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Ethyl Trifluoroacetate: A Powerful Reagent for Differentiating Amino Groups

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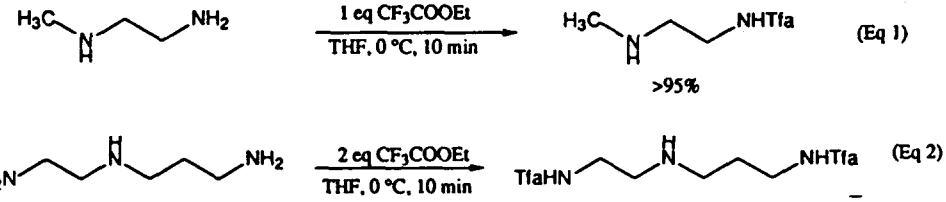
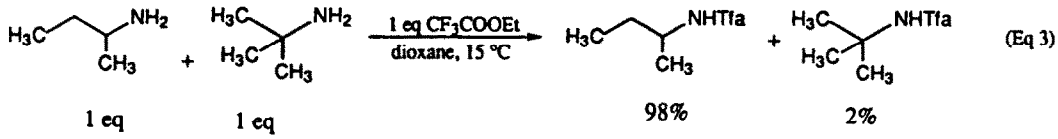
Abstract: Selective protection of primary amines in the presence of secondary amines and monofunctionalization of symmetric primary and secondary diamines using ethyl trifluoroacetate is described. Effective differentiation of primary, secondary and tertiary alkyl-substituted primary amines from one another by ethyl trifluoroacetate acylation is also demonstrated. These results are explained on the basis of steric and electronic effects of the substrate amines.

The trifluoroacetyl (Tfa) group has been widely used as an amine protecting group in organic synthesis due to the ease of its removal under mild conditions. Trifluoroacetic anhydride is the reagent most widely used for this purpose.[1] As this reagent is too reactive, all types of amino groups gets acylated under these conditions. Ethyl trifluoroacetate, a mild trifuoroacetyl transferring agent, on the other hand was used in few instances for differentiating amino groups.[2] As there is no detailed study[3] on the scope of this acyl transfer, we undertook a systematic investigation, and the details of these results are presented in this paper.

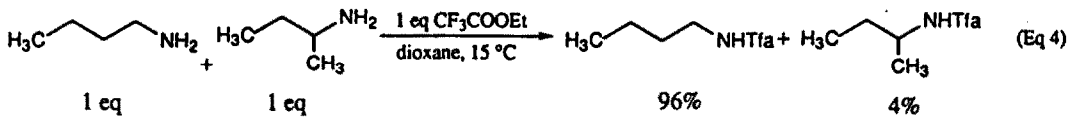
We found that trifluoroacetylation of primary amines can be conveniently achieved by simple mixing of the amine and a stoichiometric amount of ethyl trifluoroacetate under neutral conditions at 0 °C. The reaction normally goes to completion in a few minutes, and the product is isolated by evaporation of the solvent and the liberated ethanol. These mild conditions offer exclusive primary amine acylation in the presence of secondary amines[4] as exemplified by equations 1 and 2.



The observed selectivity is attributed to the differences in steric demand of primary and secondary amines in accordance with aminolysis of esters.[5] The steric influence of substituents on the amino group is clearly demonstrated by competition experiments using *t*-, *i*-, and *n*-butylamines (Eqs 3 & 4). The high selectivity and mild conditions makes this trifluoroacetylation protocol a powerful tool for the differentiation of primary, secondary and tertiary alkyl-substituted primary amines.



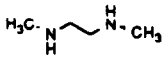
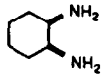
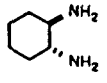
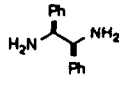
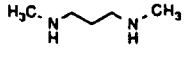
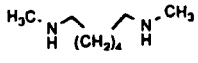
(Eq 3)



(Eq 4)

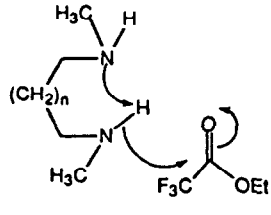
The reaction of ethyl trifluoroacetate with symmetric diamines is even more interesting. Excellent selectivities are realized for mono-trifluoroacetylation of all 1,2-diamines studied except for *trans*-1,2-diaminocyclohexane (see the Table). Even the highly reactive ethylenediamine offered moderate selectivity at 0 °C (entry 2), and the selectivity is improved to the synthetically useful range of 12.6:1 (93% of mono- vs. 7% of bis-trifluoroacetate) when the acylation is run at -70 °C (entry 3). The stark differences in selectivity among *cis*- and *trans*-diaminocyclohexanes and the 1,2-diphenylethylenediamine are most intriguing (entries 4, 5, and 6). While both *cis*-diaminocyclohexane and 1,2-diphenylethylenediamine give extremely high selectivity for mono-trifluoroacylation, *trans*-diaminocyclohexane shows statistical distribution of all the possible products in the reaction mixture after the addition of one equivalent of ethyl trifluoroacetate, with the starting diamine, the monoacylated product and the bisacylated product in the ratio of roughly 1:2:1. This clearly indicates the cooperative nature of the two nitrogens in the aminolysis i.e., general base catalysis by the other nitrogen via intramolecular hydrogen bonding likely accounting for the selectivity (see Scheme).[6] When the two nitrogens are farther apart, this intramolecular polarization becomes less entropically favored, and the attacking nitrogen also becomes more sterically crowded. This explains the reduced selectivities for mono-trifluoroacetylation in the series from ethylenediamine, propanediamine, piperazine to hexanediamine (*c.f.* entries 1, 7, 8 and 9).

