Facile syntheses of novel 2-(1,1,1-trifluoroacetonyl) imidazoles, oxazoles, quinazolines and perimidines†

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Abstract

The synthetic utility of trifluoroacetyl ketene diethylacetal has been exploited to build novel imidazoles, oxazoles, quinazolines and perimidine compounds that contain a trifluoroacetonyl group. The products themselves are interesting starting materials for a variety of new compounds.

Introduction

The introduction of a trifluoroacetonyl group into a molecule renders it a potential biologically active herbicide [1] or a juvenile hormone esterase-inhibiting agent [2]. In our search for a new organic reagent of use in introducing a trifluoroacetonyl group in heterocyclic synthesis, trifluoroacetyl ketene diethyl acetal (**1**) has attracted our attention [3].

In previously known methods, the trifluoroacetonyl group was introduced by acylation of a methyl group in a pyridine moiety with trifluoroacetyl chloride or with trifluoroacetic anhydride in the presence of a base [4]. The reaction of *o*-phenylenediamine with trifluoroethylacetoacetate produced 2-(1,1,1-trifluoroacetonyl) benzimidazole in 27% yield [5]. In our studies, we found that the reaction between **1** and *ortho*-substituted amines and other, similar nucleophiles (**2**) proceeds smoothly in refluxing toluene [eqn. (1)] in moderately good yield (40%–80%) to give the expected trifluoroacetonyl heterocyclic compounds.

Experimental

General

Melting points were determined on a microscope hot plate HMK melting point apparatus and are reported uncorrected. ^{1}H NMR spectra were recorded on an 80 MHz Varian FT-80A spectrometer. IR spectra were recorded with a Perkin-Elmer 810 spectrometer. Mass spectra and high-resolution mass spectra (HRMS) were recorded on a VG-micromass-7070H instrument.

Starting materials

Trifluoroacetyl ketene diethylacetal was prepared according to reported procedures. All other reagents were obtained from commercial sources and were used as supplied.

Preparation of 2-(1,1,1-trifluoroacetonyl) imidazolidine (3a)

Ethylenediamine (0.3 g, 5 mmol) was added to a solution of 1,1,1-trifluoroacetyl ketene diethylacetal (1.10 g, 5 mmol) in toluene (20 ml). The initial exothermicity of the reaction subsided after 0.5 h. The mixture was stirred magnetically for an additional 3 h at 90–95 °C over a water bath and was then allowed to cool to room temperature. The solids that separated were filtered and washed with toluene followed by petroleum ether (40–60 °C) and recrystallised from ethyl alcohol to give white crystals of **3a** (0.7 g, 40% yield), m.p. 225–226 °C. ^{1}H NMR ($CDCl_3$) δ: 3.6 (m, 4H, CH_2-CH_2); 5.26 (s, 1H, $-CH=$); 6.1 (s, 1H, NH); 9.2 (s, 1H, OH) ppm. IR (KBr) (cm^{-1}): 3320; 1640. MS (*m/z*): 180 (M^+); 111 ($M^+ - 69$) (base peak). HRMS: Calc. for $C_6H_7F_3N_2O$, 180.0510 Obs., 180.0509.

Preparation of compounds 3b–h

The same procedure was adopted for the remaining compounds **3b–h**. Whenever the product did not separate on cooling, the solvent was evaporated to dryness and the residue treated as above to give the desired product.

2-(1,1,1-Trifluoroacetonyl) benzimidazole (**3b**): M.p. 290–292 °C. ^{1}H NMR ($CDCl_3$) δ: 6.1 (s, 1H, $-CH=$);

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7.2–7.8 (m, 4H, aromatic H and 1H, NH); 9.1 (s, 1H, OH) ppm. IR (KBr) (cm^{-1}): 3240; 1640. MS (*m/z*): 228 (M^+); 159 ($M^+ - 69$) (base peak). HRMS: Calc. for $C_{10}H_7F_3N_2O$, 228.1733. Obs., 228.1724.

2-(1,1,1-Trifluoroacetonyl) 5-chlorobenzimidazole (**3c**): M.p. >300 °C. ^1H NMR ($CDCl_3$) δ: 6.2 (s, 1H, $-CH=$); 7.29 (s, 1H, NH); 7.4–7.9 (m, 3H, aromatic H); 9.25 (s, 1H, OH) ppm. IR (KBr) (cm^{-1}): 3280; 1640; 1620. MS (*m/z*): 262 (M^+); 193 ($M^+ - 69$) (base peak). HRMS: Calc. for $C_{10}H_6ClF_3N_2O$, 262.0120. Obs., 262.0101.

