Pergamon

Tetrahedron Letters 40 (1999) 6411–6414

TETRAHEDRON LETTERS

Hemiaminals of Trifluoroacetaldehyde, as Trifluoromethylating Agents.

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Received 23 June 1999; accepted 10 July 1999

Abstract :

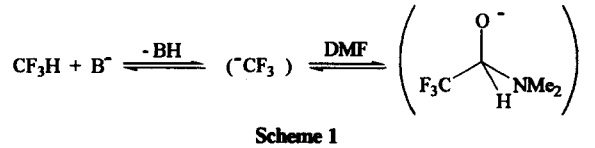
Hemiaminals of trifluoroacetaldehyde are new trifluoromethylating agents. These reagents are synthesised from amines and gaseous trifluoroacetaldehyde. tBuONa is able to deprotonate the hemiaminals to form trifluoromethyl anion equivalents $CF_3CH(O^-)NMe_2$. The trifluoromethyl anion has been transferred from such intermediates to benzaldehyde yielding phenyl (trifluoromethyl) methanol.

Keywords : trifluoromethylation / trifluoroacetaldehyde / hemiaminal / trifluoromethane.

Introduction. Nucleophilic trifluoromethylation is an important reaction in organic synthesis because the products have potential in the pharmaceutical, agrochemical and material sciences.

Many methods and reagents have been developed in the last ten years, but of these reagents, the trifluoromethyl anion, due to its low stability, is always generated in the presence of stoichiometric amounts of metal[1].

Recently we have proved that common bases (alcoholate, dimsyl anion or amide) are able to deprotonate trifluoromethane to form a trifluoromethyl anion equivalent without any metal (Zn, Cd, Cu)[2]. In this reaction, DMF plays a crucial role as solvent and stabilising agent ; the intermediate $CF_3CH(O^-)NMe_2$ has been identified as a masked and conveniently stable form of the trifluoromethyl anion (Scheme 1):



Scheme 1

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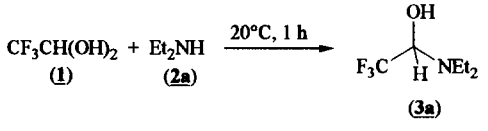
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01369-6

This masked trifluoromethyl anion is able to trifluoromethylate aldehydes, benzoic esters and sulfide derivatives.

In connection with this study, we have undertaken the synthesis of hemiaminals ($CF_3CH(OH)NR_2$) from trifluroacetaldehyde and amines in order to show that these intermediates could be new direct trifluoromethyl reagents.

Results. Fluoral hydrate ((1), $CF_3CH(OH)_2$), the most easily handled form of trifluoroacetaldehyde, was used in aqueous solution (75% w/w). As shown in Table 1, the reaction of diethylamine and (1) is an equilibrium. When the amount of diethylamine was changed from one equivalent (Entry 1) to ten equivalents (Entry 4), the yield of the hemiaminal (3a) increased from 27% to 83%.



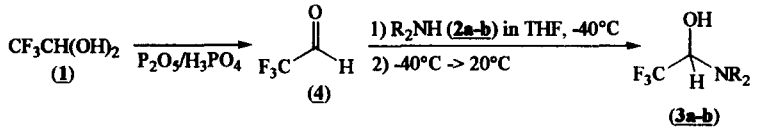
Entry	Et_2NH (eq.)	$(CF_3CH(OH)NEt_2$ % [a]
1	1	27
2	2	52
3	5	75
4	10	83

a) Determined by ^{19}F NMR with an internal standard.

Table 1 : Hemiaminal synthesis from fluoral hydrate

Unfortunately, because of this equilibrium, when the excess of diethylamine was removed in order to isolate (3a), water present in the reaction mixture induced the reverse reaction. A solution to this problem would be to use an amine forming an azeotrope with water. Dibutylamine is a good candidate because it forms such an azeotrope (Bp_{760} = 97°C, 49.5% weight in nBu_2NH). We demonstrated this to be the case.

A typical experimental procedure was as follows : to a cold (0°C) aqueous solution of fluoral hydrate (75% w/w, 0.835 g, ie 5.4 mmol of $CF_3CH(OH)_2$) was added dropwise nBu_2NH (7.30 g, 56.5 mmol). The reaction mixture was then allowed to warm to room temperature and was kept at this temperature for 4 hours. The dibutylamine-water azeotrope and the excess of dibutylamine were then distilled under reduced pressure (15 mBar, Bp : 50-56°C) leaving crude $CF_3CH(OH)NBu_2$ (3b) [3] . It was not easy to eliminate the last traces of amine without causing some decomposition of (3b). This synthesis allowed us to prepare (3b) but the method was not transposable to amines other than dibutylamine. As a result of this, we tried to synthesize hemiaminals from anhydrous trifluoroacetaldehyde (Table 2).



