Pergamon

Tetrahedron Letters, Vol. 35, No. 25, pp. 4319-4322, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00820-5

A New Approach to the Synthesis of β-Fluoropyrrole Derivatives

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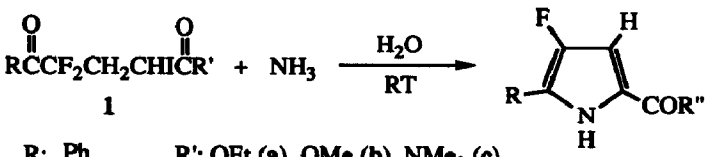
Key Words: β-fluoropyrrole derivatives; α,α-difluoro-γ-iodo-γ-(electron-withdrawing-group)-substituted ketone

Abstract: *β-Fluoropyrrole derivatives are synthesized in high yields by the reaction of α,α-difluoro-γ-iodo-γ-(electron-withdrawing-group)-substituted ketones and ammonium hydroxide at room temperature; providing a new, simple, and efficient method for the synthesis of β-fluorinated pyrrole rings. A possible mechanism is proposed.*

Pyrrole and its derivatives are one of the most important heterocyclic compounds in organic chemistry.[1] They are not only a prolific source of interesting chemical reactions, but also an important building block for many biologically important molecules; notably porphyrins, bile pigments, vitamin B_{12}, chlorophyll, and prodigiosin.[1,2] The pyrrole ring has also been widely applied to the development of modern concepts of theoretical chemistry[3] and the elucidation of the general relationship between activity and selectivity in organic chemistry.[4] In recent years, much attention has been paid to selectively fluorinated compounds because of their unique physicochemical properties and biological activities.[5] It is well-known that many naturally occurring halopyrroles[1,2a] and synthetic pyrrole derivatives[2e] have exhibited strong anti-bacterial activity, therefore, it is of interest to study fluorinated pyrroles. Although a number of methods for the introduction of perfluoroalkyl groups into the 2- or 3-positions of the pyrrole ring have been reported,[6] there is no general, efficient route for the synthesis of fluoropyrrole derivatives. *Via* the reaction of 2-chloro-2-fluoroacetophenone and bis(β-cyanoethyl)imine, 2-fluoro-3-phenyl-5-methyl pyrrole was synthesized as a fungicide and bactericide.[7] Buhr found that in the presence of nucleophilic arenes and furan, 2-azido-3,3-difluoro-cyclobutenes underwent ring expansion to give 2-fluorinated pyrroles in 3-27 % yield.[8] Also, 3,4-difluoro-1-*t*-butyl pyrrole was synthesized by the thermal [2+3] cycloaddition of 2-carbomethoxy-1-*t*-butyl-aziridine with chlorotrifluoroethylene, followed by base treatment and thermal decarboxylation with an overall yield of 20 %.[9] An alternative route for the synthesis of fluoropyrrole is *via* the modified Schieman reaction. However, only a 17 % yield of β-fluoropyrrole was obtained from the photoreaction of pyrrole-α-diazonium tetrafluoroborate.[10] Considering the disadvantages of low yields, multiple reaction steps, or difficulties in the preparation of starting materials, here we would like to report a new, efficient and practical method for the synthesis of β-fluoropyrrole derivatives.

Recently, we have developed a new method for the synthesis of α,α-difluoroketones[11] of interest as enzyme inhibitors.[12] Also, high yields of α,α-difluoro-γ-(electron-withdrawing-group)-substituted ketones (**1**) have been obtained *via* the reaction of iododifluoromethyl ketones with electron-deficient olefins under UV irradiation.[13] Treatment of the addition products, **1a-g**, with aqueous ammonium hydroxide at room temperature gave excellent yields of the β-fluoropyrrole derivatives, **2a-g**. These results are summarized in **Table I.**



R: Ph, R': OEt (**a**), OMe (**b**), NMe_2 (**c**)
R: n-C_4H_9, R': OEt (**d**), OMe (**e**)
R: n-C_6H_{13}, R': OEt (**f**), NMe_2 (**g**)

2

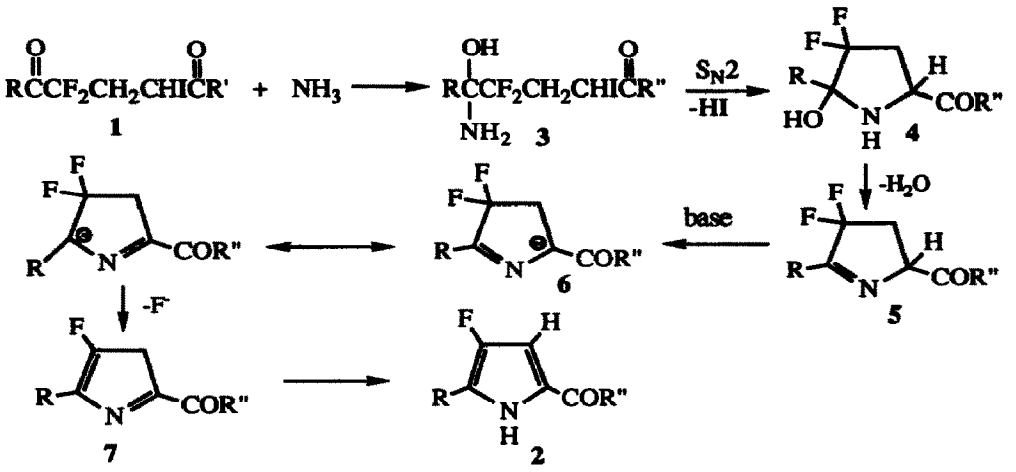
TABLE I: The Reaction of 1 with Ammonium Hydroxide[a]

