Pergamon

Tetrahedron 54 (1998) 4367–4374

TETRAHEDRON

The Special Directing Effect of Fluorine: Ligand Independent *Ortho* Lithiation of 1-(Fluorophenyl)pyrroles

Ferenc Faigl[1*], Katalin Fogassy[1], Zoltán Szántó[2], Antal Lopata[2] and László Tőke[3]

[1]Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, Hungary

[2]CheMicro Ltd. H-1108 Budapest, Salamon u 13/a., Hungary

[3]Research Group for Organic Chemical Technology of Hungarian Academy of Sciences, H-1521 Budapest, Hungary

Received 10 December 1997; revised 10 February 1998; accepted 12 February 1998

Abstract: Lithiation of 1-(fluorophenyl)pyrroles occurred exclusively *ortho* to the fluorine substituent independently of the structure of the tertiary amine type ligands used. Semiempirical quantum chemical calculations confirmed that the special directing effect of fluorine atom is manifested by increasing kinetic acidity of the neighbouring position while the α hydrogens of the pyrrole rings are the most acidic in ground state.

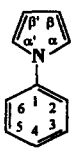
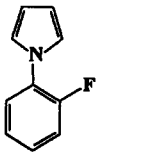
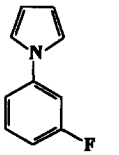
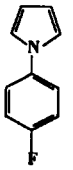
We recently reported the regioselective lithiation reactions of 1-(methoxyphenyl)pyrroles using butyllithium (BuLi) in the presence of di- or tri-dentate tertiary amine type ligands as N,N,N`,N`-tetramethylethylene-diamine (TMEDA) or N,N,N`,N`,N``-pentamethyldiethylenetriamine (PMDTA).[1] Clean α lithiation at the pyrrole ring occurred when PMDTA was used while the fast co-ordination of the lithiating agent to the methoxy oxygen atom resulted in the clean *ortho* lithiation in the presence of TMEDA.[1] The methoxy group is known from the literature as a medium-strong directing group having dual (inductive electron withdrawal and co-ordinative) character.[2] At the same time, the fluorine atom is mentioned as a moderate or weak *ortho* directing group that has only a strong *-I* effect without significant electron donating ability for co-ordination.[2] The difference between the two directing groups has been demonstrated in site-selective metallation reactions of fluoroanisoles where the intramolecular competition between the two groups could be studied.[3] Practically clean *ortho* lithiation related to the methoxy group was observed with butyllithium (BuLi), while the hydrogen metal exchange reaction occurred *ortho* to the fluorinated carbon in the presence of BuLi-PMDTA. Furthermore, fluorine has several times been referred to as a "mysterious" substituent which causes special effects depending on its position related to the reaction centre.[4] For example, fluorotoluenes underwent clean *ortho* metallation with the superbasic mixture of butyllithium and potassium *tert.*-butoxide (LICKOR) reagent at low temperature, but only the *ortho*- and *meta*-fluorotoluenes reacted at the benzylic position with the lithium diisopropylamide - potassium *tert.*-butoxide (LIDAKOR) mixture, while *para*-fluorotoluene yielded again mainly the *ortho*-substituted product.[5]

PII: S0040-4020(98)00150-1

As part of an ongoing program aimed to study the effects of di- and tri-dentate ligands on the regioselectivity of lithiation reactions, a detailed investigation of the metallation of 1-(fluorophenyl)pyrroles was performed in our laboratory. We wanted to compare the charge distribution maps as well as our results obtained in the lithiation reactions of the methoxy and fluoro substituted series of compounds in order to shed light onto the details of the directed metallation and the role of the activating agents in that processes.

Semiempirical quantum chemical calculations (HyperChem,[6] AM1 method) were carried out stepwise on the parent compound (1-phenylpyrrole, **1**) and the fluoro derivatives (**2**, **3** and **4**), respectively. In the first run we determined the energetically most stable conformers of the molecules starting from different conformations. It turned out that the pyrrole and the phenyl rings do not lie in the same plane. The C(2)-C(1)-N-C(α) torsion angles are far from zero in the most stable conformers (Table 1).

Table 1. Calculated Torsion Angles and Total Energies of the Most Stable Conformers of **1**, **2**, **3** and **4**.

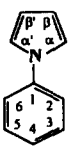
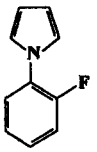
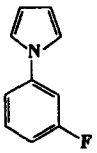
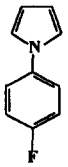
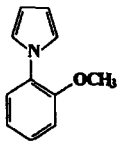
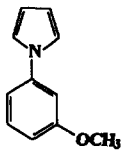
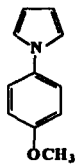
	 **1**	 **2**	 **3**	 **4**
C(2)-C(1)-N-C(α) torsion angle (°)	28	37	27	29
E (kcal/mol)	-37108.3	-47977.6	-47979.0	-47979.1

The charge distribution values of the hydrogen atoms were practically independent of the torsion angle (Table 2 shows these data in the model compounds having the above mentioned optimum geometry). From these calculations we concluded that in the ground state the most acidic hydrogen atoms are again those in the α position similar to the parent compound (**1**) and the previously investigated methoxy derivatives[1] (**5**, **6** and **7** in Table 2).

