Convenient One-Pot Synthesis of N-Substituted 3-Trifluoroacetyl Pyrroles

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Received 1 December 2008

Abstract: A new one-pot strategy for the synthesis of a series of new N-substituted 3-trifluoroacetyl pyrroles is presented. These compounds were obtained by the reaction of 3-trifluoroacetyl-4,5-dihydrofuran with primary amines, which generated 1,1,1-trifluoro-3-(2-hydroxyethyl)-4-alkylaminobut-3-en-2-one intermediates. In most cases these intermediates were not stable enough to be isolated. Thus, in the same reaction vessel they were directly submitted to oxidation with PCC (Corey's reagent) to furnish 1,1,1-trifluoro-3-(2-ethanal)-4-alkylaminobut-3-en-2-ones, which under reflux underwent intramolecular cyclization to give the desired N-substituted 3-trifluoroacetyl pyrroles, in moderate yields. All of these pyrroles were tested against pan-susceptible *Mycobacterium tuberculosis* H37Rv and clinical isolates INH- and RMP-resistant strain and some of these compounds showed significant in vitro antimicrobial activity.

Key words: pyrroles, 3-trifluoroacetylpyrroles, dihydrofuran, N-substituted pyrroles, antimicrobial activity

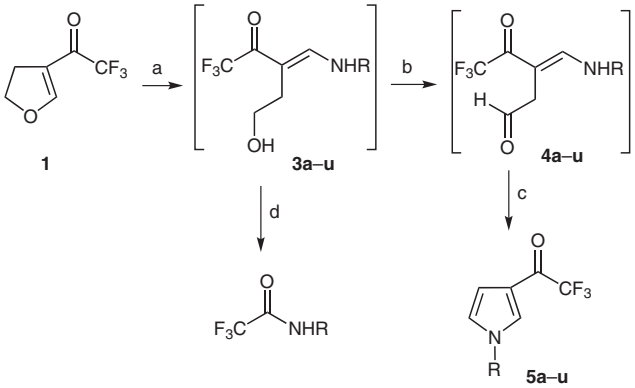
Pyrroles are among the most important heterocycles due both to their wide distribution in nature and to the fact that they comprise the structure of numerous synthetic compounds with significant pharmacological activities.[1] In addition, pyrroles are the main scaffold of biologically important molecules such as, chlorophyll, hemoglobin, and vitamin B_{12}.[2]

The presence of a pyrrole residue in important drugs such as Lipitor®, a cholesterol-lowering agent;[3] Chloripac® and Keterolac®, potent nonsteroidal anti-inflammatory agents;[4] and Netropsin® and Distamicin®,[5] antibiotics with a wide range of antimicrobial activity, has considerably increased interest in pyrrole chemistry in recent years.

The two most widespread methods to introduce a trifluoroacetyl group in heterocycles is by direct trifluoroacetylation[6] and through a cyclocondensation reaction of a bis(trifluoroacetyl)vinyl ether[7] and -amines[8] with dinucleophiles. Other methods include oxidative dimerization of 1,1,1-trifluoro-4-arylbut-3-yn-2-one, carried out by treatment of lead dioxide in a CH_2Cl_2–TFA mixture,[9] dipolar cycloaddition of diazo compounds[10] and azides[11] with α,β-unsaturated trifluoromethyl ketones,[12] photoinduced cyclization of sulfimino uracil substituted with α,β-unsaturated trifluoromethyl ketones, and intramolecular cyclization of trifluoro(dimethoxyethylamino)alkenones.[13] More specifically, the synthesis of 3-trifluoroacetyl pyrroles are much less reported and very few of them are N-substituted.[7a,13]

It is widely known that 2- or 5-substituted pyrroles are easily synthesized by aromatic electrophilic substitution,[14] whereas a special strategy is necessary to obtain 3- or 4-substituted pyrroles.[15] In addition, the introduction of N-substituents in pyrroles is a difficult task because N-alkylation competes with C-alkylation.[16] Therefore, it is important to note that there is a clear demand for the development of a modular and simple reaction to strategically access 3-substituted as well as N-substituted pyrroles.[17] Trifluoromethyl-containing pyrroles are relatively rare, however, some of these compounds have demonstrated important insecticidal action and mitochondrial uncoupling activity.[18]

