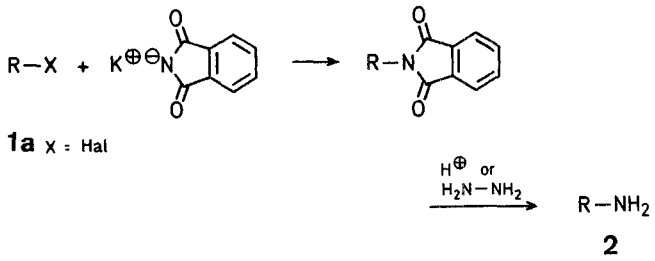
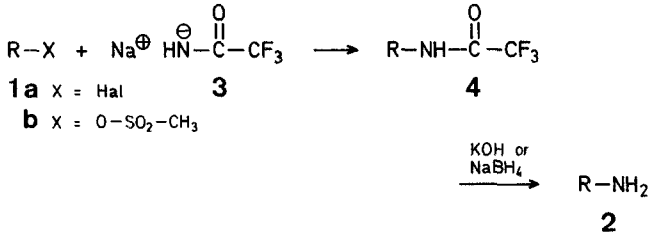


Scheme A

We report a method of similar scope but where removal of the blocking group is relatively easy. This involves treating the alkyl halides **1a** with the sodium salt of trifluoroacetamide **(3)** to give the *N*-alkyltrifluoroacetamide **4**, which is then either hydrolysed[5] or reduced by sodium borohydride[6] (Scheme **B**). *Secondary* amines have been synthesized previously via alkylation of *N*-alkyltrifluoroacetamides[7], but we find that alkylation of trifluoroacetamide itself is significantly easier and that this allows primary amines **2** to be prepared free of secondary amines.

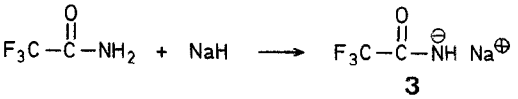


Scheme **B**

A range of halides **1a** and mesylates **1b** was treated with **3** in dimethylformamide at 70 °C, the salt being prepared *in situ* from trifluoroacetamide and sodium hydride. Generally the derived *N*-alkylamide **4** was isolated by distillation and was then either hydrolyzed with alkali or reduced with sodium borohydride in ethanol. In some cases the crude alkylation product was cleaved directly (Table 1).

Thus, several primary amines **2** were prepared satisfactorily from the corresponding primary alkyl iodides or mesylates, benzyl and allyl halides, α-bromo-carbonyl compounds, and 2,4-dinitrochlorobenzene. With other substrates, especially primary chlorides and secondary halides or mesylates, elimination to give the corresponding olefin is an important competing reaction (Table 1). Interestingly there appears to be little or no tendency for bis-alkylation. Even in the reaction of 1,5-diiodopentane with two molar equivalents of **3** where bis-alkylation results in a 6-membered ring, only 55% of the di-iodide reacted in this way, whilst 43% reacted once at each end.

Attempts to prepare secondary amines **6** from trifluoroacetamide by treating it successively with 1 mol equivalent of sodium hydride and **1**, followed later by a further one mol equivalent of each (Scheme **C**) were generally unsatisfactory, mixtures of mono- and di-alkylamides being obtained (Table 2). Conversion of primary amines **2** into secondary amines **6** by trifluoroacetylation of the primary amine **2** and alkylation of the product **4** was more successful (Scheme **C**, Table 2). The current base-solvent system results in comparable or better yields than those obtained with similar systems studied previously[7,8].



Synthesis of Primary Amines via Alkylation of the Sodium Salt of Trifluoroacetamide: An Alternative to the Gabriel Synthesis

Philip A. HARLAND, Philip HODGE*

Department of Chemistry, University of Lancaster, Lancaster, LA1 4YA, Great Britain

Wilfrid MAUGHAN, Eric WILDSMITH

Lancaster Synthesis Ltd., Eastgate, White Lund, Morecambe, LA3 1BR, Great Britain

The classical method for converting alkyl halides **1a** into *primary* amines **2** without polyalkylation is the Gabriel synthesis[1,2,3]. This involves reacting the alkyl halide **1a** with the sodium or potassium salt of phthalimide, then decomposing the product either by hydrolysis[2] or hydrazinolysis[3] (Scheme **A**). Alternatives have been reported[4].

