Synthesis of Trifluoromethyl-substituted Methanols: a Barbier Procedure under Pressure

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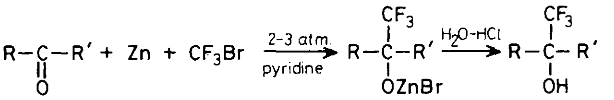
Synthesis of trifluoromethyl methanols can be achieved by stirring a mixture of carbonyl compound, zinc powder, and pyridine under a slight pressure of trifluoromethyl bromide.

Numerous studies have shown that trifluoromethyl substitution on organic compounds confers very interesting properties, particularly in the biological field.[1] However, for direct introduction of this group, the use of trifluoromethyl halides is not obvious because of their unusual reactivity.[2] For example, their condensation with carbonyl compounds in the presence of a metal (Zn, Mn, Mg, Al, or Fe) usually needs some type of activation, *i.e.* ultrasonic irradiation,[3] catalysis by metal complexes,[4] or electrolysis.[5]

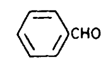
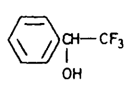
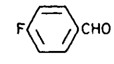
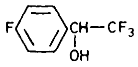
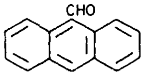
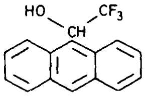
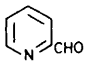
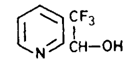
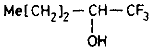
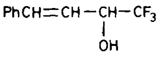
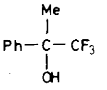
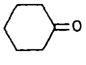
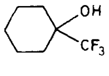
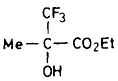


$$R{-}\underset{\underset{O}{\|}}{C}{-}R' + Zn + CF_3Br \xrightarrow[\text{pyridine}]{\text{2-3 atm.}} R{-}\overset{\overset{CF_3}{|}}{\underset{\underset{OZnBr}{|}}{C}}{-}R' \xrightarrow{H_2O\text{-}HCl} R{-}\overset{\overset{CF_3}{|}}{\underset{\underset{OH}{|}}{C}}{-}R' \quad (1)$$

Nevertheless, we have shown that reaction of trifluoromethyl bromide with sulphur dioxide in the presence of Zn, Mn, Al, or Cd can be achieved simply under a slight pressure of CF_3Br,[6] in a manner similar to its condensation with soft nucleophiles.[7]

In this communication we report the use of this procedure for a simple synthesis of trifluoromethyl-substituted methanols. The method consists of stirring for 1 or 2 h a mixture of carbonyl compound, commercial zinc powder, and pyridine under a slight pressure of trifluoromethyl bromide, at room

Table 1. Formation of trifluoromethyl-substituted methanols from the corresponding carbonyl compound.

Carbonyl compound	Product	T/°C[a]	Yield[b]/%	B.p. (mm Hg) [sublimation T]	^{19}F N.m.r. $\delta(CF_3)$/p.p.m.; J/Hz
		20	52	75 (12)	−77.8; J(F–H) 7.1
		20	60	74—76 (15)	−77.8; J(F–H) 7.1
		20	37[c]	[130—131]	−74.7; J(F–H) 8.5
		20	65[c]	[46]	−77.7; J(F–H) 6.6
$Me[CH_2]_2CHO$	 $Me[CH_2]_2{-}\underset{\underset{OH}{\mid}}{CH}{-}CF_3$	0—10	30	92—94 (760)	−79.5; J (F–H) 7.5
$PhCH{=}CH{-}CHO$	 $PhCH{=}CH{-}\underset{\underset{OH}{\mid}}{CH}{-}CF_3$	20	55	98—102 (0.5)	−77.7; J(F—H) 6.6
$Ph{-}CO{-}Me$	 $Ph{-}\overset{\overset{Me}{\mid}}{\underset{\underset{OH}{\mid}}{C}}{-}CF_3$	20	20[d]	—	−80
		20	20[e]	—	−83
$MeCO{-}CO_2Et$	 $Me{-}\overset{\overset{CF_3}{\mid}}{\underset{\underset{OH}{\mid}}{C}}{-}CO_2Et$	0—10	35	60 (65)	−79.7