In this paper, we wish to report a new, simple, and highly chemoselective one-pot method to synthesize N-substituted 3-trifluoroacetylpyrroles from the reaction of 3-trifluoroacetyl-4,5-dihydrofuran and primary amines, followed by an in situ oxidation with PCC and intramolecular cyclization (Scheme 1). To the best of our knowledge, no description of such a procedure has been reported for the synthesis of the title pyrroles. In addition, all the pyrroles obtained in this study are new and their in vitro antimicrobial activity was tested against pan-susceptible *Mycobacterium tuberculosis* H37Rv and clinical isolates INH and RMP-resistant strains.[19]



Scheme 1 *Reaction conditions*: (a) RNH_2 (**2a**–**u**), CH_2Cl_2, 0.5 h, r.t., (b) PCC, CH_2Cl_2; (c) reflux, 3 h; (d) spontaneous conversion.

SYNLETT 2009, No. 5, pp 0755–0758
Advanced online publication: 24.02.2009
DOI: 10.1055/s-0028-1087821; Art ID: S12108ST

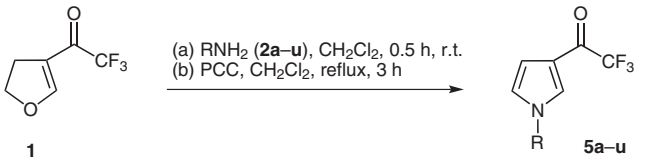
Scheme 1 outlines the synthetic strategy used to synthesize the N-substituted 3-trifluoroacetylpyrroles. The 3-trifluoroacetyl-4,5-dihydrofuran (**1**) was prepared according to the literature.[20] The reaction of compound **1** with primary amines **2a**–**r** (1 equiv) and amines **2s**–**u** (0.5 equiv), in dichloromethane, furnished the enamino alcohols **3**, which were oxidized in situ with pyridinium chlorochromate (PCC)[21] to generate the corresponding aldehydes **4**. These aldehydes underwent cyclization to give the pyrroles **5a**–**r** and the bispyrrole compounds **5s**–**u**, in moderate yields. The relative low overall yields (20–56%) were probably due to the difficulty to isolate the pyrroles from the oxidation medium[22] and the partial solubility of these compounds in water. However, if one considers that these are overall yields of a three-step reaction, they may not be considered so low (Table 1). In order to improve yields, other oxidants such as pyridinium dichromate (PDC)[23] and pyridinium fluorochromate (PFC)[24] were used, but both furnished the desired products in lower yields than the PCC method.

During the development of this study, many efforts were taken to isolate the alcohol intermediates **3**. In fact, many of these alcohol intermediates were isolated, however, they were relatively unstable as they slowly decomposed to the corresponding trifluoroacetamides (Scheme 1). The spontaneous conversion of compound **3l** to *N*-benzyltrifluoroacetamide was followed by ^{13}C NMR spectroscopy, where, during the spectral acquisition of compound **3l**, for example, the quartet of the $C(O)CF_3$ ($^2J_{CF}$ = 30 Hz), at δ = 173.8 ppm tended to decrease in intensity while a signal of a new quartet appeared at δ = 158.7 ppm, which is consistent with the chemical shift of a carbonyl of a trifluoroacetamide. The formation of the *N*-benzyltrifluoroacetamide was also confirmed by GC-MS. To further confirm the formation of *N*-benzyltrifluoroacetamide, this compound was synthesized by the reaction of benzylamine and trifluoroacetic anhydride, which confirmed our expectation. Thus, the reactions were carried out without the isolation of the alcohol intermediate **3**. The formation of alcohols **3** were monitored by TLC and it was observed that the reaction was completed in approximately 30 minutes, at room temperature. After this period, 1.2 equivalents of PCC were added to the reaction vessel, and the reaction was refluxed for three hours to give the pyrroles **5** in 20–56% overall yields. The aldehydes **4** were not isolated because cyclization began soon after the addition of PCC, even keeping the reaction at room temperature. An attempt to isolate aldehydes **4** furnished mixtures of aldehydes **4**, alcohols **3**, and pyrroles **5**. Based on these results, we decided to carry out the reaction in a one-pot procedure to obtain the final pyrroles without the isolation of their intermediates (see Table 1 for reaction conditions and yields).[25]

Reaction products **5** were isolated by the evaporation of dichloromethane from the reaction mixture and the remaining black residue was dissolved in a 1 M solution of sodium hydroxide and the alkaline solution was extracted with ethyl ether. Compounds **5a**–**u** were purified by column chromatography using basic alumina as the stationary phase and ethyl ether as the eluant.[26]