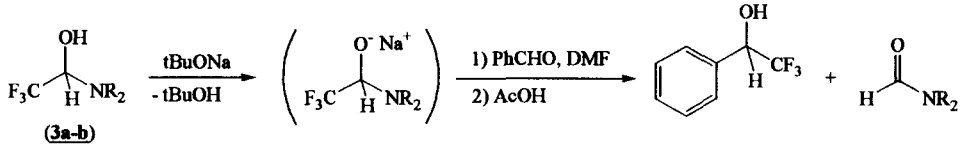
Entry	R_2NH	molar ratio (2)/(1)	Yield (3) % [a]	% $CF_3CH(OH)_2$ in (3) [b]
5	Et_2NH (2a)	1 / 2.8	90 (3a)	2
6	nBu_2NH (2b)	1 / 2.7	90 (3b)	2

a) Determined by ^{19}F NMR with an internal standard,

b) Determined by ^{19}F NMR (hydratation of CF_3CHO in excess).

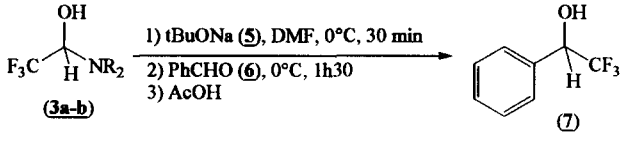
Table 2 : Hemiaminal synthesis from anhydrous trifluoroacetaldehyde

Trifluoroacetaldehyde was obtained by dehydratation of the hydrate with a P_2O_5 / H_3PO_4 mixture[4] and then added to a solution of amine in anhydrous THF at -40°C. The reaction mixture was allowed to warm to room temperature affording hemiaminals (3a) and (3b) in 90% yield in THF solution (as determined by ^{19}F NMR using an internal standard). These solutions were used directly in the trifluoromethylation reaction. As shown in Scheme 2, we expected t-BuONa to deprotonate (3a-b), DMF to stabilise the trifluoromethyl anion and efficient trifluoromethylation of benzaldehyde to occur.



Scheme 2

Indeed , as shown in Table 3, (3a-b) achieved trifluoromethylation of benzaldehyde, albeit in yield lower than by fluoroform (67%)[2c].



Entry	(3a-b)/(5)/(6) [a]	Yield (7) % [b]
7	1.1/1.3/1	48
8	1.1/1.1/1	37

a) Molar ratio,

b) Determined by ^{19}F NMR and GC with an internal standard.

Table 3 : Trifluoromethylation of benzaldehyde

In conclusion, we have shown that hemiaminals $CF_3CH(OH)NEt_2$ and $CF_3CH(OH)NBu_2$ can be synthesised from CF_3CHO and the corresponding amine and used in THF solution to effect the trifluoromethylation of benzaldehyde.
Work is underway to improve the yield of trifluoromethylation and to generalise the reaction to other electrophiles.

Typical procedure for trifluoromethylation :

To a cold (0°C) solution of tBuONa (0.6 g, 6.2 mmol) in anhydrous DMF (30 ml) was added dropwise, under a nitrogen atmosphere a solution of (3a-b) (6.2 mmol) in anhydrous THF (6 ml). The solution was kept at 0°C for 0.5 h. Benzaldehyde (0.61g, 5.8 mmol) was then added dropwise to this solution at 0°C. The reaction mixture was kept at 0°C for 1.5 h. Acetic acid (0.42 g, 7.0 mmol) was then introduced dropwise at 0°C and the reaction mixture was allowed to warm to room temperature.
The yield of $CF_3CH(OH)Ph$ present in the reaction mixture was determined on the crude material by ^{19}F NMR and GLC using internal standards.

References.

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3. NMR identification of $CF_3CH(OH)NBu_2$: ^1H NMR (DMSO d_6, 300 MHz, ref : HMDS), δ : 4.36 (q, $^3J_{HF}$ = 7.5 Hz, 1H, $CF_3\underline{CH}$-), 2.61 (t,$^3J_{HH}$ = 8 Hz, 4H, 2 N-$\underline{CH_2}$), 1.34 (m, 4H, 2 CH_2), 1.26 (m, 4H, 2 CH_2), 0.82 (t, $^3J_{HH}$ = 8 Hz, 6H, 2 CH_3);^{19}F NMR (DMSO d_6, 282 MHz, ref : TFA[with $\delta_{(TFA)}$ = -76 ppm /$CFCl_3$]), δ : -7.8 (d, $^3J_{HF}$ = 7.5 Hz, 3F, CF_3); ^{13}C NMR (DMSO d_6, 75 MHz, ref : TMS), δ : 124.0 (q, $^1J_{CF}$ = 285 Hz, 1C, CF_3), 80.8 (q,$^2J_{CF}$ = 32 Hz,1C, $CF_3\underline{C}H$), 49.0 (s, 2C, 2 N-CH_2), 31.5 (s, 2C, 2 CH_2), 19.8 (s, 2C, 2 CH_2), 13.0 (s, 2C, 2 CH_3).
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