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Trifluoroethylidenation of Compounds with Activated Methylene Groups

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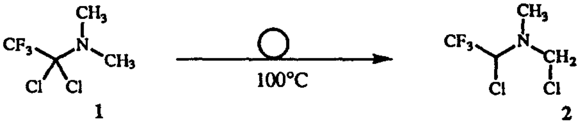
Dedicated to Professor Horst Böhme on the occasion of his 85th anniversary.

Key Words : Trifluoromethyl iminium salts, β-trifluoromethyl vinyl ketones, captodative carbocations, Polonovsky-Potier reaction.

Abstract: *α-trifluoromethyl iminium trifluoroacetates 5 can be prepared from N-oxides 4 and used in situ or after isolation. Condensation occurs with carbonyl activated methylene groups to give useful β-trifluoromethyl vinyl ketones 8.*

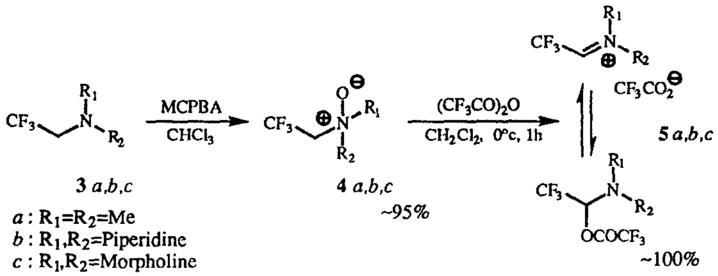
Our earlier report on the synthesis of N,N-dimethyl trifluoroacetamide chloride **1** and its facile thermal isomerisation to the α,α'-dichloroamine **2** elicited mechanistic and preparative interest[1].



Both **1** and **2** are covalent but very reactive towards nucleophiles; in particular **2** can be regarded as a twofold Mannich reagent and as an efficient carrier of the trifluoromethyl group. Such fluorinated synthons have increasing synthetic interest due to the recognition of the biological importance of fluorine substitution. At this oxidation level, the simplest reagent should be trifluoroethanal but this compound is a gas which is difficult to handle and furthermore the condensation products are trifluoromethyl carbinol derivatives which are difficult to dehydrate[2]. Therefore, the search for other equivalents is of interest.

The commercial hemiacetal of fluoral was described to be a valuable reagent under Friedel-Crafts type conditions and was also found to react with nucleophilic organosilanes[3]. The corresponding N,O and S,O-acetals were also reported recently[4, 5].

Our title reaction is based on the new α-trifluoromethyl iminium trifluoroacetates **5** which in fact are iminium salts of fluoral. They are obtained regioselectively, in nearly quantitative yield by the Polonovsky-Potier reaction[6] from N-oxides **4**[7] of trifluoroethylamines **3**[8].



3 *a,b,c*

4 *a,b,c* ~95%

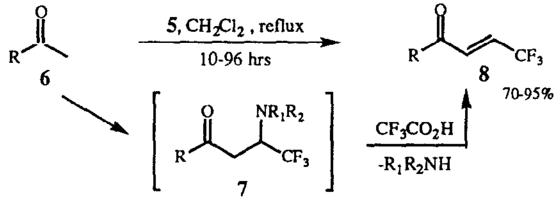
5 *a,b,c*

~100%

a : $R_1=R_2=Me$
b : R_1,R_2=Piperidine
c : R_1,R_2=Morpholine

The iminium salts **5***a,b,c* generated in dichloromethane or chloroform can be used *in situ*[9]. Moreover, the dimethylamino derivative **5***a* can be easily purified by distillation before use to remove traces of trifluoroacetic acid[10] which is important for reactions with enolates or enol ethers[11].

The new trifluoromethyl iminium salts **5** can be regarded as reactive capto-dative cations. Their condensation with α-methylene ketones furnishes, with concomittant loss of the amino group, β-trifluoromethyl vinyl ketones **8** in high yield.

