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ALKALINE HYDROLYSIS OF 2-(TRIFLUOROMETHYL)IMIDAZO[4,5-f] AND -[4,5-h]QUINOLINES

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SUMMARY

2-(Trifluoromethyl)imidazo[4,5-f] and -[4,5-h]quinoline have been prepared from 5(6)-acetamido-2-(trifluoromethyl)benzimidazole and 7,8-diaminoquinoline respectively. These (trifluoromethyl)-quinolines like 2-(trifluoromethyl)imidazoles but unlike 2-(trifluoro-methyl)benzimidazoles, undergo hydrolysis in dilute sodium hydroxide to give ultimately the corresponding imidazo[4,5-f] and -[4,5-h]-quinoline, respectively.

INTRODUCTION

The facile alkaline hydrolysis (0.1M KOH) of 2-(trifluoromethyl)-imidazole to imidazole-2-carboxylic acid has been reported recently. [1] Kinetic data indicate that the hydrolysis proceeds via a vinylogous Elcb mechanism involving initial loss of the acidic NH proton and subsequent formation of a transient difluorodiazafulvene intermediate (1) as outlined in Scheme 1.*

In contrast, 2-(trifluoromethyl)benzimidazole (2a) is inert towards aqueous alkali [2,3] as formation of the corresponding diazafulvene intermediate (3a) entails loss of benzenoid character throughout the whole system. 2-(Trichloromethyl)benzimidazole (2b) is hydrolysed by aqueous alkali, a result which is explained by the superior leaving ability of chloride ion and the greater stabilising (+M) effect of chlorine over that of fluorine on the dihalogenodiazafulvene intermediate (3b). [4]

* Apparently, 1,3,4-tris(trifluoromethyl)imidazole does not hydrolyse easily [14].

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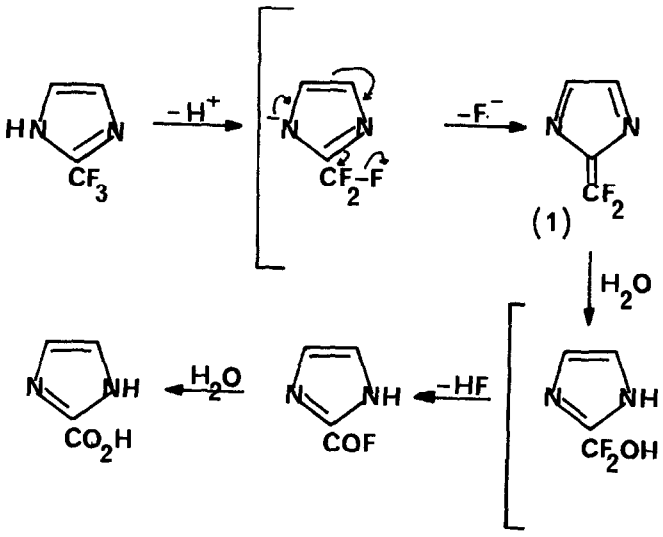


Scheme 1

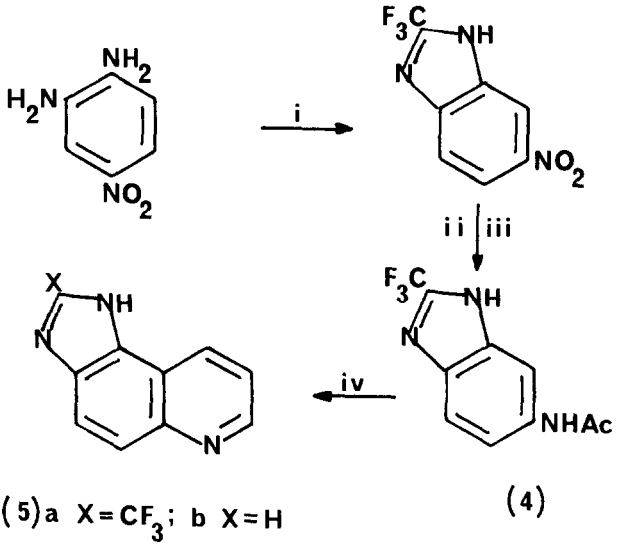
(2) (3)

a; X=F
b; X=Cl

RESULTS AND DISCUSSION

We now find that the tricycles 2-(trifluoromethyl)imidazo[4,5-f] (5a) and -[4,5-h]quinoline (7a) undergo ready hydrolysis with dilute sodium hydroxide and subsequent decarboxylation of the resulting 2-carboxylic acids, to give the respective imidazo-quinolines (5b) and (7b).

The (trifluoromethyl)imidazo-quinolines were prepared as outlined in Schemes 2 and 3.



