Synthesis of 3-Trifluoromethylfurans from β,β-Bis(trifluoromethyl) α,β-Unsaturated Ketones and Tin(II) Chloride

Klaus Burger* and Brigitte Helmreich

Department of Organic Chemistry, Technical University Munich, Lichtenbergstrasse 4, W-8046 Garching, Germany

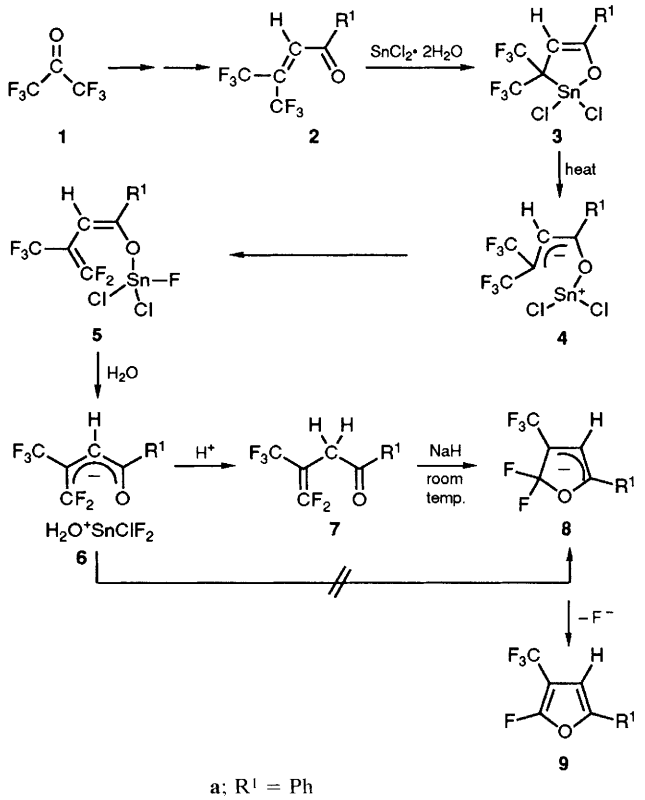
A new building block strategy for the synthesis of 3-trifluoromethyl-substituted furans **9** and **10** is described from β,β-bis(trifluoromethyl) α,β-unsaturated ketones **2** *via* reductive fluoride elimination and 1,5-electrocyclization with elimination.

The development of synthetic methodologies for the selective introduction of short chain perfluoroalkyl groups into organic molecules is of current interest because of their ability to enhance biological activity.[1] The building block strategy for introduction of perfluoroalkyl groups is often found to be superior to a selective introduction of the fluorinated side chain in a final step of the reaction sequence.

In the case of five-membered heteroaromatic compounds some effective synthetic concepts have already been developed. Cyclocondensation reactions with CF_3-substituted starting materials offer a versatile access to CF_3-substituted heterocyclic as well as heteroaromatic compounds.[2] CF_3-substituted 1,3-dipoles are especially valuable building blocks for the synthesis of a wide variety of CF_3-substituted five-membered heterocycles.[3] In addition, introduction of CF_3 groups can be achieved *via* [3 + 2] cycloaddition using CF_3-substituted dipolarophiles.[4] Recently, a novel and preparatively valuable CF_3-containing building block, ethyl 3,3,3-trifluoro-2-diazopropionate, has been described.[5] 1,5-Electrocyclization of CF_3-substituted heteropentadienyl anions and subsequent elimination with aromatization offers an elegant route to perfluorinated and partially fluorinated heteroaromatic systems.[6] A promising reaction sequence for the synthesis of five-membered heteroaromatic compounds consists of a Diels–Alder reaction of perfluoroalkyl-substituted triple bonds to five-membered heteroaromatic compounds followed by a thermally induced [4 + 2] retro reaction of the bicyclic adducts obtained.[7] Recently, we have reported on two new types for transformation of β,β-bis(trifluoromethyl)-substituted α,β-unsaturated compounds into CF_3-substituted azoles.[8] Here we report on a versatile new route to 3-trifluoromethylfurans starting from hexafluoroacetone.

