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TRIFLUOROMETHANESULFONYL CHLORIDE, A MILD CHLORINATING AGENT[1]

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Carbon acids (pK_A range: dialkyl malonate → methyl dichloroacetate) are efficiently chlorinated with CF_3SO_2Cl/NEt_3, even in the presence of alcohols.

It is well known that trifluoromethanesulfonyl chloride is an effective sulfonating agent for alcohols and amines. We wish to report that it is also a very effective mild chlorinating agent.

A series of carbon acids was treated with one equivalent of CF_3SO_2Cl and one equivalent of NEt_3 or DBu (1,5-diazabicyclo[5.4.0]undec-5-ene) per "acidic" hydrogen in CH_2Cl_2at 20-25^o for 1 hr. The results are summarized in the table, and show that fairly acidic compounds such as dimethyl malonate, methyl dichloroacetate or diethyl phosphite, and nucleophiles such as phenyl lithium are chlorinated.

Starting material	Product	Yield	
		DBU	NEt_3
$CH_3COCH_2COCH_3$	$CH_3COCCl_2COCH_3$ [3]	100%	100%
CH_3COCH_2COOEt	CH_3COCCl_2COOEt [3]	100%	100%
$CH_3COCH(CH_3)COOEt$	$CH_3COCCl(CH_3)COOEt$ [3]	96%	87%
$CH_2(COOMe)_2$	$CCl_2(COOMe)_2$ [3]	100%	100%
$NC\text{-}CH_2COOMe$	$NCCCl_2COOMe$ [3]	100%	100%
$(EtO)_2PHO$	$(EtO)_2PClO$ [3]	100%	85%
$Cl_2CHCOOMe$	$Cl_3CCOOMe$ [3]	70%	20%
$(MeOOC)_2HCNHCOCH_2N_3$	$(MeOOC)_2CO$ [3]		70%
PhLi	PhCl [3]	80%	

In the chlorination of dimethyl malonate, triethylammonium trifluoromethyl sulphinate[3] was isolated as the second product of the reaction. Dimethyl malonate did not react with trifluoromethanesulfonyl anhydride/NEt_3.

Other substrates bearing less acidic hydrogens such as methyl phenylacetate, cyclohexanone, acetophenone, methyl chloroacetate, phenylacetonitrile and methyl diphenylacetate, did not react under the conditions employed. Highly nucleophilic olefins such as 1-piperidinylcyclohexene gave a mixture of α,α and α,α'-dichlorocyclohexanone in moderate yield.[4] Other unsaturated compounds such as Δ^5-steroids, ethyl acrylate or anisole did not react.

In order to compare the relative sulfonating and chlorinating properties of CF_3SO_2Cl with respect to alcohols and carbanions, a methanolic solution of dimethyl malonate (pK_A 13.5) was treated with 2 eq of CF_3SO_2Cl and 2 eq of NEt_3 (pK_B 3.0). Dimethyl dichloromalonate was the exclusive reaction product at concentrations as low as 5×10^{-2} molar ($MeOH:CH_2(COOMe)_2$ = 500:1).

At higher dilution, mixtures of dimethyl malonate and dimethyl dichloromalonate were isolated, and only at a concentration of 3.85×10^{-3} molar did sulfonation of methanol become the main reaction, as evidenced by recovery of dimethyl malonate only. It should be mentioned that both chlorination of dimethyl malonate in methanol (5×10^{-2} molar) and triflation of methanol (5×10^{-2} molar) were complete after 5 minutes reaction time at 22°.

The ratio of the rate of chlorination of carbanions versus that of sulfonation of alcohols by CF_3SO_2Cl/NEt_3 in CH_2Cl_2 must therefore be $>10^5$.

A comparison of the relative halogenating properties of CF_3SO_2Cl, N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS) and Br_2 towards a series of "acidic" compounds was carried out, using the conditions outlined in the experimental section, and the yields of mono (entries 1-4) and dihalo (entry 5) compounds obtained are summarized in the following table.

	CF_3SO_2Cl	NCS	NBS	Br_2
1. 2-Carbethoxybutyrolactone	100%	30	5	35
2. Diethyl methylmalonate	100	40	10	35
3. Ethyl 2-methylacetoacetate	100	35	7	30
4. Diethyl 2-(3-azidopropyl)malonate	100	25	3	20
5. Triethyl phosphonoacetate	100	0	0	0

Experimental

To a solution of 1 mmol of substrate in 15 ml of CH_2Cl_2 at 20° was added per n "acidic" hydrogen of substrate n mmol of NEt_3 and n mmole of CF_3SO_2Cl. After 1 hr, the solution was washed with water, dried and the solvent evaporated, and the product purified by chromatography.

References, Footnotes and Acknowledgements

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3. Structures were proven by i.r., n.m.r., C.I.-mass spectroscopy, mass spectroscopy, and by elemental analysis or comparison with an authentic sample.
4. Established by g.c.-mass spectrometry and n.m.r. only.

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