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Facile synthesis of 1-substituted 5-trifluoromethylimidazole-4-carboxylates

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Abstract

Base-induced cycloaddition of ethyl isocyanoacetates to trifluoroacetimidoyl chlorides gives ethyl 5-trifluoromethylimidazole-4-carboxylates with high regioselectivity.

Keywords: Trifluoromethylimidazole carboxylate; Isocyanoacetate; Trifluoroacetimidoyl chloride; NMR spectroscopy; IR spectroscopy

1. Introduction

Trifluoromethylated compounds have received an increasing attention in recent years because many of them exhibit interesting biological activity and high performance as materials [1,2]. Much current effort has been devoted to the development of methods for the regioselective synthesis of trifluoromethylated heterocycles [3]. The imidazole ring plays an important role in many biological processes as the functional nucleus of the amino acid histidine, which acts as a base to bind transition metal ions and protons. Some trifluoromethylated imidazoles have been found as xanthine oxidase inhibitors or used as drugs [4,5]. However, the methods for the preparation of trifluoromethylated imidazoles are quite limited [6]. Herein we wish to report a base-induced cycloaddition of ethyl isocyanoacetate to trifluoroacetimidoyl chloride, providing 1-substituted-5-trifluoromethylimidazole-4-carboxylates.

2. Results and discussion

We are interested in the synthesis of biologically active heterocyclic compounds from functionalized isonitriles [7]. Uneyama and coworkers reported that by the reaction of *N*-aryltrifluoroacetimidoyl chlorides with the carbanion derived from dimethyl malonate a β-arylamino-β-trifluoromethyl-α,β-unsaturated ester resulted [8]. We envisaged obtaining β-amino-α,β-unsaturated isonitriles by the similar reaction of *N*-substituted trifluoroacetimidoyl chlorides with isonitriles containing an active methylene group, e.g. an isocyanoacetate. The unsaturated isonitriles thus formed were expected to afford imidazole compounds by an intramolecular cyclization, as the result of a simple 1,1-addition of the amino group to the isocyano group [9] (Scheme 1).

We first attempted the reaction of ethyl isocyanoacetate with *N*-(*p*-nitrophenyl)trifluoroacetimidoyl chloride. Reaction occurred immediately at 0 °C and the mixture turned to brown and then black when a solution of isocyanoacetate and imidoyl chloride in THF was added dropwise to the suspension of NaH in THF. The formation of solid NaCl could be observed after completion of the reaction. Usual work-up gave a yellow solid which was characterized as ethyl 1-(*p*-nitrophenyl)-5-trifluoromethylimidazole-4-carboxylate. The imine or enamine intermediate was not isolated due to rapid cyclization. Usually, the addition of amines to an isocyano carbon requires the participation of a catalyst [9]. The driving force for such cyclizations seems to be a tendency towards aromatization.

We then extended this reaction to other trifluoroacetimidoyl chlorides. As shown in Table 1, the imidazole derivatives were obtained in moderate to good yields. The substituent on N-1 could be an alkyl, acyclic or aryl group. The electronic nature and position of the substituent on the *N*-phenyl ring did not cause any pronounced difference in this reaction.

The structure of the imidazole derivatives was supported by NMR and IR spectra and by analysis. Signals at δ 7.51–7.73 ppm (N=CH–N–) in the ^{1}H NMR spectra definitely revealed the formation of an imidazole ring. The regioiso-