[a] Temperature of water bath. [b] Unless stated otherwise yields are of purified product after distillation. [c] Yield after sublimation. [d] Yield after preparative g.l.c. (column: 10% dinonylphthalate on Chromosorb WDMCS-60/80 mesh) at 145 °C. [e] As footnote d, at 120 °C. [f] ^{19}F n.m.r. data referenced to external $CFCl_3$.

temperature in most cases. After hydrolysis, alcohols are obtained on extraction with diethyl ether, equation (1).†[8]

Both *N,N*-dimethylformamide or dimethyl sulphoxide can be used instead of pyridine but in these solvents, the reaction procedes more slowly with an induction period (between 0.25—3.0 h) and yields are lower. Various aldehydes (*e.g.* aliphatic, aromatic, allylic) and ketones can be used as starting material but the reaction is more difficult with ketones. Results, on a 0.1 mol. carbonyl compound scale, are summarized in Table 1. The reaction is very exothermic; we used a water bath round the glass flask.

Temperature control is more difficult when the reaction is scaled up. Nevertheless, we obtained a 40% yield with 0.5 mol. benzaldehyde when the internal temperature of the reaction was maintained between 30—40 °C by a slow introduction of trifluoromethyl bromide.

The order of introduction of the reagents is very important. The condensation was observed only when the carbonyl compound was placed in the medium, before, and not after, the addition of trifluoromethyl bromide. Moreover, this Barbier procedure[9] requires a slight pressure to reach fair yields.

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† *Typical procedure:* A thick glass flask containing benzaldehyde (10 ml, 0.0985 mol) and commercial zinc powder (6.5 g, 0.1 mol) in pyridine (25 ml) was placed in a Parr apparatus. The air was evacuated and then the flask was shaken for 1 or 2 h under a pressure of trifluoromethyl bromide maintained between 2.5—4 bar. The solution was filtered and hydrolysed with ice-cold 20% hydrochloric acid. This solution was extracted with diethyl ether and the unreacted benzaldehyde removed using a 38% sodium hydrogen sulphite solution. Distillation under vacuum gave 1-phenyl-2,2,2-trifluoroethanol in a yield of 52%; b.p. 75 °C at 12 mm Hg, ^{1}H n.m.r. δ_H 7.5 (ArH); 5 (q, CH), 3.5 (OH).

References

1 R. E. Banks, 'Organofluorine Chemicals and their Industrial Applications,' Soc. Chem. Ind., London, 1979, p. 123, 154, 169.

2 'Rodd's Chemistry of Carbon Compounds,' 2nd edn., ed. S. Coffey, Elsevier, Amsterdam, vol. 1, part A, 1964, p. 507; P. Tarrant, *J. Fluorine Chem.*, 1984, **25**, 69; R. N. Haszeldine, *ibid.*, 1986, **33**, 307; C. Wakselman and C. Kaziz, *ibid.*, 1986, **33**, 347.

3 T. Kitazume and N. Ishikawa, *Chem. Lett.*, 1981, 1679; *Bull. Chem. Soc. Jpn.*, 1984, 1725.

4 N. J. O'Reilly, M. Maruta, and N. Ishikawa, *Chem. Lett.*, 1984, 517; T. Kitazume and N. Ishikawa, *J. Am. Chem. Soc.*, 1985, **107**, 5186.

5 S. Sibille, E. D'Incan, D. Lefort, and J. Perichon, *Tetrahedron Lett.*, 1986, **27**, 3219.

6 C. Wakselman and M. Tordeux, Fr. Dem. 8 408 010; *Bull. Soc. Chim. Fr.*, 1986, 868.

7 M. Tordeux and C. Wakselman, Fr. Dem. 8 301 593; C. Wakselman and M. Tordeux, *J. Chem. Soc., Chem. Commun.* 1984, 793; *J. Org. Chem.*, 1985, **50**, 4047.

8 C. Francese, M. Tordeux, and C. Wakselman, Fr. Dem. 857 696.

9 For review on Barbier procedure, C. Blomberg and F. A. Hartog, *Synthesis*, 1977, 18.