

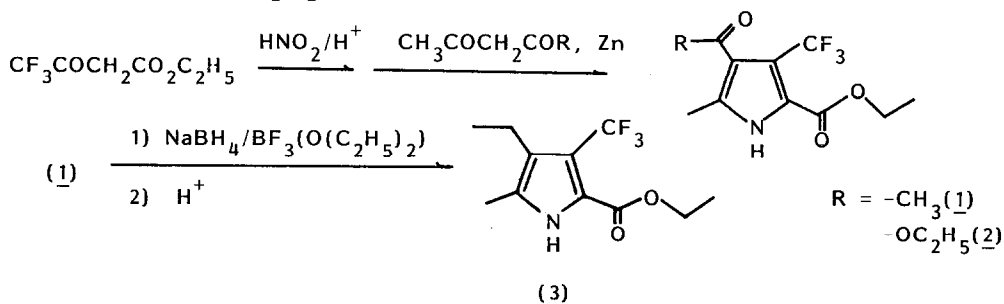
SYNTHESIS OF β -TRIFLUOROMETHYLPYRROLES

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Abstract; The β -trifluoromethylpyrroles have been synthesized by the modified Knorr condensation in strong acid media.

Synthetic pathway to the β -trifluoromethylpyrrole derivatives has never been reported yet to our knowledge except for the 3-trifluoromethylindole¹. Photochemical reaction of pyrrole and trifluoromethyl iodide gave only a site-specific product of 2-trifluoromethylpyrrole². The pyrroles substituted with the trifluoromethyl group at the β -position are available for further synthesis of new pyrroles and a component to construct electron-deficient porphyrins. Despite of recent progress in trifluoromethylation of heterocycles, synthetic manipulations are generally hazardous and reagents are expensive. The Knorr condensation utilizing the β -dicarbonyls containing the trifluoromethyl group seems to be more accessible to obtain the β -trifluoromethylpyrroles. It was found that usual Knorr condensation through the oximide intermediate by nitrous acid in glacial acetic acid afforded the desired pyrroles in very low yields less than 5% in preliminary experiments. We have attempted to prepare the target pyrroles in moderate yields by facile condensation reaction.

Dry hydrogen chloride was introduced into a solution of ethyl trifluoroacetoacetate (44 mmol) in 20 mL of trifluoroacetic acid at 0°C for 30 min. Then freshly generated HNO₂ was introduced into the solution at 0°C until uptake of gas ceased³. After stirring for 20 hr, the solution was condensed into small portion under reduced pressure. Acetylacetone (150 mmol) in a mixture of CF₃CO₂H (13 mL) and CH₃CO₂H (30 mL) was dropwise added to the residue. Small portions of well pulverized zinc powder (153 mmol) was added to the reaction mixture for 2 hr. This was further stirred at 70°C for 3 hr followed by treatment of sodium acetate (10 g) and additional stirring for 20 min at 100°C. The mixture was poured into ice-water. Crystallization of crude solid material from n-hexane-CH₂Cl₂ gave ethyl 4-acetyl-3-trifluoromethyl-5-methylpyrrole-2-



carboxylate (1) as colorless crystals (5.4 g, 47% yield). A solution of ethyl trifluoroacetoacetate (26 mmol) in a mixture of $\text{CF}_3\text{CO}_2\text{H}$ (10 mL) and conc H_2SO_4 (1 mL) was treated with freshly generated HNO_2 at 0°C for 3 hr. Similar procedure described above by using ethyl acetoacetate (51 mL), zinc powder (89 mmol), and sodium acetate gave diethyl 3-trifluoromethyl-5-methylpyrrole-2,4-dicarboxylate (2) as colorless crystals (3.0 g, 41% yield). Ethyl trifluoromethylacetoacetate is considerably enolized in neutral solvents. Strong acid media cause marked shift of its tautomerism to the keto form which may give preferential formation of the oximide intermediate⁴. In fact, the larger content of the keto tautomer in the reaction condition results in the higher yield of the desired pyrroles.

To a mixture of (1) (10.3 mmol) and sodium borohydride (57 mmol) in dry tetrahydrofuran (30 mL) was added boron trifluoride etherate (68 mmol) at -10°C . The reaction mixture was stirred at 20°C for 4 hr and treated with 5% HCl solution followed by neutralization with sodium bicarbonate. Extract with ether was chromatographed on silica gel. Crystallization of collected solid from n-hexane furnished ethyl 4-ethyl-3-trifluoromethyl-5-methylpyrrole-2-carboxylate (3) as colorless crystals (2.1 g, 83% yield). Remarkable decrease in the basicity of (2) (pK_a 11.3) was observed in comparison with that of diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate (pK_a 13.9) due to replacement of the 3-methyl group with strong electron-withdrawing CF_3 group. Thus obtained pyrrole (1)-(3) are very stable even in strong acid, whereas the polyalkylated pyrroles are usually unstable in the acidic media. As is listed in Table 1, mass spectra and spectroscopic data support structures of (1)-(3).

Table 1. Melting points and spectroscopic data of β -trifluoromethylpyrroles

Comp.	mp, $^\circ\text{C}$	m/e	^1H nmr (δ)	ir(cm^{-1})
(<u>1</u>)	110	263(M^+)	1.40($\text{CH}_3\text{CH}_2\text{O}$ -, 3H,t), 2.38(CH_3 -, 3H,s) 2.45(CH_3CO -, 3H,s), 4.40($\text{CH}_3\text{CH}_2\text{O}$ -, 2H,q), 10.10(NH, 1H,s)	ν_{CO} 1690, 1675 ν_{CF_3} 1280, 1120
(<u>2</u>)	98	298(M^+)	1.37($\text{CH}_3\text{CH}_2\text{O}$ -, 3H,t), 1.41($\text{CH}_3\text{CH}_2\text{O}$ -, 3H,t), 2.49(CH_3 -, 3H,s), 4.28($\text{CH}_3\text{CH}_2\text{O}$ -, 2H,q), 4.37($\text{CH}_3\text{CH}_2\text{O}$ -, 2H,q), 10.03(NH, 1H,s)	ν_{CO} 1690, 1710 ν_{CF_3} 1285, 1120
(<u>3</u>)	113	248 [($\text{M}-1$) ⁺]	1.07(CH_3CH_2 -, 3H,t), 1.34($\text{CH}_3\text{CH}_2\text{O}$ -, 3H,t), 2.23(CH_3 -, 3H,s), 2.53(CH_3CH_2 -, 2H,q), 4.35($\text{CH}_3\text{CH}_2\text{O}$ -, 2H,q), 9.50(NH, 1H,s)	ν_{CO} 1680 ν_{CF_3} 1280, 1120

REFERENCES AND NOTES

1. Y. Kobayashi, I. Kumadaki, Y. Hirose, and Y. Hanasawa, *J. Org. Chem.*, **39**, 1836(1974)
2. Y. Kobayashi, I. Kumadaki, A. Ohsawa, S. Murakami, and T. Nakano, *Chem. Pharm. Bull.* (Tokyo), **26**, 1247(1978).
3. F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry" Fourth Ed., p 429(1980) John Wiley & Sons. In the gas phase, dissociation of HNO_2 occurs to give NO, NO_2 , and H_2O according to the following equilibrium; $2\text{HNO}_2 \rightleftharpoons \text{NO} + \text{NO}_2 + \text{H}_2\text{O}$
4. Ratio of enol and keto tautomers was determined by nmr measurement.

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