2-(1,1,1-Trifluoroacetonyl) 5-benzoylbenzimidazole (**3d**): M.p. 274–275 °C. ^1H NMR ($CDCl_3$) δ: 5.9 (s, 1H, $-CH=$); 7.5–8.2 (m, 8H, aromatic H and 1H, NH); 9.3 (br., s, 1H, OH) ppm. IR (KBr) (cm^{-1}): 3240; 1680; 1640; MS (*m/z*): 332 (M^+); 263 ($M^+ - 69$) (base peak). HRMS: Calc. for $C_{17}H_{11}F_3N_2O_2$, 332.2813. Obs., 332.2808.

2-(1,1,1-Trifluoroacetonyl) benzoxazole (**3e**): M.p. 165–166 °C. ^1H NMR ($CDCl_3$) δ: 6.01 (s, 1H, $-CH=$); 7.2–7.6 (m, 4H, aromatic H); 9.1 (br.s, 1H, OH) ppm. IR (KBr) (cm^{-1}): 1640; 1620. MS (*m/z*): 229 (M^+); 160 ($M^+ - 69$) (base peak). HRMS: Calc. for $C_{10}H_6F_3NO_2$, 229.0350. Obs., 229.0341.

2-(1,1,1-Trifluoroacetonyl) oxazolopyridine (**3f**): M.p. 202–205 °C. ^1H NMR ($CDCl_3$) δ: 6.1 (s, 1H, $-CH=$); 7.5–7.9 (m, 3H, aromatic H); 9.3 (br., s, 1H, OH) ppm. IR (KBr) (cm^{-1}): 1640; 1620. MS (*m/z*): 230 (M^+); 161 ($M^+ - 69$) (base peak). HRMS: Calc. for $C_9H_5F_3N_2O_2$, 230.0303. Obs., 230.0303.

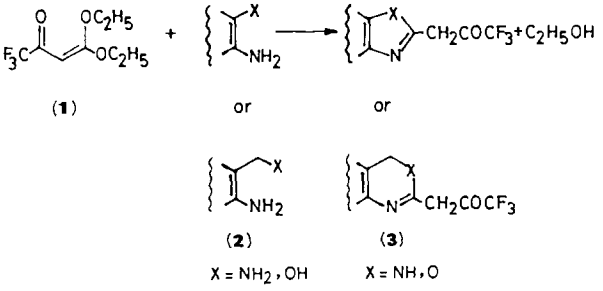
2-(1,1,1-Trifluoroacetonyl) 4-quinazolinone (**3g**): M.p. 297–298 °C. ^1H NMR (DMSO-d_6) δ: 5.45 (s, 1H, $-CH=$); 7.2–8.2 (m, 4H, aromatic H); 10.2 (br., s, 1H, NH); 12.4 (br., s, 1H, OH) ppm. IR (KBr) (cm^{-1}): 3400; 1680; 1640. MS (*m/z*): 256 (M^+); 187 ($M^+ - 69$). HRMS: Calc. for $C_{11}H_7F_3N_2O_2$, 256.1865. Obs., 256.1806.

2-(1,1,1-Trifluoroacetonyl)-1*H*-perimidine (**3h**): M.p. 289.0 °C. ^1H NMR (DMSO-d_6) δ: 5.2 (s, 1H, $-CH=$); 6.5–7.3 (m, 6H, aromatic H); 10.8 (br., s, 1H, NH); 12.6 (br., s, 1H, OH) ppm. IR (KBr) (cm^{-1}): 3400; 1640. MS (*m/z*): 278 (M^+); 209 ($M^+ - 69$). HRMS: Calc. for $C_{14}H_9F_3N_2O$, 278.2374. Obs., 278.2348.

4-(Trifluoromethyl)-1*H*-1,5-benzodiazepin-2(3*H*)-one (**4**) [5]: M.p. 190.4 °C (reported as 184–185 °C in ref. 5). ^1H NMR ($CDCl_3$) δ: 3.39 (s, 2H, CH_2); 7.15–7.52 (m, 4H, aromatic H); 8.75 (s, 1H, NH) ppm (no signal for OH). MS (*m/z*): 228 (M^+, 25.7%); 186 ($M^+ - 42$) (base peak). HRMS: Calc. for $C_{10}H_7F_3N_2O$, 228.1733. Obs., 228.1723.

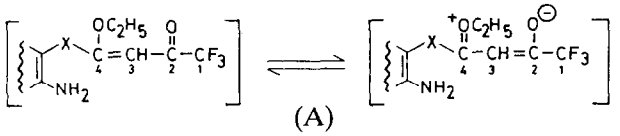
Results and discussion

The reaction between ketene acetal **1** and 1,2-diamines, 2-aminophenol, 2-amino-3-hydroxypyridine and other similar nucleophiles proceeds according to eqn. (1). The results are summarised in Table 1.



