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PREPARATION OF SECONDARY AMINES THROUGH EFFICIENT ALKYLATION OF N-SUBSTITUTED TRIFLUOROACETAMIDES

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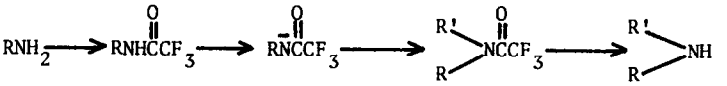
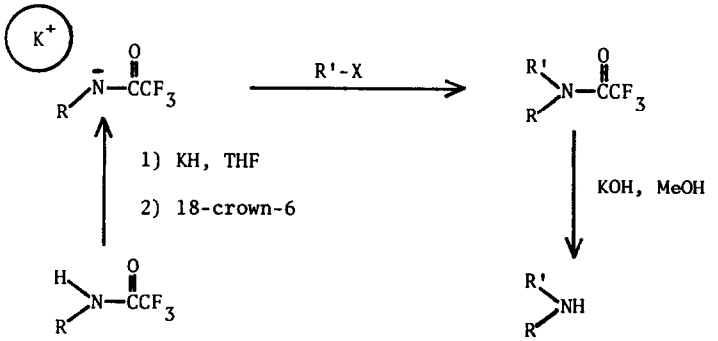
Trifluoroacetamides are attractive intermediates for the Gabriel-like[1] transformation of primary to secondary amines through a sequence of acylation, ionization, alkylation, and hydrolysis. Overalkylation is precluded, and the trifluoroacetyl group is readily introduced[2] to furnish a carboxamide of exceptional acidity[2a] and, later, ease of saponification.[2a,3]



Such reactions have in fact been carried out by several workers,[4,5] but no convenient and efficient general procedure can yet be said to have been developed.

We wish to report that characteristically high yields of secondary amines are produced following saponification when N-alkyl or -aryl trifluoroacetamides are primary-alkylated in tetrahydrofuran using potassium hydride as base and 18-crown-6 as alkylation catalyst. We believe the method should find wide applicability.



Deprotonation of the starting amide under these conditions is immediate, preventing significant condensation (distillation residues are negligible). The derived anions, cation-separated through crown-ether complexation,[6] are moderately reactive nucleophiles, typical alkylations reaching completion in 6-30 hr in boiling THF. Ambident selectivity is high; only N-alkylation has been observed in the reactions studied thus far. Deacylation of the dialkylamides is easily conducted by treatment with KOH in methanol at room temperature.[2a,3]

Our results to date are presented in Table I. All compounds here have been previously reported in the literature with the exception of N-methyl-N-benzyltrifluoroacetamide and N-allyltrifluoroacetanilide. Products were identified by melting and boiling points where available and in all cases (except o-bis(anilinomethyl)benzene) by ^{1}H NMR spectral comparison with data published or obtained for authentic samples. The disubstituted trifluoroacetamides were prepared for this purpose by trifluoroacetylation[2b,c] of the corresponding secondary amines.

In a representative reaction, 1.44 g (0.036 mole, 20% excess) of potassium hydride (Ventron, freed from protective mineral oil by three 10-ml hexane washings each followed by centrifugation) was added to 60 ml of anhydrous tetrahydrofuran under nitrogen at 0-5°C. The addition in several portions of 5.67 g (0.030 mole) of trifluoroacetanilide[2d] to the magnetically stirred suspension was attended by vigorous gas (H_2) evolution. After 5 min 50 mg of 18-crown-6 (Aldrich) and 5.08 g (0.042 mole, 40% excess) of freshly distilled allyl bromide were added, and the reaction mixture was stirred at room temperature for 2 hr and then at reflux temperature overnight. Most of the THF was removed by distillation at 30 mm, whereupon 150 ml of ether was added to the residue followed cautiously by 100 ml of 1% aqueous HCl. The mixture was transferred to a separatory funnel and shaken, the layers separated, and the aqueous layer extracted with three 50-ml portions of ether. The combined ether solution was washed with 100 ml of 5% $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. Distillation of the solvent and vacuum distillation of the product yielded 5.9 g (0.0258 mole, 86%) of colorless liquid, bp 69-72° (0.5 mm) (which yellowed on standing). The compound was identical in bp and ^{1}H NMR and IR spectra with that prepared by trifluoroacetylation[2d] of N-allylaniline (Aldrich).