Table

Entry	Substrate	Mono/Bis[a,b]	Rxn Temp	Solvent[c]
1		43.7	RT	THF
2		3.0	0 °C	MeCN
3		12.6	-70 °C	EtOH
4		68.0	0 °C	MeCN/EtOH
5		1.8	0 °C	THF
6		> 100[d]	0 °C	THF
7		8.3	RT	THF
8		5.8	RT	THF
9		3.6	RT	THF

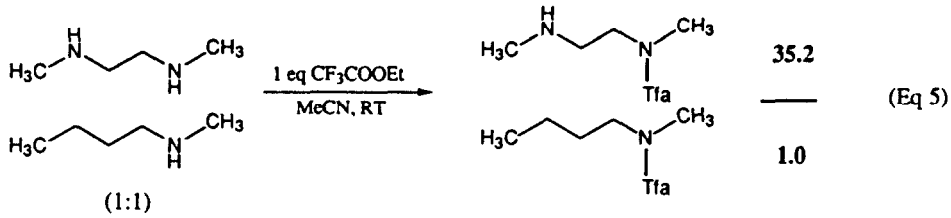
a) The ratio of monotrifluoroacylated product and the bistrifluoroacylated product upon complete reaction with 1 equivalent of ethyl trifluoroacetate; b) The ratios were determined by GC using a DB-1 column and were confirmed by ^{1}H NMR spectra after the completion of the reactions; c) Solvents were chosen for solubility and GC considerations; d) No further acylation was observed even with excess ethyl trifluoroacetate.

Scheme:

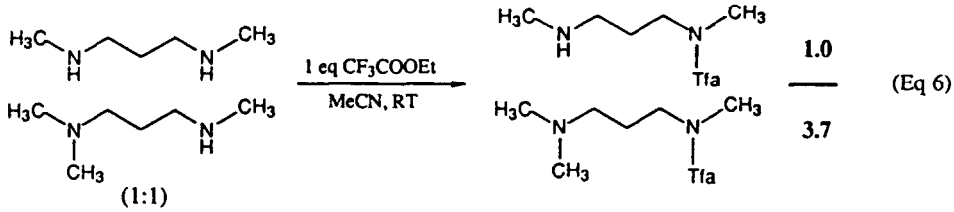


(n = 0,1,...)

The intramolecular catalysis assumption is further supported by the competition studies illustrated in equations 5 and 6. The secondary amino group in N,N',N'-trimethylpropanediamine is more selectively trifluoroacetylated over the one in N,N'-dimethylpropanediamine probably due to higher basicity of the trimethyl analog.



(Eq 5)



(Eq 6)

In conclusion, we have demonstrated the broad scope of trifluoroacetylations with ethyl trifluoroacetate for differentiating amino groups from one another. This trifluoroacetylation is highly sensitive to the steric and electronic influences of the amines and, therefore, promises a wide variety of applications in synthetic organic chemistry for selective amino group functionalizations.

References and Notes:

1. Green, T. W. and Wuts, P. G. M. *Protective Groups in Organic Synthesis* John Wiley & Sons, Inc. New York, 1991.
2. (a) Mitchinson, A; Golding, B.T.; Griffin, R.J.; O'Sullivan, M. C. *J. Chem. Soc., Chem. Commun.* **1994**, 2613. (b) Rizo, J.; Albericio, F.; Giralt, E. and Pedroso. *Tetrahedron Lett.* **1992**, *33*, 397. (c) Aviron-Violet, P. and Gervals, C. US Patent 4943679.
3. Recently, O'Sullivan and Dalrymple reported (*Tetrahedron Lett.* **1995**, *36*, 3451) the extension of their earlier finding (ref. 2 (a)) on the differentiation of primary amines in spermidine to other polyamines.
4. The products obtained as described have purities of $\geq$ 98%, determined by ^{1}H NMR.
5. (a) Mc. Arnett, E.; Miller, J. G. and Day, A. R. *J. Am. Chem. Soc.* **1950**, *72*, 5635. (b) *ibid*, **1951**, *73*, 5393.
6. Werner, B. H. H. and Fischer, E. O. *Angew. Chem. Int . Ed. Engl.* **1968**, *7*, 817.

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