A Simple Synthesis of 3-Substituted 5-Trifluoromethylpyrroles via Modified Hantzsch Reaction[1]

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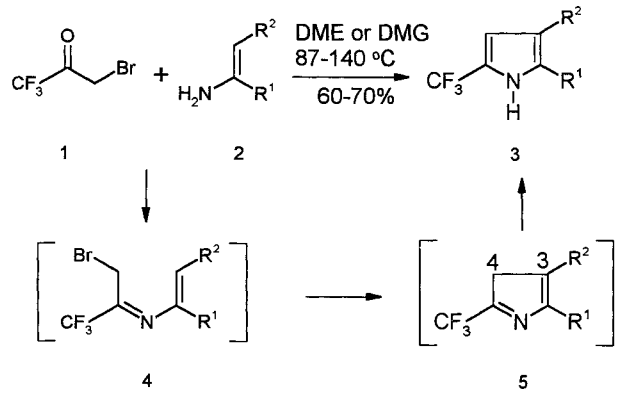
5-Trifluoromethyl-substituted pyrroles have been prepared in high yields via the Hantzsch reaction.

The synthesis of trifluoromethylated heteroaromatic compounds has received growing interest in recent years since many of them exhibit unique biological activities[2] such as 2-aryl-5-trifluoromethylpyrrole derivatives which are a new class of insecticides. The search for a simple and efficient access to heteroaromatic compounds with a trifluoromethyl (CF_3) group at a specific position is one of the important goals in this area.[3] However, regiospecific syntheses of CF_3-substituted heteroaromatic compounds in good yields are still quite limited.[4] The trifluoromethyl-3-cyanopyrroles have been prepared by the 1,3-dipolar cycloaddition reaction of oxazolinones[5] or trifluoroacetimidoyl chloride[6] with 2-chloroacrylonitriles. As we know, pyrrole derivatives can be readily synthesized by the Hantzsch reaction of oxo esters with α-halo ketones[7,8] in the presence of amines. However, to our knowledge, no description of the use of 3-bromo-1,1,1-trifluoropropanone **(1)** for the synthesis of CF_3-substituted pyrroles has been reported. Normal Hantzsch reaction of 3-bromo-1,1,1-trifluoropropanone **(1)** with β-oxonitriles gave only a furan instead of pyrrole, due to the enolizability of the oxo group and the high electrophilicity of the trifluoromethyl ketone. In order to circumvent this problem for the synthesis of 2-aryl-5-trifluoromethylpyrroles, we prepared enamine **2** prior to reaction with 3-bromo-1,1,1-trifluoropropanone **(1)** thereby utilizing the unusual electrophilic nature of the trifluoromethyl ketone. Herein we would like to describe our results on a facile synthesis of 5-trifluoromethyl-substituted pyrroles.

3-Bromo-1,1,1-trifluoropropanone **(1)** was obtained by bromination of the readily available 1,1,1-trifluoroacetone.[9] Reaction of **1** with enamines **2** in refluxing dimethoxyethane (DME) or by heating in diglyme (DGM) at 140 °C for a certain period (see Table 1) readily gave the corresponding 5-CF_3 substituted pyrrole **3** in moderate to good yields (Scheme 1).



Scheme 1

As shown in Table 1, reaction of **1** with β-aminocrotononitrile in refluxing DME for 2 hours afforded 2-methyl-5-trifluoromethylpyrrole-3-carbonitrile **(3a)** in 67 % yield (entry 1) whereas β-aminocrotonic acid methyl ester reacted with **1** in refluxing DME for 1.5 hours gave 2-methyl-5-trifluoromethylpyrrole-3-carboxylic acid **(3b)** in 60 % yield (entry 2). The expected methyl ester was hydrolyzed by the HBr generated in the reaction. The reactions of β-amino-β-aryl-substituted acrylonitriles with **1** were found to proceed sluggishly in refluxing DME, but could be readily completed by heating in diglyme at 140 °C for 6–12 hours, giving the corresponding 2-aryl-3-cyano-5-trifluoromethylpyrroles **(3c–e)** (entries 3–7) in moderate yields.

