63% yield and with 1:1 diastereomeric ratio of the inseparable (*R*,*R*) (befloxatone) and (*R*,*S*) diasteromers. Development of an asymmetric variant of the conjugate trifluoromethylation is currently underway in our laboratories and would lead to an asymmetric synthesis of (+)-**18** and thus befloxatone ((*R*,*R*)-**20**).

In summary, we have developed a mild procedure for the conjugate addition of the trifluoromethyl anion to activated acceptors such as arylidenemalononitriles and arylidene Medrum's acids using readily available phenyl trifluoromethyl sulfone (**5**) through a magnesium metal reductive procedure. This methodology has been applied to a total synthesis of the MAO-A inhibitor befloxatone. Future work will be to expand the process to other conjugate acceptors and the development of an asymmetric variant.

Acknowledgments

We thank the University of North Carolina at Greensboro for financial support and Dr. Franklin J. Moy and Dr. Brandie M. Ehrman for assistance with NMR and mass spectrometry data analysis. This work was supported by the University of North Carolina at Greensboro.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.132.

References and notes

1. (a) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15–24; (b) Kirsh, P. *Mordern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004; (c) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994; (d) Filler, R.; Kobayashi, Y.; Yagupolskii, Y. L. *Organofluorine Compounds in Medicinal Chemistry and Biological Applications*; Elsevier: Amsterdam, 1993.
2. Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886.
3. Hird, M. *Chem. Soc. Rev.* **2007**, *36*, 2070–2095.
4. Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975–996.
5. (a) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393–395; (b) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195–2198.
6. Ramaiah, P.; Krishnamurti, R.; Prakash, G. K. S. *Org. Synth.* **1995**, *72*, 232.
7. Prakash, G. K. S.; Jog, P. V.; Batamack, P. T. D.; Olah, G. A. *Science* **2012**, *338*, 1324–1327.
8. (a) Kremsner, J. M.; Rack, M.; Pilger, C.; Kappe, C. O. *Tetrahedron Lett.* **2009**, *50*, 3665–3668; (b) Chen, Q.-Y.; Duan, J.-X. *J. Chem. Soc., Chem. Commun.* **1993**, 918–919.
9. Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457–4463.
10. Prakash, G. K. S.; Hu, J.; Olah, G. A. *Org. Lett.* **2003**, *5*, 3253–3256.
11. Zhao, Y.; Zhu, J.; Ni, C.; Hu, J. *Synthesis* **2010**, 1899–1904.
12. (a) Wu, S.; Zeng, W.; Wang, Q.; Chen, F.-X. *Org. Biomol. Chem.* **2012**, *10*, 9334–9337; (b) Kawai, H.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Eur. J. Org. Chem.* **2011**, 5959–5961; (c) Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6324–6327; (d) Prakash, G. K. S.; Panja, C.; Vaghoo, H.; Surampudi, V.; Kultyshev, R.; Mandal, M.; Rasul, G.; Mathew, T.; Olah, G. A. *J. Org. Chem.* **2006**, *71*, 6806–6813; (e) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1133–1145; (f) Caron, S.; Do, N. M.; Arpin, P.; Larivée, A. *Synthesis* **2003**, 1693–1698; (g) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137–3138.
13. (a) Zemtsov, A. A.; Levin, V. V.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Tartakovsky, V. A. *Tetrahedron Lett.* **2009**, *50*, 2998–3000; (b) Dilman, A. D.; Levin, V. V.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *Tetrahedron Lett.* **2008**, *49*, 4352–4354; (c) Sosnovskikh, V. Y.; Usachev, B. I.; Sevenard, D. V.; Röschenthaler, G.-V. *J. Org. Chem.* **2003**, *68*, 7747–7754; (d) Sevenard, D. V.; Sosnovskikh, V. Y.; Kolomeitsev, A. A.; Königsmann, M. H.; Röschenthaler, G.-V. *Tetrahedron Lett.* **2003**, *44*, 7623–7627.
14. (a) Dolle, F.; Valette, H.; Bramoulle, Y.; Guenther, I.; Fuseau, C.; Coulon, C.; Lartizien, C.; Jegham, S.; George, P.; Curet, O.; Pinquier, J. L.; Bottlaender, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1771–1775; (b) Dolle, F.; Bramouelle, Y.; Hinnen, F.; Demphel, S.; George, P.; Bottlaender, M. *J. Labelled Compd. Radiopharm.* **2003**, *46*, 783–792; (c) Rabasseda, X.; Sorbera, L. A.; Castañer, J. *Drugs Future* **1999**, *24*, 1057–1067; (d) Curet, O.; Damoiseau, G.; Aubin, N.; Sontag, N.; Rovei, V.; Jarreau, F. X. *J. Pharm. Exp. Ther.* **1996**, *277*, 253–264; (e) Caille, D.; Bergis, O. E.; Fankhauser, C.; Gardes, A.; Adam, R.; Charieras, T.; Grosset, A.; Rovei, V.; Jarreau, F. X. *J. Pharm. Exp. Ther.* **1996**, *277*, 265–277.
15. Shibatomi, K.; Narayama, A.; Abe, Y.; Iwasa, S. *Chem. Commun.* **2012**, 7380–7382.