(5)a X=CF_3; b X=H (4)

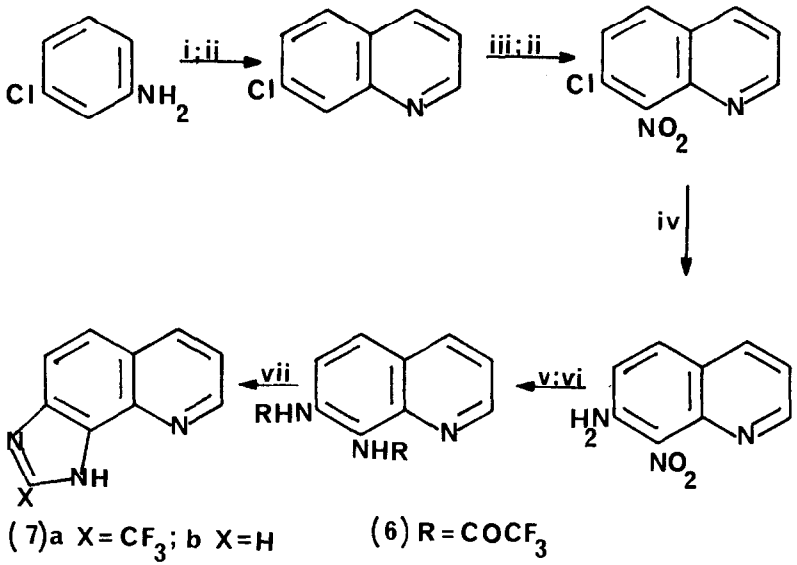
i CF_3CO_2H; ii Fe, NH_4Cl; iii Ac_2O; iv Skraup

Scheme 2

Skraup reaction on 5(6)-acetamido-2-(trifluoromethyl)benzimidazole (4) gave (as shown by ^1H n.m.r.) only the angular imidazo-quinoline (5a) in accord with other Skraup reactions on 2H- [5a] and 2-benzyl- [6] 5(6)-aminobenzimidazoles.

7,8-Diaminoquinoline in a mixture of hot trifluoroacetic and hydrochloric acids unexpectedly gave the bis-(trifluoroacetyl) derivative (6) rather than the (trifluoromethyl)imidazo-quinoline (7a). However, treatment of (6) with aqueous sodium carbonate at room temperature gave the required imidazo-quinoline in good yield.

2-(Trifluoromethyl)imidazo[4,5-h]quinoline (7a) in cold (1M) sodium hydroxide at room temperature undergoes rapid (1 hour) hydrolysis and decarboxylation to imidazo[4,5-h]quinoline (7b). Similarly 2-(trifluoromethyl)imidazo[4,5-f]quinoline (5a) yields the parent system (5b) albeit more slowly (ca. 4 hours) and with some heating.



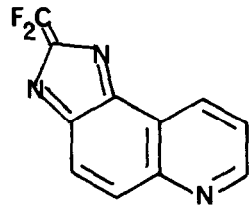
(7)a X=CF_3; b X=H (6) R=$COCF_3$

i Skraup; ii separate isomers; iii conc. H_2SO_4, KNO_3, -10°C; iv NH_3, 180 atmos., 160°C; v 5% Pd-C, H_2; vi CF_3CO_2H, HCl; vii Na_2CO_3-H_2O

Scheme 3

The structures of the imidazo-quinolines (5b) and (7b) were confirmed by synthesis from the appropriate diaminoquinoline and formic acid. Presumably, as with 2-(trifluoromethyl)imidazole, hydrolysis proceeds via a diazafulvene intermediate (8) or (9) which in these systems can be formed without total loss of aromatic character of the tricycle, as in the benzimidazole analogue (3). It is tempting to suggest that, on this reasoning, 2-(trifluoromethyl)imidazo[4,5-g]-quinoline (10) should be inert towards alkaline hydrolysis, as formation of diazafulvene intermediate (11) will again involve total dearomatisation of the heterocyclic system.

So far, however, all attempts to prepare this isomer from 6,7-diaminoquinoline by standard methods have failed; even though the unsubstituted derivative (10; H in place of CF_3) has been prepared with no difficulty [5b]. Unlike 2-(trifluoromethyl)imidazole, which



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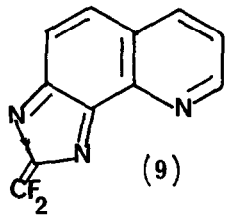

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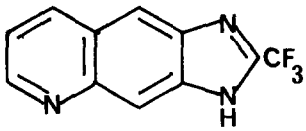

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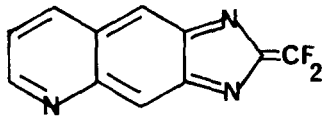

(11)

with 5% aqueous ammonia yields 2-cyanoimidazole, [1] the 2-(trifluoromethyl)-imidazo-quinolines (5a) and (7a) proved to be inert towards nucleophilic displacement of fluorine by ammonia under a wide range of conditions.