During the investigation on the preparation of **3d**, we observed that 4-chlorobenzoylacetonitrile was always present in the reaction mixture and use of various dehydrating agents did not completely eliminate its formation. The enamine was also stable under the reaction conditions. We therefore concluded that 4-chlorobenzoylacetonitrile was not formed by hydrolysis of **2d** and that it may at least in part be the result of an enamine exchange

Table 1. Preparation of 5-CF_3 Substituted Pyrroles **3** via Hantzsch Reaction

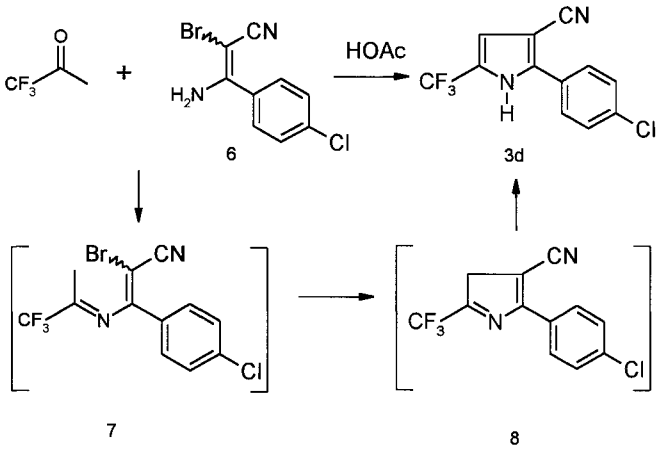
Entry	Enamine **2** R^1	R^2		Solvent	Reaction Temp. (°C)/ Time (h)	Product **3** R^1	R^2		Yield (%)
1	CH_3	CN	**2a**	DME	87/2	CH_3	CN	**3a**	67
2	CH_3	CO_2CH_3	**2b**	DME	87/2.5	CH_3	CO_2H	**3b**	60
3	C_6H_4	CN	**2c**	DME	87/24	C_6H_4	CN	**3c**	68
4	C_6H_4	CN	**2c**	DGM	140/6	C_6H_4	CN	**3c**	71
5	4-ClC_6H_4	CN	**2d**	DGM	87/24	4-ClC_6H_4	CN	**3d**	63
6	4-ClC_6H_4	CN	**2d**	DGM	140/8	4-ClC_6H_4	CN	**3d**	70
7	4-$CH_3C_6H_4$	CN	**2e**	DGM	140/6	4-$CH_3C_6H_4$	CN	**3e**	69

Table 2. Compounds **3** Prepared

Product[a] **3**	mp (°C)	IR (KCl) ν (cm^{-1})	^1H NMR (60 NMR, CD_3COCD_3/TMS) δ, J (Hz)	^{19}F NMR δ	MS (EI, 70 eV) m/z (%)
3a	139–140	3200, 2200, 1600, 1530	2.34 (s, 3H), 6.88 (s, 1H)	−16.2 (s)	174 (100), 153 (49)
3b	125–127	3300, 3150, 1690, 1640, 1600, 1510	2.31 (s, 3H), 5.63 (br s, 1H), 7.07 (s, 1H), 9.23 (br s, 1H)	−16.0 (s)	193 (100), 136 (98)
3c	219–220 (dec)	3200, 2200, 1600, 1515, 1480	6.65 (s, 1H), 7.23–7.60 (m, 5H)	−16.0 (s)	236 (100), 216 (21)
3d	240–242 (dec)	3300, 2200, 1655, 1520, 1480	7.10 (d, J = 2, 1H), 7.50–7.81 centered at 7.65 (A_2B_2, J = 8, 4H)	−16.0 (s)	271 (100), 250 (39), 215 (28)
3e	142–144	3300, 1640, 1480, 1346	1.89 (s, 3H), 7.05 (s, 1H), 7.48–7.80 centered at 7.64–15.8 centered at 7.64 (A_2B_2, J = 8, 4H)	−15.8 (s)	250 (100)

[a] Satisfactory microanalyses obtained: C ± 0.3, H ± 0.19, N ± 0.29, F ± 0.28.

reaction between **1** and **2**. Whereas the Hantzsch reaction in general is known to proceed by the alkylation of the enamine with the α-halo ketone to form the 3,4-pyrrole bond first, followed by cyclization, we postulated that the current modified route might involve the initial formation of the N–C5 bond of the pyrrole due to the high electrophilicity of the trifluoromethyl group, followed by an enamine alkylation to form the final C3–C4 pyrrole bond. This would account for the formation of 4-chlorobenzoylacetonitrile by an enamine exchange reaction. Furthermore, it should not matter whether the leaving group is present on the enamine or the ketone molecule. Bromination of **2d** gave the bromoenamine **7** which on reaction with trifluoroacetone gave the desired pyrrole **3d** in 33% yield (Scheme 2). Analysis of the reaction progress by ^{19}F NMR showed no in situ bromine transfer reaction, thereby supporting such a mechanism for this reaction. Even though the yields are not optimized this variation of the Hantzsch synthesis provides an easy access to the trifluoromethylpyrroles. We are currently investigating this approach to *N*-alkylpyrroles.