Under the reaction conditions reported in this study, aniline and arylamines, such as 3-hydroxy-4-methylaniline, 2-hydroxy-4-methylaniline, 2-chloro-aniline, 2,4-dichloroaniline, and 4-fluoroaniline, failed to react with 3-trifluoroacetyl-4,5-dihydrofuran (**1**). Additionally, reactions of 3-trichloroacetyl-4,5-dihydrofuran with amines furnished 3-aminomethylenedihydrofuran-2-ones[27] instead of N-substituted 3-trifluoroacetyl pyrroles. All pyrroles obtained in this study were tested for their antimycobacterial activity. Four of these pyrroles

Table 1 Optimized Reaction Conditions for the Synthesis of **5a**–**u**

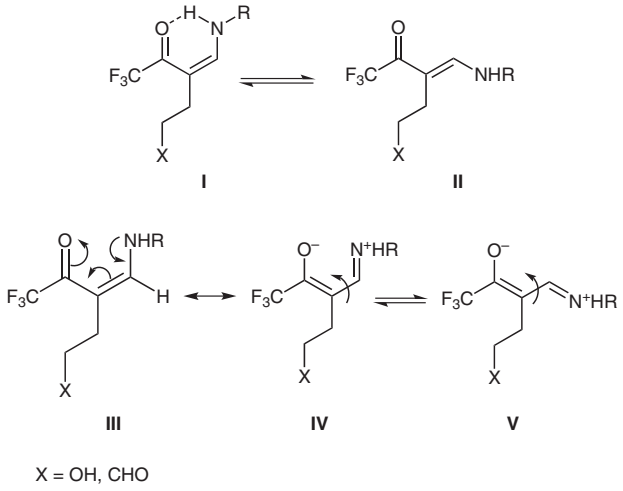


Entry	Compd	Amine **2a**–**u**[a]	Yield (%)[b]	Product
1	**2a**[c]	NH_4OH	28	**5a**
2	**2b**[c]	$MeNH_2$	36	**5b**
3	**2c**	$EtNH_2$	41	**5c**
4	**2d**	$PrNH_2$	46	**5d**
5	**2e**	*i*-$PrNH_2$	52	**5e**
6	**2f**	$allylNH_2$	43	**5f**
7	**2g**	$HO(CH_2)_2NH_2$	20	**5g**
8	**2h**	$HO(CH_2)_3NH_2$	45	**5h**
9	**2i**	$MeCH(OH)CH_2NH_2$	56	**5i**
10	**2j**	$MeCH_2CH(NH_2)CH_2OH$	54	**5j**
11	**2k**	$HOCH_2C(CH_3)_2NH_2$	41	**5k**
12	**2l**	$BnNH_2$	55	**5l**
13	**2m**	$Ph(CH_2)_2NH_2$	50	**5m**
14	**2n**	(pyridin-2-yl)methylamine	47	**5n**
15	**2o**	(pyridin-3-yl)methylamine	51	**5o**
16	**2p**	(pyridin-4-yl)methylamine	39	**5p**
17	**2q**	$Me_2N(CH_2)_2NH_2$	25	**5q**
18	**2r**	$Et_2N(CH_2)_2NH_2$	41	**5r**
19	**2s**[d]	$H_2N(CH_2)_2NH_2$	27	**5s**
20	**2t**[d]	$H_2N(CH_2)_3NH_2$	46	**5t**
21	**2u**[d]	$H_2N(CH_2)_4NH_2$	34	**5u**

[a] Reaction conditions (except otherwise indicated): 1) amine (1 equiv), CH_2Cl_2, 30 min, r.t.; 2) PCC (1.2 equiv), 3 h, reflux.
[b] Yields after purification by column chromatography.
[c] In aqueous solution. Amine was used in excess and the alcohol **3** was extracted with CH_2Cl_2 before reaction with PCC.
[d] Amine used: 0.5 equiv.

