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A NEW AND EFFICIENT SYNTHESIS OF 2-TRIFLUOROMETHYL SUBSTITUTED PYRROLES AND ETHYL-2,3-BIS(ETHOXYCARBONYL)-1H-PYRROLE-1-PROPIONATE[1]

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Abstract: Dirhodium tetraacetate catalyzed decomposition of trifluoromethyl acetyl diazoacetates **6a** and **6b** in ethyl vinyl ether gives rise to the dihydrofuroates **7a** and **7b**, respectively, which can be converted into the corresponding 2-(trifluoromethyl)pyrroles. This two step pyrrole synthesis is also suitable for the preparation of ethyl 2,3-bis(ethoxycarbonyl)-1H-pyrrole-1-propinate, an important intermediate for the synthesis of necin bases.

INTRODUCTION

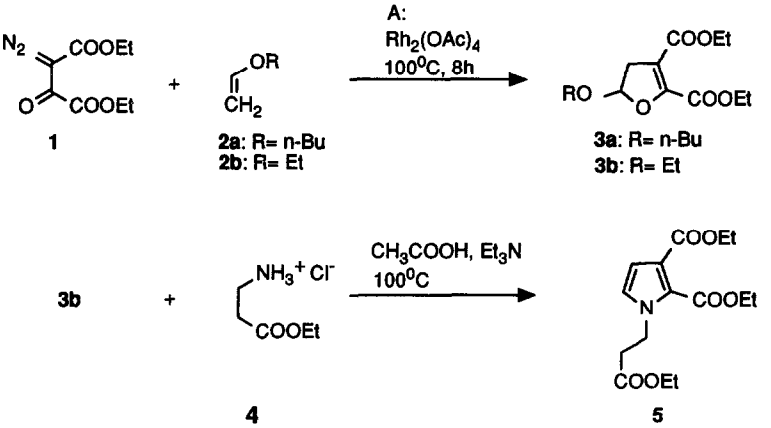
The fungicidal and insecticidal activities of many naturally occurring pyrroles[2] have led to a considerable endeavor in the synthesis of these compounds[3] and, to a greater extent, of their natural product analogues.[4] A very important derivatization in the synthesis of biological active compounds consists of the introduction of perfluoroalkyl, especially trifluoromethyl, groups[5] and consequently, many valuable methods have been reported dealing with this problem.[6] In addition to the direct trifluoroalkylation[7] the de novo synthesis of heterocycles starting from perfluoroalkyl or CF_3-containing aliphatic precursors plays an important role in heterocyclic chemistry.[8] Although several methods for the synthesis of pyrroles starting from unsaturated furans have been reported,[9] there has been no mention in the literature of the conversion of CF_3-containing 4,5-dihydrofurans into the corresponding pyrroles.[10]

Recently, E. Wenkert and coworkers have published a procedure for a simple synthesis of the dihydrofuroate **3a** via a dirhodium tetraacetate catalyzed reaction of diethyl oxalyl diazoacetate **1a** in *n*-butyl vinyl ether **2a**.[11]

Furthermore, it was also possible to convert the dihydrofuran derivative **3a** into 2,3-bis(ethoxycarbonyl)-N-benzyl-pyrrole by treatment with benzylamine in acetic acid.[12] Thus, this two step pyrrole synthesis should also be a convenient entry into the preparation of 2-trifluoromethyl substituted pyrroles, and we first utilized this method for the synthesis of ethyl-2,3-bis(ethoxycarbonyl)-1H-pyrrole-1-propionate **5**, a very important compound for the formation of 1,7-disubstituted pyrrolizines and pyrrolizidines, which are intermediates for the preparation of necin bases.[13]

RESULTS

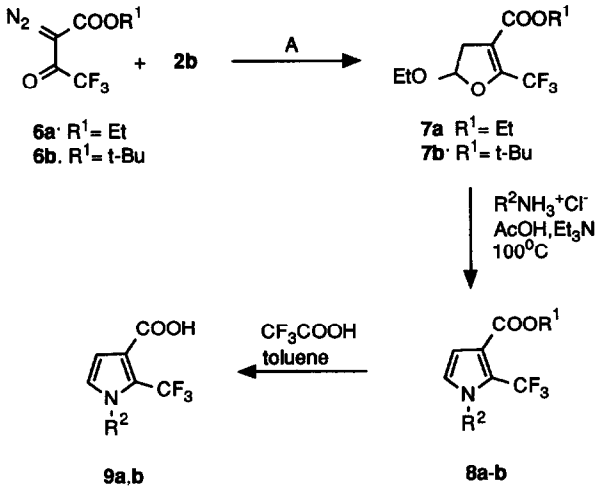
As depicted in scheme **1**, we have employed ethyl vinyl ether **2b** instead of *n*-butyl vinyl ether **2a** as in the original synthesis[11] for the dihydrofuroate formation reaction since 5-ethoxy-dihydrofuran **3b** afforded higher yields on pyrroles upon reaction with primary amines than the corresponding dihydrofuran **3a**. Thus, the dirhodium tetraacetate catalyzed decomposition of **1** in ethyl vinyl ether at 100°C in a closed steel vessel led to the formation of dihydrofuroate **3b** in over 80% yield, which could then be converted into the corresponding pyrrole[13] **5** on exposure to β-alanine ethylester hydrochloride **4** in acetic acid and triethylamine.