Scheme 2

In summary, we have developed a highly efficient and regiospecific synthetic procedure for the preparation of 3-substituted 5-trifluoromethylpyrroles.

3-Bromo-1,1,1-trifluoroacetone[9] and β-amino-β-aryl-substituted acrylonitriles[10] were prepared by the literature procedure. β-Aminocrotonitrile and β-aminocrotonic acid methyl ether were obtained from Tokyo Chemical Industry Company.

β-Amino-β-(4-chlorophenyl)acrylonitrile (2d):
To a suspension of NaH (500 mg, 80%, 16 mmol) in anhyd DMF (15 mL) was added 4-chlorobenzonitrile (1.36 g, 10 mmol) and anhyd MeCN (656 mg, 16 mmol). After stirring at r.t. for 3 days, the mixture was poured into ice water (100 g) and the solid precipitated out was filtered. It was then purified by flash column chromatography on silica gel [eluent: EtOAc/petroleum ether (bp 60–90 °C); 3:7] to afford **2d** (1.25 g, 70%). Crystallization from EtOAc gave a white solid, mp 130–132 °C.

IR (KCl): ν = 3400, 2100, 1640, 1590, 1540, 1490 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.23 (s, 1H), 4.91 (br s, 2H), 7.37–7.47, centered at 7.42 (A_2B_2, J = 8 Hz, 4H).

MS (EI, 70 eV): m/z (%) = 179 (100), 151 (70).

$C_9H_7ClN_2$ Calcd: C, 60.51; H, 3.39; N, 15.69 (178.6) Found: C, 60.19; H, 3.56; N, 15.57.

β-Amino-α-bromo-4-chlorocinnamonitrile (6):
A slurry of **2d** (17.8 g, 0.1 mol) in glacial HOAc (200 mL) and NaOAc (11.0 g, 0.13 mol) was treated with Br_2 (17.0 g, 0.16 mol) at 30 °C. The product was filtered and washed with heptane to give **6** (28.1 g), mp 189–191 °C. Crystallization from MeCN gave a white solid, mp 190–191.5 °C.

5-Trifluoromethyl-Substituted Pyrroles 3; General Procedure:
A solution of 3-bromo-1,1,1-trifluoropropanone (126.8 mg, 1.2 mmol) and an enamine **2** (1 mmol) in DME (10 mL) or diglyme (10 mL) was stirred at refluxing temperature for 2–24 h or heated at 140 °C for 6–8 h respectively (see Table 1). The mixture was poured into a sat. aq $NaHCO_3$ solution (10 mL). The mixture was then extracted with EtOAc (3 × 5 mL) and the extract was washed with brine and dried (Na_2SO_4). Removal of solvent under reduced pressure and the residue thus obtained was subjected to flash column chromatography on silica gel (eluent: EtOAc/petroleum ether 1:9) to give the corresponding 5-trifluoromethyl-substituted pyrrole **3**.

2-(4-Chlorophenyl)-5-trifluoromethylpyrrole-3-carbonitrile (3d):
A solution of trifluoroacetone (3.36 g, 0.03 mol) in HOAc was added dropwise at 100 °C to a solution of α-amino-β-bromo-4-chlorocinnamonitrile (**4**, 5.15 g, 0.02 mol) in HOAc over 4.5 h. The mixture was treated at 100 °C overnight, diluted with H_2O and extracted with EtOAc. The combined organic extracts were washed with H_2O, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography on silica gel using 15% EtOAc/heptane as eluent gave the product **3d** as a yellow solid (1.8 g, 33%); mp 238–240 °C (dec).

(1) The preliminary work was presented in part at the Symposium *"Advances in the Chemistry of Insect Control III"* held at Queens College, Cambridge on July 18–21, 1993; the presentation was published as a monograph, G.G. Briggs ed.; RSC, 1994, pp 141–155.
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