(**5f**,**h**,**l**,**m**) showed significant in vitro antimycobacterial activity against pan-susceptible *Mycobacterium tuberculosis* $H37_{Rv}$ and clinical isolates isoniazid (INHr) and rifampin (RMPr) resistant strains.[19]

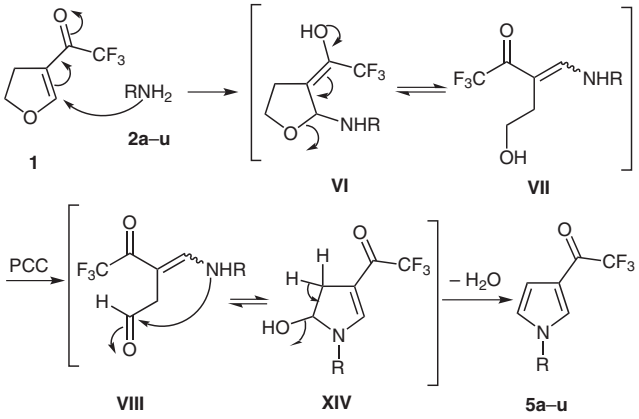
The intermediates **3** and **4** (Scheme 1) may exist in both *Z*- and *E*-isomers, as shown in Scheme 2, by structures **I** and **II**, respectively. The mechanism that such interconversion may occur is represented by structures **III**, **IV**, and **V**. The formation of the intermediate **I** (*Z*-isomer) is preferred in nonpolar or low polar solvents, such as chloroform, due to the hydrogen-bond formation between the N–H and the carbonyl. In high polar solvents, such as DMSO, structure **II** may be more favorable. Structure **I** has a wrong stereochemistry for intramolecular cyclization, however, a low energy barrier of the carbon–carbon double bond of the enaminone **III**, driven by the push–pull effect of the carbonyl (π-acceptor) and the β-amino group (π-donor) allows easy rotation around this bond as shown by structures **IV** and **V**.[28] Thus, because of the easy interconversion between the *E*- and *Z*-isomers (structures **IV** and **V**), the aldehyde intermediates **4** can be completely converted into the corresponding pyrroles **5** regardless of the configuration of the carbon–carbon double bond.



Scheme 2

The mechanism of formation of pyrroles **5** begins with the Michael addition of the amine nitrogen at the β-carbonyl position of 3-trifluoroacetyl-4,5-dihydrofuran **1** to give structure **VI** (Scheme 3), which, upon restoring the carbonyl, opens the furan ring to give the enamino ketone **VII**. Oxidation of **VII** with PCC affords the aldehyde **VIII**, which undergoes intramolecular cyclization leading to structure **XIV**, which eliminates a water molecule to furnish the N-substituted 3-trifluoroacetyl pyrroles **5a**–**u**.

In summary, we have developed a simple and efficient one-pot procedure for the preparation of new N-substituted 3-trifluoroacetyl pyrroles, using mild reaction conditions and leading to relatively good overall yields if one considers that a three-step reaction is carried out in the same reaction vessel. In addition, this method allows the introduction of a large scope of N-substituents to the pyrrole ring, especially hydroxylated substituents without protection of the hydroxyl function. Furthermore, this study showed that 3-trifluoroacetyl-4,5-dihydrofuran is a convenient reagent for the synthesis of the title pyrroles, since it is obtained easily and in excellent yield through the trifluoroacetylation of the commercially available 4,5-dihydrofuran. Compounds **5f**,**h**,**l**,**m** showed significant in vitro antimycobacterial activity against pan-susceptible *Mycobacterium tuberculosis* ($H37_{Rv}$) and clinical isolates isoniazid (INHr) and rifampin (RMPr) resistant strains.



Scheme 3

Acknowledgment

The authors thank the financial support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq – Universal grant No. 476634/06-7), and fellowships from CAPES (A. D. Wouters, L. Fantinel and F. M. da Silva).

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(19) Unpublished results: compound **5f** exhibited activity against $H37_{Rv}$ and RMPr (MIC = 12.5 μg/mL) and INHr (MIC = 50 μg/mL); **5h** exhibited activity against $H37_{Rv}$ and RMPr (MIC = 12.5 μg/mL) and INHr (MIC = 25.0 μg/mL); **5l** exhibited activity against $H37_{Rv}$ (MIC = 6.25 μg/mL) and RMPr and INHr (MIC = 12.5 μg/mL); **5m** exhibited activity against $H37_{Rv}$ and RMPr (MIC = 6.25 μg/mL) and INHr (MIC = 12.5 μg/mL).
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(25) **Synthesis of N-Substituted 3-Trifluoroacetyl Pyrroles 5 – General Procedure**