Full details for these and additional cases will be reported shortly.

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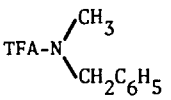
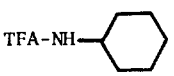
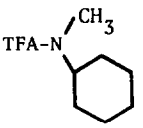
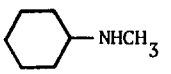
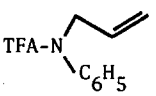
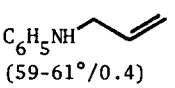
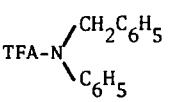
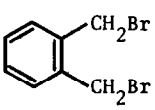
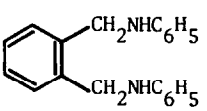
Table I. Secondary Amines from N-Alkyl- and -Aryltrifluoroacetamides.

Trifluoroacetamide reactant (moles)	Alkylating reagent (moles)	Isolated intermediate; yield (bp/mm Hg, or mp)	Amine product; yield (bp/mm Hg, or mp)	Reactant and product refs
TFA-$NHCH_3$ (0.022)	$C_6H_5CH_2Br$ (0.020)	 82%	$C_6H_5CH_2NHCH_3$ (75-78°/3.5) 85%[a]	2a,c,d, 7, 8, 9, 10
TFA-$NHCH_2C_6H_5$ (0.030)	CH_3I (0.036)	(67-67.5°/1.0) 88%		
TFA-NHC_4H_9-n (0.030)	n-C_4H_9Br (0.042)	TFA-$N(C_4H_9\text{-n})_2$ (75-78°/3.5) 93%	$(n\text{-}C_4H_9)_2NH$ (64-66°/20) 99%[a]	2d, 4d, 10, 11
TFA-NH  (0.030)	CH_3I (0.036)	 (61-62°/0.8) 93%	 (61-63°/35) 91%[a]	2d, 7, 8, 10, 12, 13
TFA-NHC_6H_5 (0.040)	CH_3CH_2Br (0.048)	———	$C_6H_5NHC_2H_5$ (77-78°/7) 87%[b]	2a,d, 10, 14
TFA-NHC_6H_5 (0.030)	$CH_2{=}CHCH_2Br$ (0.042)	 (69-72°/0.5) 86%	 (59-61°/0.4) 90%[a]	2a,d, 8, 10 14, 15
TFA-NHC_6H_5 (0.033)	$C_6H_5CH_2Br$ (0.030)	 (36-37°) 87%	$C_6H_5NHCH_2C_6H_5$ (35-36°) 95%[a]	2a,d, 10, 14, 16
TFA-NHC_6H_5 (0.0115)	 (0.0050)	———	 (108-109°) 63%[b]	2a,d, 14, 17

[a]Yield from the disubstituted trifluoroacetamide. [b]Yield from the monosubstituted trifluoroacetamide.

References and Notes

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(6) See C. L. Liotta in "Synthetic Multidentate Macrocyclic Compounds," R. M. Izatt and J. J. Christensen, Eds., Academic Press, New York, N. Y., 1978.

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(9) TFA-N(CH_3)$CH_2C_6H_5$ ^{1}H NMR ($CDCl_3$, 60 MHz): δ 2.97 (d with fine structure), 4.60 (s), 7.28 (s).

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(11) TFA-N(C_4H_9-n)$_2$ NMR: δ 0.95 (irregular t), 1.1-2.0 (m), 3.38 (broad t, J = 7.0).

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(13) TFA-N(CH_3)C_6H_{11}-c NMR: δ 0.8-2.1 (m), 2.91 (s), 2.97 (q, J = 1.6), 3.70 (broad s), 4.29 (broad s).

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(15) TFA-N(C_6H_5)CH_2CHCH_2 NMR: δ 4.33 (d, J = 6.0), 4.5-5.4 (irregular t), 5.5-6.3 (m), 7.0-7.7 (m).

(16) TFA-N(C_6H_5)$CH_2C_6H_5$ NMR: δ 4.88 (s), 6.8-7.5 (m).

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