EXPERIMENTAL

5-Acetamido-2-(trifluoromethyl)benzimidazole

5-Nitro-2-(trifluoromethyl)benzimidazole (m.p. 153°C, lit. [7] 154°C) was prepared according to the method of Lane [7]. Reduction with iron and ammonium chloride in aqueous solution gave 5-amino-2-(trifluoromethyl)benzimidazole as the dihydrochloride (64%, m.p. 290°C, lit. [8a] m.p. 262°C).

Acetylation of the amine dihydrochloride (2.74g, 0.01M) with a hot (100°C) mixture of acetic acid (15 ml) and acetic anhydride (1.05g, 0.011M) gave after addition of water (15 ml), 5-acetamido-2-(trifluoromethyl)benzimidazole (nc) (2.16g, 89%); white needles from aqueous ethanol, m.p. 294°C. Analysis: Found: C, 49.55; H, 2.44; N, 17.29%. $C_{10}H_8F_3N_3O$ requires C, 49.80; H, 2.51; N, 17.42%. ^{1}H n.m.r. ($CDCl_3$) τ 7.93 (3H, s, (CH_3), 2.63 (1H, dd, 6-H), 2.34 (1H, d, 7-H), 1.8 (1H, d, 4-H), -3.5 (1H, bs, NH). I.r. (nujol mull) 3260 cm^{-1} (NH), 1635 cm^{-1} (C=O), 1605 cm^{-1} (C=N), 1120-1200 cm^{-1} (CF_3).

2-(Trifluoromethyl)imidazo[4,5-f]quinoline

A mixture of 5-acetamido-2-(trifluoromethyl)benzimidazole (4 g), m-nitrobenzene sulphonic acid (2.6 g), glycerol (6.1 g) and concentrated sulphuric acid (6 g) was heated at 150°C for 1 h. The mixture was then cooled, and diluted with water (150 ml). 2-(Trifluoromethyl)imidazo-[4,5-f]quinoline (nc) precipitated as a brown solid (1.33 g, 56%) which crystallised from light petrol (b.p. 60-80°C)-ethyl acetate as pale brown granules, m.p. 236°C. Analysis: Found: C, 55.56; H, 2.58; N, 17.33%. $C_{11}H_6F_3N_3$ requires C, 55.70; H, 2.55; N, 17.72%. ^{1}H N.m.r. ($CDCl_3$) τ 2.31 (1H, dd, 8-H), 1.95 (2H, s, 4-H and 5-H), 1.05 (2H, m, 6-H and 9-H), -3.5 (1H, bs, NH). (The singlet at 1.95 was resolved by europium shift reagent into 2-doublets (J 9Hz) corresponding to the ortho-coupled 4- and 5-protons).

7,8-Diaminoquinoline

7-Chloro-8-nitroquinoline [9] was converted into 7-amino-8-nitro-quinoline (70%, m.p. 194°C, lit. [10] 195°C) by heating the chloronitro-quinoline with liquid NH_3 in an autoclave at 180°C and 180 atmospheres.

Reduction of the nitro-amine in ethanol solution was rapid using 5% Pd-C and hydrogen at S.T.P.. 7,8-Diaminoquinoline was obtained (86%) as pale-yellow needles from water m.p. 94°C, lit. [11] 94-7°C.

7,8-Bis(trifluoroacetylamino)quinoline

A solution of 7,8-diaminoquinoline (1.59 g, 0.01M) in trifluoro-acetic acid (4 ml) and 4M HCl (25 ml) was heated under reflux for 2 h. On cooling, the solution deposited 7,8-bis(trifluoroacetylamino)quinoline (nc) (2.7 g, 78%) as white needles from aqueous ethanol, m.p. 219°C. Analysis: Found: C, 44.31; H, 1.99; N, 11.82%. $C_{13}H_7F_6N_3O_2$ requires C, 44.46; H, 2.00; N, 11.96%. ^{1}H N.m.r. ($CDCl_3$) τ 2.28 (1H, dd, 3-H), 2.08 (1H, d, 5-H), 2.06 (1H, d, 6-H), 1.35 (1H, dd, 4-H), 0.95 (1H, dd, 2-H), -4.82 (2H, s, 2NH). I.r. (nujol) 3050 cm^{-1} (NH), 1660 cm^{-1} (C=O), 1120-1200 cm^{-1} (CF_3).