To a solution of 3-trifluoroacetyl-4,5-dihydrofuran **1** (0.50 g, 3.0 mmol) in CH_2Cl_2 (5 mL), amines **2a**,**b** (approx. 6.0 mmol), amines **2c**–**r** (3.0 mmol), and amines **2s**–**u** (1.5 mmol) were added under magnetic stirring, and the reaction was stirred for 30 min at r.t. After this period, PCC (4.5 mmol) in CH_2Cl_2 (5 mL) was added, and the reaction mixture was refluxed for 3 h. For amines **2a**,**b**, before the addition of PCC, the reaction was extracted with CH_2Cl_2 (3 × 15 mL) and dried with $MgSO_4$. The solvent was evaporated by rotary evaporator, and the reaction residue was treated with 1 M solution of NaOH and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with 1 M NaOH solution (2 × 50 mL) and distilled H_2O (1 × 50 mL). The organic phase was dried with anhyd $MgSO_4$, evaporated, and purified by column chromatography using basic alumina (60 g) with a plug of active charcoal and eluted with Et_2O (50 mL).

(26) **Spectroscopic Data of Selected Compounds**

1-Methyl-3-trifluoroacetylpyrrole (5b)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.4 (s, 1 H), 6.7 (s, 1 H), 6.6 (s, 1 H), 3.7 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0 (q, $^2J_{CF}$ = 35.3 Hz), 130.1, 124.3, 117.8, 116.9 (q, $^1J_{CF}$ = 288.7 Hz), 110.9, 36.8. GC-MS (IE, 70eV): *m/z* (%) = 117 (68) [M$^+$], 108 (100), 80 (30). ESI-HRMS: *m/z* calcd for $C_6H_4F_3NO$ [M + H]$^+$: 178.0479; found: 178.0471.

1-(Ethan-1-ol-2-yl)-3-trifluoroacetylpyrrole (5g)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.5 (s, 1 H), 6.7 (m, 2 H), 4 (t, 1 H, *J* = 9.2 Hz), 3.9 (t, 1 H, *J* = 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4 (q, $^2J_{CF}$ = 35.7 Hz), 130.1, 123.8, 117.8, 116.9 (q, $^1J_{CF}$ = 288.8 Hz), 110.9, 61.8, 52.5. GC-MS (IE, 70eV): *m/z* (%) = 207 (25) [M$^+$], 138 (100), 94 (57). ESI-HRMS: *m/z* calcd for $C_9H_8F_3NO$ [M + H]$^+$: 208.0585; found: 208.0576.

1-(2,2-Dimethyl-etan-1-ol-2-yl)-3-trifluoroacetylpyrrole (5k)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.6 (s, 1 H), 6.9 (m, 1 H), 6.7 (m, 2 H), 3.6 (s, 2 H), 1.5 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4 (q, $^2J_{CF}$ = 35 Hz), 127.5, 121, 117.3, 116.9 (q, $^1J_{CF}$ = 289 Hz), 110.5, 70.4, 60.2, 24.5. GC-MS (IE 70eV): *m/z* (%) = 235 (30) [M$^+$], 204 (97), 94 (100). ESI-HRMS: *m/z* calcd for $C_{10}H_{12}F_3NO_2$ [M + H]$^+$: 236.0898; found: 236.0891.

1-(Ethan-2-dimethylamino-1-yl)-3-trifluoroacetyl-pyrrole (5q)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 1 H), 6.74 (m, 2 H), 4.01 (t, 2 H, *J* = 3.2 Hz) 2.67 (t, 2 H, *J* = 3.1 Hz), 2.27 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2 (q, $^2J_{CF}$ = 35 Hz), 129.6, 123.5, 117.8, 116.9 (q, $^1J_{CF}$ = 288 Hz), 110.7, 59.6, 48.5, 45.4. GC-MS (IE, 70eV): *m/z* (%) = 235 (100) [MH$^+$], 165 (20). ESI-HRMS: *m/z* calcd for $C_{10}H_{13}F_3N_2O$ [M + H]$^+$: 235.1058; found: 235.1058.

1,2-Bis-3-trifluoroacetylpyrrole-1-yl-ethane (5s)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (s, 1 H), 6.77 (s, 1 H), 6.50 (m, 1 H), 4.30 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2 (q, $^2J_{CF}$ = 35 Hz), 128.8, 122.8, 118.8, 116.7 (q, $^1J_{CF}$ = 288 Hz), 111.9, 52.1. GC-MS (IE, 70eV): *m/z* (%) = 352 (31) [M$^+$], 283 (100), 176 (26), 107 (25). ESI-HRMS: *m/z* calcd for $C_{14}H_{10}F_6N_2O_2$ [M + H]$^+$: 367.0881; found: 367.0876.

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