Table 1. Alkylation of Sodium Trifluoroacetamide (**3**) to the *N*-Alkylamides **4** and Cleavage of the Latter to Primary Amines **2** (Scheme **B**)

Substrate **1a** R—X	*N*-Alkyltrifluoroacetamide **4**[a,b]			Yield [%] of Olefin	Primary Amine **2**[b]			
	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula or Lit. Data		Method of Cleavage of **4**[c]	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Lit. Data
n-C_8H_{17}—J	79	120–122°/2	160°/10[10]	19	A	83	190°/760	175–177°/745[9]
n-C_8H_{17}—Br	53	140°/4	as above	30[d]	A	87	185–187°/755	as above
n-C_8H_{17}—Cl	20	165°/11	as above	65[d]	–	–	–	–
n-C_8H_{17}—OSO_2CH_3	72	130–134°/3	as above	9[d]	–	–	–	–
n-$C_{16}H_{23}$-J	not isolated				B	86[e]	44–48°	46°[9]
n-C_6H_{13}—$CH(CH_3)$—J	14	86–90°/9[f]	$C_{10}H_{18}F_3NO$ (225.3)	71[g]	C	96	154–158°/760	163–165°/760[9]
n-C_6H_{13}—$CH(CH_3)$—Br	0	–	–	82[g]	–	–	–	–
n-C_6H_{13}—$CH(CH_3)$—OSO_2CH_3	21	79–81°/7[f]	as above	76[g]	–	–	–	–
J—$(CH_2)_5$—J	43[h]	84–86°[i]	110–112°[10]	–[j]	B	90	174–177°/755	178–180°/760[9]
	55[k]	46–51°/4	44°/1[11]	–[j]	B	91	105–106°/755	106°/760[9]
c-C_6H_{11}—Br	0	–	–	86[l]	–	–	–	–
C_6H_5—CH_2—Cl	72	69–72°	73.5–74.5°[10]	–	B	95	180–183°/755	185°/760[9]
C_6H_5—CH=CH—CH_2—Br	57	97–99°	see experimental	–	C	94	220–224°/749	235–237°/755[9]
H_3CO—CO—CH_2—Br	62[m]	80°/4	106°/14[12]	–	–	–	–	–
C_6H_5—CO—CH_2—Br	48	130–131.5°[n]	$C_{10}H_8F_3NO_2$ (231.2)	–	B	84°	185–187°[o]	188°[o,9]
2,4-di-O_2N—C_6H_3—Cl	not isolated			–	B	81	182–184°	180°[9]

[a] Unless indicated otherwise, the amide was isolated by fractional distillation.

[b] The products had satisfactory I.R. and ^{1}H-N.M.R. spectra and, when new, satisfactory microanalyses (C ±0.28, H ±0.25, N ±0.40).

[c] A = alkaline hydrolysis in a separating funnel; B = alkaline hydrolysis in a flask; C = sodium borohydride in ethanol.

[d] Oct-1-ene with b.p. in good agreement with lit. value.

[e] Overall yield.

[f] *N*-(1-Methylheptyl)-trifluoroacetamide had b.p. 113–115°C/17 torr.
I.R. (film): ν = 3400–3250, 1695, 1180 cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$): δ = 0.85 (t, 3H, $-CH_2CH_3$), 1.13 (d, 3H, $CHCH_3$), 1.65 (br. s, 10H, CH_2), 3.95 (br. q, 1H, CH—NH_2), 7.50 ppm (br. s, 1H, NH).

[g] Mixture of oct-1- and 2-enes.

[h] Yield of diamide.

[i] Approximately 97% pure by ^{1}H-N.M.R. analysis.

[j] None detected.

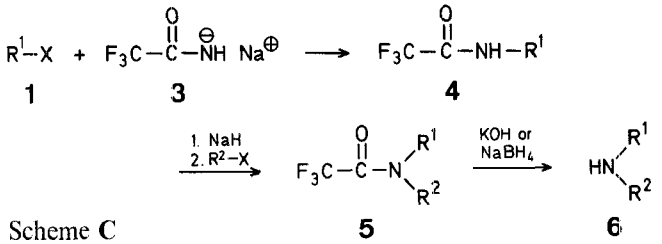
[k] Yield of piperidide.

[l] Cyclohexene b.p. 80–85°C/755 torr (Lit.[9], b.p. 83°C/760 torr).

[m] 2.0 Mol equiv of substrate used.

