A Useful Variant of the Curtius Reaction[1]

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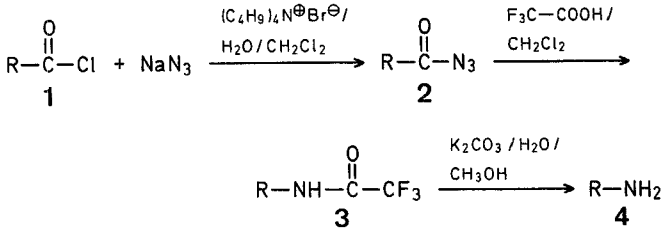
The Curtius reaction[3] consists of the conversion of acid azides to isocyanates and compounds derived therefrom. It has often been used for the preparation of primary amines uncontaminated by secondary or tertiary amines. In its original embodiment, as well as when using trimethylsilyl azide[4] or diphenylphosphoryl azide[5], serious problems may be encountered in the hydrolysis of isocyanates (formation of symmetrical ureas[3,6]) or urethanes (resistance to hydrolysis[7,8]). We have developed an operationally simple, high-yield modification of the Curtius reaction which works even in recalcitrant cases. This method comprises the reaction of acid chlorides **1** in dichloromethane with sodium azide under phase transfer conditions, followed by treatment of the dried dichloromethane solution containing the acyl azide **2** with a slight excess of trifluoroacetic acid. The resulting trifluoroacetamides **3** can easily be cleaved to the amines **4**.



1 **2** **3** **4**

This method possesses the following advantages:

- The use of phase transfer technique for the preparation of the acyl azides minimizes hydrolysis of the acid chlorides. The easily separable aqueous phase allows a convenient disposal of excess sodium azide.
- Since the acid azides are not isolated in substance, explosive azides[9] can be handled safely.
- The trifluoroacetamides formed by the reaction of the acyl azides with trifluoroacetic acid are readily purified by distillation or by recrystallization.
- Cleavage of the trifluoroacetamides occurs under mild conditions[10,11] (potassium carbonate in aqueous methanol at room temperature).

Additionally, the fact that *N*-substituted trifluoroacetamides can be alkylated efficiently[12] makes this method also useful for the preparation of secondary amines from acids.

In practice, it is advantageous to at least partially rearrange the alkanoyl azides by letting them stand overnight in dichloromethane solution over a drying agent. Trifluoroacetic acid

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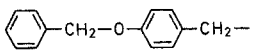
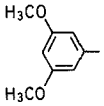
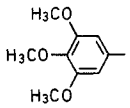
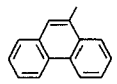
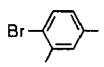
Table. Trifluoroacetamides **3** prepared

Product **3** No.	R	Method	Reaction time	Yield [%][a]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b] or Lit. m.p. or b.p.	
a	$H_2C{=}CH{-}(CH_2)_8{-}$	A	11 h	89	100–110°/0.1	$C_{12}H_{20}F_3NO$	(251.3)
b		A	6 h	86	62–63°	$C_8H_{10}F_3NO$	(193.2)
c		A	6 h	97	65–67°/0.1	$C_8H_{10}F_3NO$	(193.2)
d		A	11 h	96	129–130°	$C_{16}H_{14}F_3NO_2$	(309.3)
e	$-(CH_2)_8-$	A[c]	10 h	87	105°	$C_{12}H_{18}F_6N_2O_2$	(336.3)
f		B	60 h	80	99°	$C_{10}H_{10}F_3NO_3$	(249.2)
g		B	96 h	82	130–132°	$C_{11}H_{12}F_3NO_4$	(279.2)
h		B	24 h	80[d,e]	169–170°	174–175°[7]	
i		B[c]	144 h	80	160–164°	$C_{10}H_5BrF_6N_2O_2$	(379.1)

[a] Yield of isolated product of purity ≥95% by G.L.C. (conditions: glass column, 6 ft × 4 mm, 10% OV 101). Reaction conditions not optimized. ^{1}H-N.M.R. and mass spectra are consistent with the structures.

[b] Satisfactory microanalyses obtained: C ±0.24, H ±0.13, N ±0.35.

[c] Bis-trifluoroacetylamino product.

[d] Ref.[7] yields: 27% using trimethylsilyl azide, 53% using diphenylphosphoryl azide.

[e] The corresponding methyl carbamate (Ref.[7], m.p. 174–175 °C) is formed on recrystallization of the crude trifluoroacetamide from methanol.