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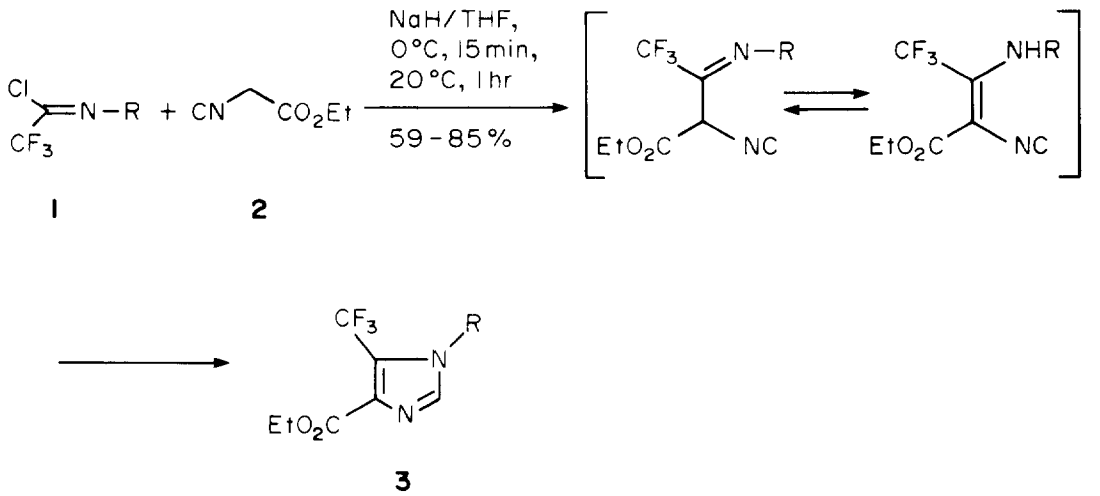
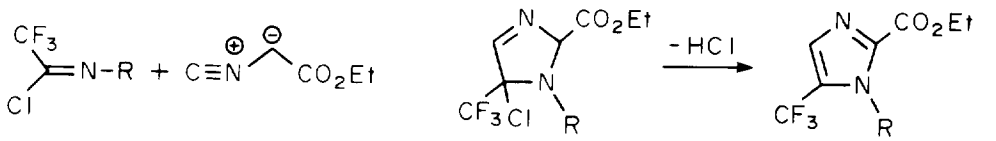


1, 3	R	1, 3	R
a	n-C_8H_{17}	**f**	*p*-$MeOC_6H_4$
b	c-C_6H_{11}	**g**	*p*-ClC_6H_4
c	C_6H_5	**h**	*p*-$NO_2C_6H_4$
d	*p*-MeC_6H_4	**i**	*o*-$NO_2C_6H_4$
e	2,4-$Me_2C_6H_3$		

Scheme 1.

Table 1
Compounds **3** prepared

Product	Yield (%)	M.p. (°C)	Molecular formula	IR (film), ν (cm^{-1})		^{19}F NMR δ (ppm)	MS *m/z* ($M^+ + 1$)
				C=O	C-H		
3a	63	oil	$C_{15}H_{23}F_3N_2O_2$ (320.4)	1750	2950	−22.5	321
3b	75	92–93	$C_{13}H_{17}F_3N_2O_2$ (290.3)	1740	2950	−22.3	291
3c	76	89–90	$C_{13}H_{11}F_3N_2O_2$ (284.2)	1735	3020	−23.2	285
3d	69	69–71	$C_{14}H_{13}F_3N_2O_2$ (298.3)	1735	3010	−23.5	299
3e	72	85–87	$C_{15}H_{15}F_3N_2O_2$ (312.3)	1740	3010	−24.0	313
3f	72	104–106	$C_{14}H_{13}F_3N_2O_3$ (314.3)	1735	3100	−23.2	315
3g	59	95–97	$C_{13}H_{10}ClF_3N_2O_2$ (318.7)	1740	3030	−23.8	320
3h	85	154–155	$C_{13}H_{10}F_3N_3O_4$ (329.2)	1720	3020	−23.7	330
3i	67	140–142	$C_{13}H_{10}F_3N_3O_4$ (329.2)	1730	3050	−22.3	330



Scheme 2.