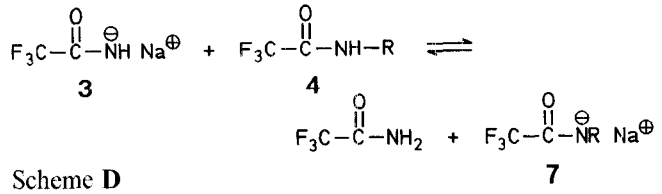
[n] *N*-Trifluoroacetyl-α-aminoacetophenone had m.p. 130–131.5°C (from acetone/water).
I.R. (Nujol): ν = 3450–3250, 1700, 1175 cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$): δ = 3.61 (d, 2H, CH_2), 7.00–7.85 ppm (m, 5H_{arom}).

[o] Isolated as the hydrochloride.



Scheme **C**

It is not clear why bis-alkylation of trifluoroacetamide should be more difficult than mono-alkylation. However, the equilibrium shown (Scheme **D**) is almost certainly mainly to the left hand side and it is probable that, for steric reasons, the nucleophile **7** is significantly less reactive than **3**.



Scheme **D**

Dimethylformamide was distilled from calcium hydride and stored over molecular sieves. Sodium hydride dispersed in paraffin oil was washed with dry benzene before use; the weights quoted are for washed material. The I.R. and ^{1}H-N.M.R. spectra of known reaction products were identical to those of authentic samples or were in excellent agreement with literature data.

1-Aminooctane (2; R = *n*-C_8H_{17}); Typical Procedure:
Trifluoroacetamide (10 g, 0.09 mol) in dimethylformamide (50 ml) is added dropwise with stirring to a suspension of sodium hydride (2.0 g, 0.083 mol) in dimethylformamide (20 ml) at 20°C under nitrogen. After 1 h 1-iodooctane (112 g, 0.05 mol) is added and the mixture stirred at 80°C for 18 h. The cooled mixture is filtered and the filtrate concentrated under vacuum to give the crude product. Fractional distillation gives two main fractions; (1) *oct-1-ene*; yield: 1.1 g (19%); b.p. 120–122°C/760 torr (Lit.[9], 121°C/742 torr) and (2) N-n-*octyltrifluoroacetamide* (**4**); yield: 8.9 g (79%); b.p. 120–122°C/2 torr (Lit.[10], b.p. 160°C/11 torr).

A portion of the amide **4** (3.4 g, 0.015 mol) is shaken for 15 min at 20°C with 20% aqueous potassium hydroxide (30 ml) in a separating funnel. Ether extraction and recovery gives *1-amino-octane* (**2**); yield: 1.6 g (83%); b.p. 190°C/760 torr (Lit.[9], b.p. 175–177°C/745 torr).

Table 2. Preparation of Secondary Amines **6** (Scheme C)

Substrates	R^2—X	*N*-Alkylamide **4**[a,b]			*N*,*N*-Dialkylamide **5**[a,b]			Secondary Amine **6**[b]			
		Yield [%]	b.p.[°C]/ torr or m.p.[°C]	Lit. Data	Yield [%]	b.p.[°C]/ torr or m.p.[°C]	Lit. Data	Method of Cleavage of **5**[c]	Yield [%]	b.p.[°C]/ torr	Lit. Data
3[d] + n-C_8H_{17}—J	n-C_8H_{17}—J	45	99–100°/ 0.5	160°/ 11[10]	46[e]	140–142°/ 0.4	130°/ 0.05[10]	C	77	150–152°/ 5	175°/ 14[13]
3[d] + C_6H_5—CH_2—Cl	C_6H_5—CH_2—Cl	59	72–76°	73.5–74.5°[10]	36	140–144°/ 0.4	125°/ 0.05[10]	B	96	175°/ 15	270°/ 250[9]
3[d] + C_6H_5—CH_2—Cl	H_3C—J	12	72–73.5°	as above	75	54–57°	67–67.5°/ 1[8]	C	90	60–62°/ 9	78°/ 14[9]
4 (R^1 = 4-H_3C—C_6H_4)	H_3C—J		not isolated					B	95	192–194°/ 74	206°/ 711[9]
4 (R^1 = n-C_8H_{17}	n-C_8H_{17}—OSO_2CH_3		not isolated					C	71[f]	150–156°/ 5	175°/ 14[13]

[a] Unless indicated otherwise, the amide was isolated by fractional distillation.
[b] The products had satisfactory I.R. and ^{1}H-N.M.R. spectra.
[c] A = alkaline hydrolysis in a separating funnel; B = alkaline hydrolysis in a flask; C = sodium borohydride in ethanol.
[d] Trifluoroacetamide was treated with sodium hydride then the first substrate (R^1—X) listed. After 18 h at 70°C, a further equivalent of sodium hydride was added followed by the second substrate (R^2—X) listed.
[e] Plus 37% oct-1-ene.
[f] Plus 18% 1-octylamine.