(usually 1.3–3 equivalents) is then added and the solution is refluxed until the reaction is complete (Method A). For the less reactive aroyl azides, it is sufficient to combine the trifluoroacetic acid with the dried azide solution and reflux the reaction mixture (Method B). A variety of aliphatic and aromatic substrates readily undergo the modified Curtius rearrangement in high yield (Table). The reaction conditions are mild; there is no benzyl ether clevage (see **3d**), whereas neat trifluoroacetic acid is known to cleave aryl benzyl ethers at room temperature[13]. In the case of product **3h**, recrystallization of the crude reaction product from methanol resulted in the formation of the known 9-methoxycarbonylaminophenanthrene[7] via methanolysis of the trifluoroacetyl group. All other crystalline trifluoroacetamides were recrystallized from hexane. This method is apparently unsuitable for the preparation of *N*-trifluoroacetylated enamines. Subjecting cinnamoyl chloride to these reaction conditions gave appreciable amounts of phenylacetaldehyde in addition to the expected trifluoroacetylaminostyrene.

4-Trifluoroacetylaminocyclohexene (3b); Typical Procedure for Method A:

A solution of cyclohexene-4-carbonyl chloride (**1b**; 28.3 g, 0.196 mol) in dichloromethane (300 ml) containing tetrabutylammonium bromide (200 mg) is cooled in an ice bath. Sodium azide (15.6 g, 0.24 mol), dissolved in water (50 ml) is added and the reaction mixture is stirred vigorously at 0 °C for 2 h. The organic phase is separated, washed with water (2 × 50 ml), and dried with magnesium sulfate for 20 h. Continued evolution of nitrogen as very small bubbles is observed during this period. Trifluoroacetic acid (20.3 ml, 0.265 mol) is added dropwise to the filtered solution which is thereafter refluxed for 6 h. The cooled reaction mixture is washed with saturated aqueous sodium hydrogen carbonate solution (2 × 50 ml), dried with magnesium sulfate, filtered, and evaporated. The crystalline residue is distilled in a Kugelrohr apparatus at 90–100 °C/1 torr to give a white crystalline mass; yield: 32.5 g (86%); m.p. 62–63 °C (hexane).

$C_8H_{10}F_3NO$	calc.	C 49.74	H 5.22	N 7.25
(193.2)	found	49.50	5.20	7.35

^{1}H-N.M.R. ($CDCl_3$): δ = 1.5–2.5 (m, 6H); 4.2 (m, 1H); 5.7 (m, 2H); 6.5–6.9 ppm (m, 1H).

3,5-Dimethoxytrifluoroacetanilide (3f); Typical Procedure for Method B:

A solution of 3,5-dimethoxybenzoyl chloride (**1f**; 5.65 g, 28 mmol) in dichloromethane (50 ml) containing tetrabutylammonium bromide (20 mg) is cooled in an ice bath. Sodium azide (2.5 g, 38.5 mmol), dissolved in water (10 ml) is added and the reaction mixture is stirred vigorously at 0 °C for 2 h. The organic phase is separated, washed with water (2 × 10 ml), dried with magnesium sulfate, and filtered. Trifluoroacetic acid (2.5 ml, 43 mmol) is added to the filtrate and the reaction mixture is refluxed for 60 h. Work-up as described for Method A gives the product; yield: 5.63 g (80%); m.p. 99 °C (acetone/hexane).

$C_{10}H_{10}F_3NO_3$	calc.	C 48.20	H 4.05	N 5.62
(249.2)	found	48.28	4.06	5.58

^{1}H-N.M.R. ($CDCl_3$): δ = 3.77 (s, 6H); 6.35 (t, J = 2 Hz, 1H); 6.78 (d, J = 2 Hz, 2H); 8.15 ppm (m, 1H).

3,5-Dimethoxyaniline (4f); Typical Procedure:

A mixture of 3,5-dimethoxytrifluoroacetanilide (**3f**; 4.5 g, 18 mmol), potassium carbonate (4.2 g, 30 mmol), methanol (20 ml), and water (80 ml) is stirred at room temperature under nitrogen for 20 h. After concentration on a rotary evaporator, the reaction mixture is extracted with ether (3 × 50 ml). The dried (potassium carbonate) organic phase is evaporated to dryness and the residue subjected to Kugelrohr distillation to give an oil which solidifies on standing; yield: 2.6 g (94%); b.p. 85–110 °C/0.2 torr; m.p. 48 °C (Ref.[6], m.p. 49–51 °C).

It has been reported that hydrolysis of the corresponding isocyanate under a variety of conditions did not lead to the desired amine[6].

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