The β,β-bis(trifluoromethyl) α,β-unsaturated ketones **2** can easily be prepared from hexafluoroacetone **1** by using procedures reported in the literature.[9] Compounds **2** were found to react smoothly with 1.1 equiv. of tin(II) chloride (commercial sample: $SnCl_2 \cdot 2H_2O$) at room temperature to give tin heterocycles **3** (Scheme 1). The [4 + 1] cycloaddition process involves an oxidation at tin ($Sn^{2+} \rightarrow Sn^{4+}$) and a reduction of the unsaturated ketone substructure. The overall result of the cycloaddition process can be interpreted as an Umpolung at the carbon atom bearing the geminal pair of trifluoromethyl groups.

Compounds **3** undergo a heterolytic bond cleavage on



1 **2** **3** **4** **5** **6** **7** **8** **9**

a; R^1 = Ph
b; R^1 = 4-MeC_6H_4
c; R^1 = 4-ClC_6H_4
d; R^1 = 4-FC_6H_4
e; R^1 = 5-methyl-2-furyl
f; R^1 = 2-thienyl

Scheme 1

heating to give a dipolar species **4**, where the negative charge is stabilized by a bis(trifluoromethyl)-substituted allylic anion. A spontaneous fluoride elimination occurs (**4** → **5**), most likely assisted by the $-OSnCl_2^+$ moiety acting as a fluoride trap. Cleavage of the O–Sn bond (**5** → **6**) by water results in a formation of the anion **6**, which is protonated (**6** → **7**). The expected 1,5-electrocyclization[6] (**6** → **8**) is not observed. The partially fluorinated unsaturated ketones **7** were obtained in high yields (80–90%) and have been fully characterized. The reaction **2** → **7** is a one-pot procedure carried out in xylene–tetrahydrofuran (THF) at 20–120 °C.

Transformation of compounds **7** into partially fluorinated furans **9** can be achieved in high yields (60–72%) on treatment with sodium hydride or lithium diisopropylamide in dipolar aprotic solvents such as dimethylformamide (DMF) at room temperature. Compounds **9** are characterized by ^1H, ^{13}C and ^{19}F NMR data as well as by mass spectrometry and elemental analysis.†

The reaction can be applied to a wide variety of aryl-substituted compounds **2**. The substitution pattern at skeletal

† *Selected data*: (^{13}C NMR, Bruker AM 360 spectrometer, 90.6 MHz; ^{19}F NMR, Bruker AM 250, 235.3 MHz, both in $CDCl_3$; *J* values in Hz): **9a**, b.p. 47 °C at 0.1 Torr, 72% yield; ^{13}C NMR, δ 153.9 (dq, ^1J 285.0, ^3J 4.5, C-2), 145.1 (C-5), 102.6 (dq, ^3J 2.0 and 2.0, C-4) and 91.6 (dq, ^2J 7.5 and 40.0, C-3); ^{19}F NMR, δ −30.1 (dq, ^4J 3.0 and 10.5, CF) and 19.4 (d, ^4J 10.5, CF_3).

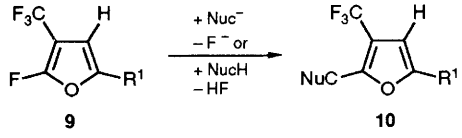
9b, m.p. 53 °C, 68% yield.

9c, m.p. 35 °C, 66% yield.

9d, b.p. 41 °C at 0.1 Torr, 70% yield.

9e, b.p. 39 °C at 0.1 Torr, 60% yield; ^{13}C NMR, δ 153.3 (dq, ^1J 285.5, ^3J 4.5, C-2), 142.1 (C-5), 101.6 (dq, ^3J 2.0 and 2.0 Hz) and 91.3 (dq, ^2J 7.0 and 40.5, C-3); ^{19}F NMR, δ −30.4 (dq, ^4J 2.5 and 11.0, CF) and 19.3 (d, ^4J 11.0).

9f, b.p. 35 °C at 0.1 Torr, 63% yield.



9 **10**

Scheme 2 Nuc = R^2O, R^2S, CN, H, Ph *etc.*; NucH = $R^2{}_2NH$

atoms 4 and 5 of the furan ring can be altered by choosing the appropriate diene **2**. The fluorine atom at C-2 is susceptible to nucleophilic displacement by a broad range of nucleophiles.[10]

The reaction described represents a convenient route to 3-trifluoromethyl-furans **9** and **10** with a variety of substitution patterns at C-2 and C-5. The possibility of introducing various side chains into the ring position 2 of the furan (**9** → **10**) (Scheme 2)‡ in the final step of the reaction sequence, in order to enhance and/or modify biological activity, makes this strategy especially versatile and valuable. A synthesis for 3-fluorofurans has been described recently.[11]

The scope of the concept of transforming CF_3-substituted hetero-1,3-dienes into partially fluorinated five-membered heteroaromatic systems and the synthetic potential of compounds of type **7** and **9** will be described elsewhere.