2-(Trifluoromethyl)imidazo[4,5-h]quinoline

7,8-Bis(trifluoroacetylamino)quinoline (1.05 g, 0.003M) was stirred at 25°C for 1 h in 1M sodium carbonate solution (25 ml). The mixture was acidified with acetic acid to precipitate 2-(trifluoromethyl)imidazo-

[4,5-h]quinoline (nc) (0.61 g, 86%), which crystallised from aqueous ethanol as white granules, m.p. 229°C. Analysis: Found: C, 55.56; H, 2.58; N, 17.32%. $C_{11}H_6F_3N_3$ requires C, 55.70; H, 2.55; N, 17.72%. ^{1}H N.m.r. ($CDCl_3$) τ 2.42 (1H, dd, 7-H), 2.20 (1H, d, 5-H), 2.1 (1H, d, 4-H), 1.55 (1H, dd, 6-H), 1.03 (1H, dd, 8-H), 0.25 (1H, bs, NH).

Imidazo[4,5-f]quinoline

A solution of 2-(trifluoromethyl)imidazo[4,5-f]quinoline (1.18 g) in 1M sodium hydroxide (25 ml) was heated on a boiling water-bath for 4 h. On cooling the solution, imidazo[4,5-f]quinoline (0.53 g, 43%) separated as an off-white solid, which crystallised from benzene as pale-brown plates, m.p. 212°C (lit. [12] 214°C).

Imidazo[4,5-h]quinoline

A solution of 2-(trifluoromethyl)imidazo[4,5-h]quinoline (1.18 g, 0.005M) in 1M sodium hydroxide (25 ml) was stirred at room temperature for 1 h, after which time imidazo[4,5-h]quinoline (nc) precipitated from the solution as a brown solid (0.38 g, 45%). The product crystallised from light petrol (b.p. 60-80°C)-ethyl acetate as red-brown granules, m.p. 227°C. Analysis: Found: C, 71.07; H, 4.15; N, 24.39%. $C_{10}H_7N_3$ requires C, 70.99; H, 4.17; N, 24.84%. ^{1}H N.m.r. ($CDCl_3$) τ 2.54 (1H, dd, 7-H), 2.37 (1H, d, 5-H), 2.1 (1H, d, 4-H), 1.72 (1H, s, 2-H), 1.62 (1H, dd, 6-H), 1.08 (1H, dd, 8-H).

The product was identical to a sample of imidazo[4,5-h]quinoline, m.p. 227°C (1.56 g, 93%) prepared by heating 7,8-diaminoquinoline (1.58 g, 0.01M) under reflux with a mixture of 4M hydrochloric acid (25 ml) and formic acid (1 ml) for 2.5 h.

Reaction of 2-(trifluoromethyl)imidazo[4,5-h]quinoline with (a) liquid ammonia; (b) 0.880 ammonia solution; (c) ammonia in dimethylformamide; or (d) ethanolic ammonia, at room temperature, and with liquid ammonia at 50°C and 50 atmospheres gave only unchanged (trifluoromethyl)imidazoquinoline.

Attempted Synthesis of 2-(Trifluoromethyl)imidazo[4,5-g]quinoline

Chlorine gas was bubbled slowly for 15 mins through a solution of 5-acetamido-2-(trifluoromethyl)benzimidazole (2.43 g, 0.01M) in glacial acetic acid (50 ml) and sufficient trifluoroacetic acid to ensure

complete solution. Removal of the solvent and addition of ice-water brought about precipitation of 5-acetamido-4-chloro-2-(trifluoromethyl)-benzimidazole (nc) (2.13 g, 77%) which crystallised from aqueous ethanol as white granules, m.p. 252-5°C. Analysis: Found: C, 43.15; H, 2.69; N, 14.73%. $C_{10}H_7ClF_3N_3O$ requires C, 43.25; H, 2.54; N, 15.13%. ^1H N.m.r. ($CDCl_3$) τ 7.87 (3H, s, CH_3), 2.43 (1H, d, 6-H), 2.32 (1H, d, 7-H), 0.4 (1H, s, CONH), -4.0 (1H, bs, NH).

A Skraup reaction on this chloroacetamido derivative using arsenic pentoxide, glycerol, and sulphuric acid as outlined in reference [5] gave only tarry products.

Similarly, attempted cyclisation of 6,7-diaminoquinoline (prepared by amination [5b] and subsequent reduction of 7-chloro-6-nitroquinoline [13]) with hot trifluoroacetic acid gave only tars.

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