Entry	1 R	1 R'	2 R''	Isolated yield of 2 (%)
1	Ph	OEt	OEt (**2a**)	92
2	Ph	OMe	NH_2 (**2b**)	95
3	Ph	NMe_2	NMe_2 (**2c**)	79
4	n-C_4H_9	OEt	NH_2 (**2d**)	88
5	n-C_4H_9	OMe	NH_2 (**2e**)	90
6	n-C_6H_{13}	OEt	NH_2 (**2f**)	92
7	n-C_6H_{13}	NMe_2	NMe_2 (**2g**)	90[b]

a: Reaction conditions: room temperature/24 hrs. with excess ammonium hydroxide; all conversions were 100% based on ^{19}F NMR analysis; all compounds gave satisfactory ^{19}F, ^{1}H, and ^{13}C NMR, IR and GC-MS data; *b*: NaOH was added to complete the conversion of **5g** to **2g**.

Although the synthesis of a pyrrole ring from γ-haloketones has not been reported, it is well known that 1,4-diketones can afford pyrrole derivatives by treatment with primary amines (Paal-Knorr reaction).[1] A similar mechanism is proposed for the formation of β-fluoropyrroles from α,α-difluoro-γ-iodoketones (**Scheme I**).

The presence of a difluoromethylene moiety increases the electrophilicity of the adjacent carbonyl group.[5a] Therefore, ammonia easily adds to the carbonyl group of the iodoketone (**1**) to form hemiaminal (**3**), instead of the α,β-unsaturated acid derivative.[14] The intramolecular substitution of **3**, followed by dehydration gives 1-pyrroline, **5**. The presence of an electron withdrawing group in **5** facilitates deprotonation by ammonium hydroxide to generate the corresponding anion, **6**. β-Elimination of fluoride anion, followed by base-catalyzed proton transfer yields the pyrrole ring. The isolation of 2-(n-hexyl)-3,3-difluoro-5-(N,N-dimethylcarbamoyl)-1-pyrroline (**5g**) in the reaction of **1g** with NH_3 and its transformation to the corresponding pyrrole ring by treatment with NaOH is in agreement with the proposed mechanism (**Scheme I**).



(Scheme I)

A typical reaction procedure is as follows: a 50 mL round-bottom flask, fitted with a stir bar and stopper, was charged with 0.35g (0.92 mmol) of ethyl 2-iodo-4,4-difluoro-4-benzoyl butyrate (**1a**) and an excess of ammonium hydroxide (>25 ml). The reaction mixture was stirred at room temperature overnight. The precipitate formed was isolated by gravity filtration. After recrystallization from diethyl ether and hexane, 0.20 g (92 %) of ethyl 4-fluoro-5-phenylpyrrole-2-carboxylate (**2a**) was obtained. The structure was assigned on the basis of ^{19}F, ^{1}H, and ^{13}C NMR, FT-IR, GC-MS and high resolution GC-MS spectroscopy.[15]

In conclusion, this reaction provides a new, efficient, and practical method for the synthesis of β-fluoropyrrole derivatives under mild conditions. Further studies for the application of α,α-difluoro-γ-iodo-ketones in the synthesis of selectively fluorinated heterocyclic compounds continue.

Acknowledgement:

We would like to thank the National Science Foundation for financial support of this work.

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14. a) The reaction of $CF_3CH_2CHICO_2Et$ with NH_3 has been reported to give $CF_3CH(NH_2)CH_2CONH_2$ *via* HI elimination and NH_3 addition; Walborsky, H. M.; Baum, M.; Loncrini, D. F. *J.Am.Chem.Soc.*, **1955**, *77*, 3637; b) We also isolated $C_3F_7CH{=}CHCONH_2$ as the intermediate product when $C_3F_7CH_2CHICO_2Et$ was treated with ammonium hydroxide.
15. Typical analysis data of **2a**: m.p. 103-104 °C; ^{19}F nmr ($CFCl_3$, $CDCl_3$): -159.44 (s) ppm; ^1H nmr (TMS, $CDCl_3$): 9.47 (s, broad, 1H), 7.66 (dd, J = 7.34, 1.44 Hz, 2H), 7.42 (dt, J = 7.57, 1.49 Hz, 2H), 7.30 (tt, J = 7.40, 1.49 Hz, 1H), 6.69 (d, J = 2.88 Hz, 1H), 4.32 (q, J = 7.13Hz, 2H), 1.35 (t, J = 7.13Hz, 3H) ppm; ^{13}C nmr (TMS, $CDCl_3$) : 161.28 (s), 148.84 (d, J = 246.8 Hz), 129.14 (d, J = 4.86), 128.98 (s), 127.56 (s), 125.13 (s), 120.54 (d, J = 19.40 Hz), 118.02 (d, J = 7.30 Hz), 103.40 (d, J = 160.2 Hz), 60.86 (s), 14.41 (s) ppm; FT-IR (CCl_4): 3455.85, 3301.70, 2984.66, 1701.90, 1721.90, 1685.66, 1445.12, 12161.46, 1213.69 cm^{-1}; GC-MS: 234 (M^++1, 73.27), 188 (M^+-OEt, 26.73), 187 (100), 159 (42.08), 133 (68.81), 77 (6.99); High Resolution GC-MS: Obsvd.: 233.0845, $C_{13}H_{12}O_2FN$, Calc'd: 233.0852.

(*Received in USA* 7 *March* 1994; *revised* 20 *April* 1994; *accepted* 21 *April* 1994)