Cinnamylamine (2; R = C_6H_5—CH=CH=CH_2); Typical Procedure:

Cinnamyl bromide (11.8 g, 0.06 mol) is reacted with the sodium salt of trifluoroacetamide (**3**; 6.75 g, 0.05 mol) in dimethylformamide as described above. The crude solid product is recrystallised from chloroform/petroleum ether (60–80°C) to give white needles of *N-cinnamyltrifluoroacetamide* (**4**); yield: 7.8 g (57%); m.p. 97–99°C.

$C_{11}H_{10}F_3NO$ (229.2) calc. C 57.64 H 4.40 N 6.11; found 57.51 4.21 6.03

I.R. (Nujol): ν = 3400–3200, 1700, 1170 cm^{-1}

^{1}H-N.M.R. ($CDCl_3$): δ = 4.06 (br.d, 2H, CH_2N); 6.25 (m, 2H, =CH) 7.25 (s, 5H_{aron}); 8.15 ppm (s, 1H, NH).

N-Cinnamyltrifluoroacetamide (4.6 g, 0.02 mol) is treated with sodium borohydride (6.1 g, 0.16 mol) in ethanol (20 ml) at 20°C for 1 h. Distillation of the crude reaction product gives *cinnamylamine*; yield: 2.5 g (94%); b.p. 220–224°C/749 torr (Lit.[9], b.p. 235–237°C/torr).

***N*-Methylbenzylamine (6; R^1 = $C_6H_5CH_2$, R^2 = CH_3); Typical Procedure:**

A solution of trifluoroacetamide (11.3 g, 0.1 mol) in dimethylformamide (30 ml) is added dropwise with stirring to a suspension of sodium hydride (2.4 g, 0.10 mol) in dimethylformamide (20 ml). After 1 h, benzyl chloride (12.7 g, 0.1 mol) is added and the mixture heated to 70°C and stirred for 18 h. The mixture is then transferred to a dropping funnel and added dropwise to a further portion of sodium hydride (1.2 g, 0.05 mol). After 1 h, methyl iodide (14.0 g, 0.098 mol) is added and the mixture heated to 70°C and stirred for 6 h. Isolation of the products by fractional distillation gives two main fractions: (i) N-*benzyltrifluoroacetamide* **4**; yield: 2.4 g (12%); b.p. 84–95°C/11 torr; m.p. 72–73.5°C (Lit.[10], m.p. 73–75°C) and (ii) N-*methyl*-N-*benzyltrifluoroacetamide* **5**; yield: 16.3 g (75%); b.p. 125–128°C/21 torr; m.p. 55.5–57°C (Lit.[8], b.p. 67–67.5°C/1 torr.

Sodium borohydride reduction (60°C, 15 min) of *N*-methyl-*N*-benzyltrifluoroacetamide **5** (8.7 g, 0.04 mol) gives *N*-methyl-*N*-benzylamine **6**; yield: 4.3 g (90%); b.p. 60–62°C/9 torr (Lit.[9], b.p. 78°C/torr).

***N*-Methyl-*p*-toluidine (6; R^1 = 4-H_3C—C_6H_4, R^2 = CH_3); Typical Procedure:**

Trifluoroacetylation[5] of *p*-toluidine gives *N*-(4-methylphenyl)-trifluoroacetamide; yield: (86%); m.p. 110–110°C (Lit.[5], m.p. 111–112°C). The amide (10.2 g, 0.05 mol) in dimethylformamide (30 ml) is added dropwise with stirring to sodium hydride (1.2 g, 0.05 mol) in dimethylformamide (20 ml). After 1 h, methyl iodide (7.2 g, 0.05 mol) in dimethylformamide (20 ml) is added and the mixture heated to 70°C and stirred for 18 h. The crude product is isolated and hydrolysed by base as described above. Distillation gives *N*-methyl-*p*-toluidine **6**; yield: 5.7 g (95%); b.p. 192–194°C/740 torr (Lit.[9], b.p. 206°C/761 torr).

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