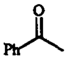
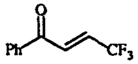
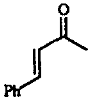
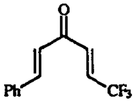
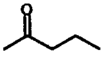
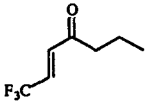
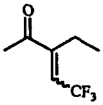
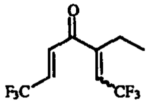
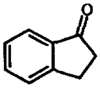
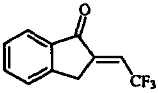
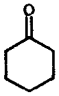
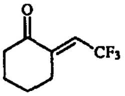
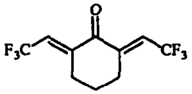
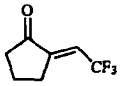
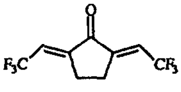
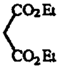
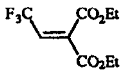
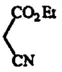
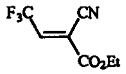


6

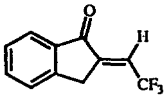
7

8

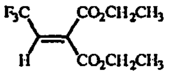
The following table clearly illustrates the scope of this reaction when applied to various ketones, malonate and cyanoacetate. The reactions of **5** with other substrates will be reported in a forthcoming publication.

	Starting Ketones	Products a	b	c	Eq. of 5	Time (hrs)	Yield(%) a : b : c
1.					1,2	96	88
2.					1,2	96	84
3.					1,2	72	40 : 20 : 10
4.					1,2	96	78
5.					1	72	56 : 18
					2	72	0 : 73
6.					1	72	40 : 26
					2	72	0 : 71
7.					1,2	15	83
8.					1,2	10	86

The configurations Z or E of the double bonds were determined by the vicinal $^3J_{C,H}$ coupling constants deduced from off-resonance decoupled experiments[12]. Their values for 4, 7 and 8 are listed below.

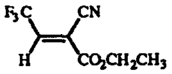


$^3J_{CH_2,H}$ = 7,7 Hz



$^3J^{Cis}_{COO,H}$ = 7,3 Hz

$^3J^{Trans}_{COO,H}$ = 11,3 Hz



$^3J^{Cis}_{COO,H}$ = 6,6 Hz

$^3J^{Trans}_{CN,H}$ = 13,5 Hz

β-Trifluoromethyl vinyl ketones **8** are useful reagents for heterocyclisations and are efficient partners in cycloaddition[13]. Our method makes this class of compounds readily accessible for further study as building blocks for the synthesis of trifluoromethylated compounds.

Besides the reaction with ketones, the scope of reactions starting with **5** includes nucleophiles in general, enolisable aldehydes, electron rich olefins and aromatics.

ACKNOWLEDGEMENTS

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7. N-oxides *4a,b,c* were synthetised in analogy to a reported procedure : see J. C. Craig and K. K. Purushothaman, *J. Org. Chem.*, **35**, 1721 (1970). The following procedure was applied: dry MCPBA-$CHCl_3$ solution was obtained by dissolving the commercial MCPBA (50-60%) in $CHCl_3$, stirred with $MgSO_4$ for 15 min and then filtered. Since *4a* is hygroscopic, it must be kept under dry atmosphere.
8. Trifluoroethylamines were synthetised according to a reported procedure : T. Fuchigami, Y. Nakagawa, T. Nonaka, *J. Org. Chem.*, **52**, 5489 (1987); E. R. Bissel and M. Finger, *J. Org. Chem.*, **24**, 1256 (1959).
9. The N-oxide *4a,b* or *c* is dissolved in dry CH_2Cl_2 and stirred at 0°C under argon. To this solution, trifluoroacetic anhydride (1.2 eq.) is added over a period of 5 min and the temperature maintained for 30 min at 0°C and 30 min at r. t.. Carbonyl compounds can be added and reaction started. Extractive work-up, chromatographic purifications and horizontal distillations gave the condensation products as oils. All compounds were identified by NMR, IR, Mass and elementary analyses.
10. To remove traces of trifluoroacetic acid, iminium salts are concentrate *in vacuo* ; *5a* can be distilled.
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