Table 2
^{1}H NMR spectra of compounds **3**

Compound	^{1}H NMR (300 MHz) δ (ppm), J (Hz)
3a	7.51 (1H, s, N=CH); 4.30 (2H, q, J=7.1, OCH_2); 4.03 (2H, t, J=7.4, NCH_2); 1.72 (2H, tt, J=7.4, 6.8, NCH_2CH_2); 1.30 (3H, t, J=7.1, OCH_2CH_3); 1.22–1.18 (10H, m); 0.78 (3H, t, J=6.6, CH_3)
3b	7.73 (1H, s, N=CH); 4.40 (2H, q, J=7.1, OCH_2); 4.18–4.11 (1H, m, NCH); 2.21–2.13 (2H, m); 2.01–1.93 (2H, m); 1.85–1.45 (5H, m); 1.40 (3H, t, J=7.1, OCH_2CH_3); 1.36–1.20 (1H, m)
3c	7.64 (1H, s, N=CH); 7.55–7.53 (3H, m); 7.38–7.35 (2H, m); 4.45 (2H, q, J=7.1, OCH_2); 1.42 (3H, t, J=7.1, CH_3)
3d	7.59 (1H, s, N=CH); 7.31 (2H, d, J=8.3); 7.23 (2H, d, J=8.3); 4.44 (2H, q, J=7.2, OCH_2); 2.45 (3H, s, CH_3); 1.42 (3H, t, J=7.2, OCH_2CH_3)
3e	7.51 (1H, s, N=CH); 7.22–6.95 (3H, m, phenyl), 4.36 (2H, q, J=7.1, OCH_2); 2.27, 2.26 (6H, s, 2 Me); 1.35 (3H, t, J=7.1, OCH_2CH_3)
3f	7.60 (1H, s, N=CH); 7.27 (2H, d, J=7.3); 6.99 (2H, d, J=7.3); 4.44 (2H, q, J=7.1, OCH_2); 3.89 (3H, s, OCH_3); 1.42 (3H, t, J=7.1, OCH_2CH_3)
3g	7.63 (1H, s, N=CH); 7.52 (2H, d, J=8.7); 7.31 (2H, d, J=8.7); 4.44 (2H, q, J=7.1, OCH_2); 1.42 (3H, t, J=7.1, CH_3)
3h	8.41 (2H, d, J=8.8); 7.68 (1H, s, N=CH); 7.59 (2H, d, J=8.8); 4.43 (2H, q, J=7.1, OCH_2); 1.40 (3H, q, J=7.1, CH_3)
3i	8.28 (1H, dd, J=7.6, 1.9, phenyl proton *ortho* to NO_2); 7.87–7.77 (2H, m); 7.63 (1H, s, N=CH); 7.53 (1H, dd, J=7.3, 1.8, phenyl proton, N–C–CH); 4.45 (2H, q, J=7.1, OCH_2); 1.43 (3H, t, J=7.1, CH_3)

mers, 1-substituted 5-trifluoromethylimidazole-2-carboxylates, were avoided since this reaction proceeded by an anionic cycloaddition rather than by a 1,3-dipolar cycloaddition process (see Scheme 2). The single signal in the ^{19}F NMR spectra confirmed the regioselectivity. The regiochemistry was also verified from the ^{1}H NMR spectra. If an imidazole-2-carboxylate was formed, the coupling of C(4)H with the fluorine atoms of trifluoromethyl group should be observed [1]. However, the imidazole proton appeared as a very sharp singlet rather than a quartet.

Another pathway where the cyclization precedes the elimination of chlorine is possible [11]. The carbanion produced in situ from isocyanoacetate and NaH would attack the C=N bond of the imidoyl chloride to form an *N*-anion, the latter species cyclizing to a new carbanion with an imidazoline structure by intramolecular addition of the *N*-anion to the isocyano carbon. The resulting imidazoline intermediate, upon 1,3-hydrogen shift followed by the displacement of chlorine, would give the imidazole compound. This addition–cyclization–prototropic elimination process, however, was precluded since the reaction of 1-isocyanopropionate with *N*-phenyltrifluoroacetimidoyl chloride gave 1-isocyano-2-imino carboxylate rather than the imidazoline derivative. This result indicates the elimination of chlorine from the *N*-anion is more rapid than cyclization.