Scheme 1

To demonstrate the general applicability of this approach, we have extended this dirhodium tetraacetate catalyzed reaction to the readily available trifluoromethyl acetyl diazoacetates **6a** and **6b**. As shown in scheme **2** decomposition of the diazocompounds[14] **6a** or **6b** in the presence of a catalytic amount of dirhodium tetraacetate in ethyl vinyl ether **2b** at 100°C gave rise to the dihydrofuroates **7a** or **7b** in 92% and 76% yield, respectively. Reaction between the dihydrofuroates **7a** or **7b** and ammonium or methylammonium hydrochloride in acetic acid and triethylamine yielded the corresponding 2-trifluoromethyl substituted pyrroles **8a-d** in reasonable yields (table).

Finally, exposure of the *t*-butyl-3-pyrrole carboxylates **8c** and **8d** to trifluoro acetic acid in toluene afforded the pyrrole carboxylic acids **9a** and **9b** (table).



Scheme 2

Table: Formation of Pyrroles **8** and **9**

Compound	R^1	R^2	(%)yield[a]
8a	Et	Me	67
8b	Et	H	69
8c	*t*-Bu	Me	63
8d	*t*-Bu	H	54
9a		Me	71
9b		H	63

[a]Isolated yield of pure compound

In conclusion, a further and convenient method for the synthesis of 2-trifluoromethyl substituted 3-pyrrole carboxylates has been developed which utilizes the dirhodium tetraacetate catalyzed decomposition of trifluoro acetyl diazoacetates **6a** and **6b** in ethyl vinyl ether. This leads to the formation of dihydrofuroates **7a** and **7b**, which can then be converted into the corresponding pyrroles by condensation with primary amines.

EXPERIMENTAL SECTION

General: Melting points are not corrected. Preparative column chromatography was performed on silica gel S, 0.063-0.200mm (Riedel-deHaen). ^{1}H NMR spectra were obtained at 100 MHz and chemical shifts are reported relative to tetramethylsilane. Microanalyses of all new compounds were performed in our analytical labatory.

General Procedure for the Formation of Dihydrofuroates 3b, 7a, 7b: A mixture of 100 mg of hydroquinone, 100 mg of dirhodium tetraacetate and 0.28 mol of diazocompound (**1, 6a, 6b**) in 500 ml of ethyl vinyl ether was stirred at 100^{0}C over a 8-h period in a closed steel vessel. The mixture was concentrated under vacuum, the residue was passed through a column of silica gel and eluted with 4:1 heptane-ethyl acetate.

Diethyl 5-*n*-Ethoxy-4,5-dihydrofuran-2,3-dicarboxylate (3b): 65 g (90%) oil; ^{1}H NMR ($CDCl_3$) δ: 1.25, 1.27, 1.37 (3t, 9H, $3CH_3$); 2.98 (ddd, 2H, furan CH_2); 3.70 (m, 2H, ethoxy OCH_2); 4.17, 4.32 (2q, 4H, 2 OCH_2); 5.70 (dd, 1H, J=7.5, 3.8Hz, furan O_2CH). Anal. calcd for $C_{12}H_{18}O_6$: C 55.81; H 7.02. Found: C 56.10; H 7.30.

Ethyl 5-*n*-Ethoxy-2-trifluoromethyl-4,5-dihydro-3-furancarboxylate (7a): 65 g (92%) oil; ^{1}H NMR ($CDCl_3$) δ: 1.25, 1.29 (2t, 6H, 2 CH_3); 3.10 (m, 2H, furan CH_2); 3.75 (m, 2H, OCH_2); 4.20 (q, 2H, $COOCH_2CH_3$); 5.68 (dd, 1H, J=7.5, 3.0Hz, furan O_2CH). Anal. calcd for $C_{10}H_{13}F_3O_4$: C 47.25; H 5.12. Found: C 47.80; H 5.60.

***t*-Butyl 5-*n*-Ethoxy-2-trifluoromethyl-4,5-dihydro-3-furancarboxylate (7b):** 60 g (76%) oil: ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H, OCH_2CH_3); 1.45 (s, 9H, CO_2tBu); 3.00 (m, 2H, furan CH_2); 3.75 (m, 2H, OCH_2CH_3); 5.65 (dd, 1H, J=7.5, 3.8Hz, furan O_2CH). Anal. calcd for $C_{12}H_{17}F_3O_4$: C 51.06; H 6.07. Found: C 50.90; H 5.90.