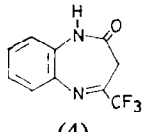
(1)

The reaction is general and proceeds with aliphatic as well as aromatic 1,2-diamines and similar functional nucleophiles such as OH and $CONH_2$. The reaction of 2-amino-3-hydroxypyridine and other *o*-aminophenols with trifluoroacetyl ketene diethylacetal gave the expected products (**3e** and **3f**) in good yield. The reaction proceeds through the intermediate (A) in which C-4 is more susceptible than C-2 to internal nucleophilic attack resulting in the formation of products **3**



(A)

The alternative 4-(trifluoromethyl)-1*H*-1,5-benzodiazepin-2(3*H*)-one (**4**) formulation for the products has been eliminated by an independent preparation of **4** and examination which showed that it was different from **3b**.



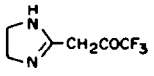
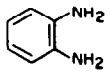
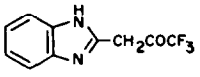
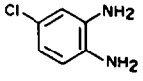
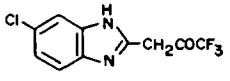
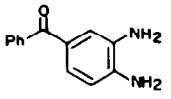
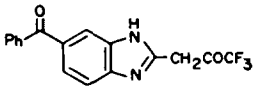
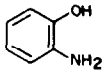
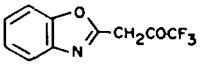
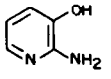
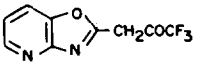
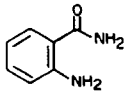
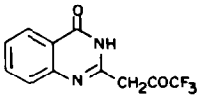
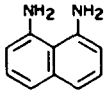
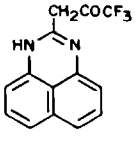
(4)

Such differences in melting point, ^1H NMR spectra and mass spectra are brought out in the Experimental section as well as below in the discussion of the various spectra.

Spectra

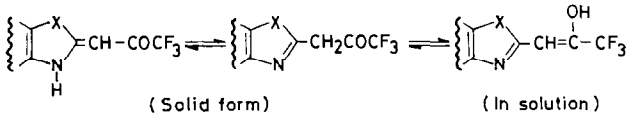
All the compounds exhibited a CF band in the 1200 cm^{-1} region of their IR spectra. In addition to the other usual absorptions, the products when in the solid state exhibited the characteristics of a conjugated ketone, as evidenced by the intense bands at 1630–1640 cm^{-1} in the IR (KBr) spectra. The ^1H NMR spectrum of compound **3b** in $CDCl_3$ solution shows the presence of a vinylic proton at δ 6.1 ppm and of an enolic proton at δ 9.1 ppm (exchangeable with D_2O). This indicates the presence of the $-CH=C(OH)-CF_3$ functional group. The same pattern was observed in the spectra

TABLE 1. Trifluoroacetonyl compounds*

Entry	Substrate 2	Product 3	M.p. (°C)	Yield (%)
a			255–256	40
b			290–292	70
c			> 300	72
d			274–275	55
e			202–205	80
f			165–166	70
g			297–298	70.5
h			289–290	50

*All, except **3b**, are new compounds.

of the other compounds in this series. In the case of compound **4**, the ^1H NMR spectrum in $CDCl_3$ solution showed the presence of active methylene protons at δ 3.39 ppm and of an NH proton at δ 8.75 ppm with no enolic OH proton present in contrast to the spectrum of **3b**. This provides evidence that compound **3b** is different from compound **4**. Methanolic solutions of **3a–h** turned violet in colour on addition of a few drops of iron(III) chloride solution, thus confirming the enol form of the products.



The mass spectra of compounds **3a–h** all exhibited a stable molecular ion, the significant feature of these mass spectra being the loss of a mass content of 69 from M^+, i.e. the loss of a CF_3 group. This was the base peak in the spectra of all the compounds. The mass spectrum of compound **4** contained a peak corresponding to the stable molecular ion with a characteristic loss of ketene ($CH_2=C=O$) to produce the base peak. Thus the alternative structure for the products, i.e. that of compound **4**, may be eliminated.

In conclusion, trifluoroacetyl ketene diethylacetal can be reacted with a wide variety of 1,2-diamines, 1-amino-2-hydroxy compounds and other similar nucleophiles to produce the hitherto unknown (except for **3b**) new 2-trifluoroacetonyl heterocyclic systems of biological interest.

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