In summary, we describe an effective and regiospecific preparation of 1-aryl(alkyl)-5-trifluoromethylimidazole-4-carboxylate from trifluoroacetimidoyl chloride and isocyanoacetate by an addition–elimination and cyclization process. The present methodology is practical since trifluoroacetimidoyl chloride can be conveniently prepared by refluxing a mixture of trifluoroacetic acid and primary amine in carbon tetrachloride in the presence of triethylamine and triphenylphosphine [12]. Moreover, the method described provides 1-aryl-imidazoles which are otherwise not easily attainable due to the fact that nucleophilic alkylation at N-1 by an aryl halide is not possible. The ester moiety in the molecule, being a versatile functional group, can be manipulated in a number of different ways to provide a variety of imidazole derivatives [13].

[1] The coupling of the fluorine atoms of the trifluoromethyl group with C(4)H in 1,2,3-trisubstituted 5-trifluoromethylpyrrole has been reported [10].

Table 3
Microanalysis data for compounds **3**

Compound	Calculated (%)			Found (%)		
	C	H	N	C	H	N
3a	56.2	7.2	8.7	56.4	7.15	8.7
3b	53.8	5.9	9.65	53.7	6.0	9.7
3c	54.9	3.9	9.9	55.0	4.0	9.8
3d	56.4	4.4	9.4	56.3	4.3	9.6
3e	57.7	4.8	9.0	57.5	4.9	9.0
3f	53.5	4.2	8.9	53.6	4.15	9.0
3g	49.0	3.2	8.8	49.1	3.0	8.8
3h	47.4	3.1	12.8	47.4	3.0	13.0
3i	47.4	3.1	12.8	47.3	3.1	12.7

3. Experimental details

Melting points are uncorrected. IR spectra were taken on a Shimadzu-440 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. Chemical shifts for ^{1}H and ^{13}C NMR spectra are reported in ppm downfield from Me_4Si in $CDCl_3$. ^{19}F NMR spectra were obtained on a Varian EM 360A spectrometer using CF_3CO_2H as an external standard, positive for upfield shifts. Coupling constants are given in Hz. EI MS were recorded on a HP5989A mass spectrometer.

N-Substituted trifluoroacetimidoyl chlorides were prepared by literature methods [12]. Ethyl isocyanoacetate was synthesized by the dehydration of *N*-formylglycine ethyl ester [14]. NaH was purchased from Merck Co. Other reagents

were available commercially from a local source (Shanghai Chemical Co.). THF was freshly distilled from sodium benzophenone ketyl.

3.1. Ethyl 1-(p-nitrophenyl)-5-trifluoromethylimidazole-4-carboxylate (3h): typical procedure

To an oven-dried three-necked 50 cm^3 round-bottom flask fitted with a magnetic stirring bar, a rubber septum, a thermometer and charged with dry N_2, was added NaH (150 mg, 5 mmol, 80% in mineral oil) and dry THF (10 cm^3). To the stirred suspension was added slowly a mixture of ethyl isocyanoacetate (565 mg, 5 mmol) and *N*-(*p*-nitrophenyl)trifluoroacetimidoyl chloride (1.26 g, 5 mmol) in dry THF (10 cm^3) at 0 °C. Stirring was continued for 15 min at 0 °C and then for 1 h at r.t. After quenching with saturated aqueous NH_4Cl (10 cm^3), the resulting mixture was partitioned between EtOAc (20 cm^3) and sat. aq. NaCl (10 cm^3). The organic layer was separated and the aqueous layer extracted with EtOAc (3×20 cm^3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the crude product which upon column chromatography on silica gel (30% EtOAc in petroleum ether) gave pure **3h** as a pale yellow solid (1.4 g, 85%). ^{13}C NMR (75.5 MHz) δ: 160.7 (C=O); 139.4 (C_2); 136.3 (C_4); 124.9 (q, $J_{C-F} = 40.2$ Hz, C_5); 119.5 (q, $J_{C-F} = 270.0$ Hz, CF_3); 148.6, 140.0, 127.4, 125.1 (benzene); 61.9 (CH_2); 14.0 (CH_3) ppm. Other analytical data for compounds **3a–i** are listed in Tables 1–3.

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