Ethyl-2,3-bis(ethoxycarbonyl)-1H-pyrrole-1-propionate(5):[13] 6.1 g (60 mmol) of triethylamine and a solution of 10.3 g (40 mmol) dihydrofuroate (**3b**) in 15 ml of acetic acid were added subsequently at 0^{0}C to a mixture of 9.2 g (60 mmol) of ß-alanine ethylester hydrochloride in 20 ml of acetic acid. This mixture was stirred at 100^{0}C for 2-4 hours (the reaction was followed by tlc), then cooled, and poured into 100 ml of water. The aqueous layer was extracted with methylene chloride, and the combined organic layer was dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel and elution with 7:3 heptane-ethyl acetate afforded 10 g (81%) of colorless, liquid pyrrole **5**: ^{1}H NMR ($CDCl_3$) δ: 1.20, 1.30, 1.32 (3t, 9H, $3CH_3$); 2.80 (t, 2H, J=6.5Hz, CH_2COOEt); 4.10, 4.26, 4.30 (3q, 6H, 3 OCH_2); 4.45 (t, 2H, J=6.5Hz, N-CH_2); 6.40, 6.80 (2d, 2H, J=3Hz, pyrrole H).

General Procedure for the Synthesis of Pyrroles 8a-8d: A solution of 0.132 mol of 4,5-dihydrofuroate (**7a, 7b**) in 50 ml of acetic acid was added to a mixture of 1.32 mol of the hydrochloride of the corresponding amine and 1.32 mol of triethylamine in 500 ml of acetic acid. The mixture was stirred for 2-4h at 100^{0}C (the reaction was followed by tlc), then cooled and poured into 1l of icewater. The aqueous layer was extracted several times with methylene chloride, and the combined organic layer (dried over Na_2SO_4) was evaporated. The products were purified by chromatography on silica gel and elution with 4:1 heptane-ethyl acetate.

Ethyl 2-Trifluoromethyl-N-methyl-3-pyrrolecarboxylate (8a): 19.5 g (67%) oil; ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, 3H, OCH_2CH_3); 3.75 (q, 3H, N-CH_3); 4.30 (q, 2H, OCH_2CH_3); 6.56, 6.63 (2d, 2H, J=2.5Hz, pyrrole H). Anal. calcd for $C_9H_{10}F_3NO_2$: C 48.87; H 4.55; N 6.33. Found: C 48.60; H 4.70; N 6.20.

Ethyl 2-Trifluoromethyl-3-pyrrolecarboxylate (8b): 18.8 g (69%); m.p.64-66^{0}C; ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, 3H, OCH_2CH_3); 4.30 (q, 2H, OCH_2CH_3); 6.76 (m, 2H, pyrrole H); 9.50 (bs 1H, NH). Anal. calcd for $C_8H_9F_3NO_2$: C 46.39; H 3.89; N 6.76. Found: C 46.90; H 3.70; N 6.40.

***t*-Butyl 2-Trifluoromethyl-N-methyl-3-pyrrolecarboxylate (8c):** 20.7 g (63%) oil; ^{1}H NMR ($CDCl_3$) δ: 1.55 (s, 9H, CO_2tBu); 3.75 (q, 3H, N-CH_3); 6.50, 6.58 (2d, 2H, J=2.5Hz, pyrrole H). Anal. calcd for $C_{11}H_{14}F_3NO_2$: C 53.01; H 5.66; N 5.62. Found: C 52.70; H 5.80; N 5.60.

***t*-Butyl 2-Trifluoromethyl-3-pyrrolecarboxylate (8d):** 16.8 g (54%) viscous oil; ^{1}H NMR ($CDCl_3$) δ: 1.55 (s, 9H, CO_2tBu); 6.75 (m, 2H, pyrrole H); 9.20 (bs, 1H, NH). Anal. calcd for $C_{10}H_{12}F_3NO_2$: C 51.07; H 5.14; N 5.95. Found: C 50.80; H 5.20; N 5.60.

General Procedure for the Synthesis of 3-Pyrrolecarboxylic Acids 9a, 9b: A mixture of 72 mmol of pyrrole (**8c, 8d**) and 720 mmol of trifluoromethyl acetic acid in 210 ml of methylene chloride was stirred for several hours at room temperature. The mixture was evaporated and the residue was purified by crystallization in toluene.

N-Methyl-2-trifluoromethyl-3-pyrrolecarboxylic Acid (9a): 9.8 g (71%); m.p. 160-162^{0}C; ^{1}H NMR (DMSO-d_6) δ: 3.75 (q, 3H, N-CH_3); 6.45, 7.05 (2d, 2H, J=2.5Hz, pyrrole H); 12.5 (bs, 1H, COOH). Anal. calcd for $C_7H_6F_3NO_2$: C 43.51; H 3.13; N 7.26. Found: C 43.60; H 3.10; N 7.10.

2-Trifluoromethyl -3-pyrrolecarboxylic Acid (9b): 8.1 g (63%); m.p. 166-168^{0}C; ^{1}H NMR (DMSO-d_6) δ: 6.55 (m, 1H, pyrrole H); 6.97 (dd, 1H, J=2.5Hz, pyrrole H); 12.50 (bs, 2H, NH,COOH). Anal. calcd for $C_6H_4F_3NO_2$: C 40.24; H 2.25; N 7.82. Found: c 40.80; H 2.30; N 7.50.

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