We thank Stiftung Volkswagenwerk for financial support, and Hoechst AG, Frankfurt, for generous supply of chemicals.

Received, 4th November 1991; Com. 1/05602F

References

1 R. Filler and Y. Kobayashi, *Biomedicinal Aspects of Fluorine Chemistry*, Kodansha, Tokyo, 1982; Rhône Poulenc Conference: *Synthesis of Aromatic and Heteroaromatic Compounds Substituted by a Limited Number of Fluorine Atoms or Short-Chain Fluorinated Groups*, Lyon, September 1986; Abstracts: *L'Actualité Chimique*, 1987, 135; J. T. Welch, *Selective Fluorination in Organic and Bioorganic Chemistry*, ACS Symposium Series 456, 1991, and literature cited therein.

2 M. S. Mustafa, A. Takaoka and N. Ishikawa, *Heterocycles*, 1986, **24**, 593, 1541; *Bull. Soc. Chim. Fr.*, 1986, 944.

3 W. Steglich, P. Gruber, H.-U. Heininger and F. Kneidl, *Chem. Ber.*, 1971, **104**, 3816; W. J. Middleton, *J. Org. Chem.*, 1984, **49**, 919; K. Tanaka, S. Maeno and K. Mitsuhashi, *J. Heterocycl. Chem.*, 1985, **22**, 565.

4 J. M. Crossman, R. N. Haszeldine and A. E. Tipping, *J. Chem. Soc., Dalton Trans.*, 1973, 483; W. Stegmann, P. Gilgen, H. Heimgartner and H. Schmid, *Helv. Chim. Acta*, 1976, **59**, 1018; R. E. Banks and S. M. Hitchen, *J. Fluorine Chem.*, 1980, **15**, 179; R. E. Banks and S. N. Mohialdin, *J. Fluorine Chem.*, 1986, **34**, 275.

5 G. Shi and Y. Xu, *J. Chem. Soc., Chem. Commun.*, 1989, 607; *J. Org. Chem.*, 1990, **55**, 3383.

6 R. D. Chambers, A. A. Lindley, P. D. Philpot, H. C. Fielding, J. Hutchinson and G. Whittaker, *J. Chem. Soc., Perkin Trans. 1*, 1979, 214.

7 A. Nezis, J. Fayn and A. Cambon, *J. Fluorine Chem.*, 1991, **53**, 285, 297; R. D. Chambers, J. Moilliet and M. H. Rock, *J. Fluorine Chem.*, 1991, **54**, 249.

8 K. Burger, K. Geith and D. Hübl, *Synthesis*, 1988, 189, 194, 199, and literature cited therein; K. Burger and B. Helmreich, *Chem.-Ztg.*, 1991, **115**, 253; K. Burger and T. Kahl, *Chem.-Ztg.*, 1988, **112**, 109.

9 T. Ishihara, H. Shinjo, Y. Inoue and T. Ando, *J. Fluorine Chem.*, 1983, **22**, 1; K. Burger and B. Helmreich, *Chem.-Ztg.*, in the press.

10 For similar reactions see: D. Hübl, M. Ganzer, F. Arndt and R. Rees, Ger. Offen. DE 3614229 (1988) (*Chem. Abstr.*, 1988, **109**, 124415c); K. Burger, E. Höss and K. Geith, *Synthesis*, 1990, 360, and literature cited therein.

11 For a synthesis of 3-fluorofurans see: H. L. Sham and D. D. Betebenner, *J. Chem. Soc., Chem. Commun.*, 1991, 1134.

‡ *E.g.* **10a** R^1 = Ph, Nuc = EtO: *selected data*: m.p.: 47 °C; yield: 96%; ^{13}C NMR ($CDCl_3$): C-2, δ 157.43 (q, ^3J 4 Hz); C-3, δ 94.16 (q, ^2J 38 Hz); C-4, δ 104.30 (q, ^3J 2 Hz); C-5; δ 145.24; ^{19}F NMR ($CDCl_3$): δ 20.38 (s, 3F, CF_3).