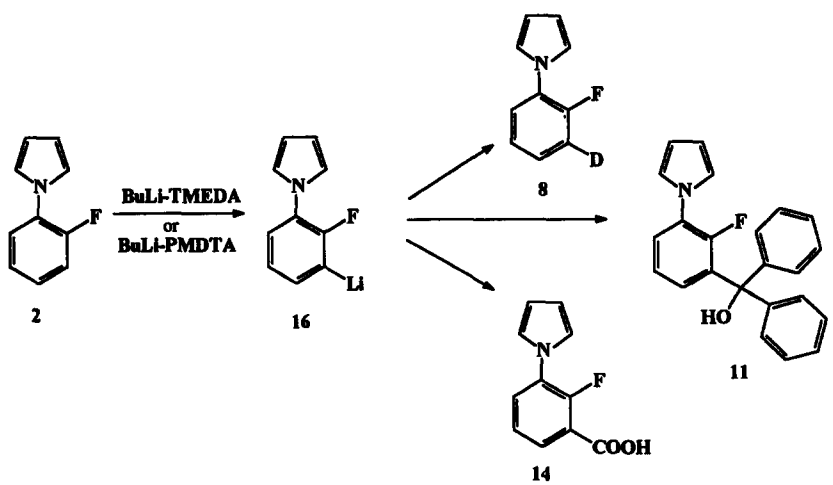
Lithiation reactions of **2**, **3** and **4** were accomplished under the same conditions irrespective of the activating agent used in order to compare the effects of fluorine in different positions and the effects of the activating agents, respectively. The positions of the hydrogen metal exchange were determined by the analysis of the products obtained from the reactions with three different electrophilic reagents, separately. It was found that the substitution occurred always in the *ortho* position to the fluorine atom independently of the structure of the activating agent (TMEDA or PMDTA).

Consecutive treatment of **2**, **3** or **4** with BuLi-TMEDA or BuLi-PMDTA and heavy water resulted in practically quantitative formation of **8**, **9** and **10**, respectively. Similarly we obtained the benzophenone adducts (**11**, **12**, **13**) and the acid derivatives (**14** and **15**) (Schemes 1, 2 and 3.).

Table 2. Calculated Charge Distribution of the Hydrogen Atoms in the Model Compounds

	 1	 2	 3	 4	 5[a]	 6[a]	 7[a]
H(α)	0.167	0.176	0.169	0.167	0.175	0.156	0.165
H(α`)	0.167	0.166	0.168	0.167	0.152	0.159	0.165
H(β)	0.153	0.155	0.155	0.155	0.151	0.153	0.153
H(β`)	0.153	0.154	0.155	0.155	0.150	0.153	0.153
H(2)	0.142	-	0.159	0.148	-	0.131	0.143
H(3)	0.136	0.153	-	0.154	0.136	-	0.154
H(4)	0.136	0.143	0.153	-	0.140	0.146	-
H(5)	0.136	0.142	0.143	0.154	0.141	0.143	0.142
H(6)	0.142	0.149	0.147	0.148	0.142	0.137	0.140

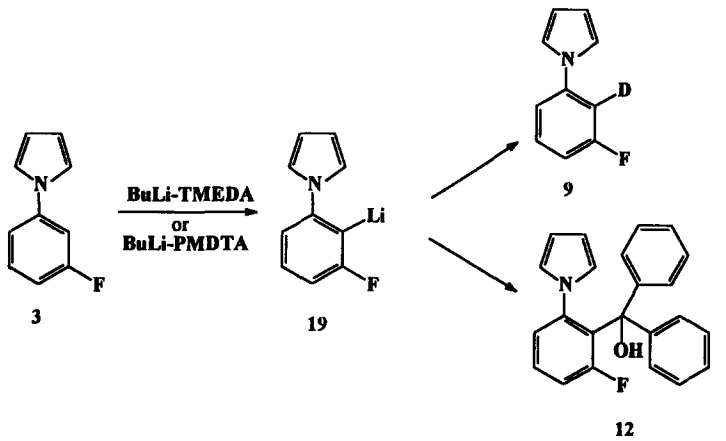
[a]The net atomic charges were determined previously[1].



Scheme 1. *Electrophilic reagents*: heavy water, benzophenone, dry ice

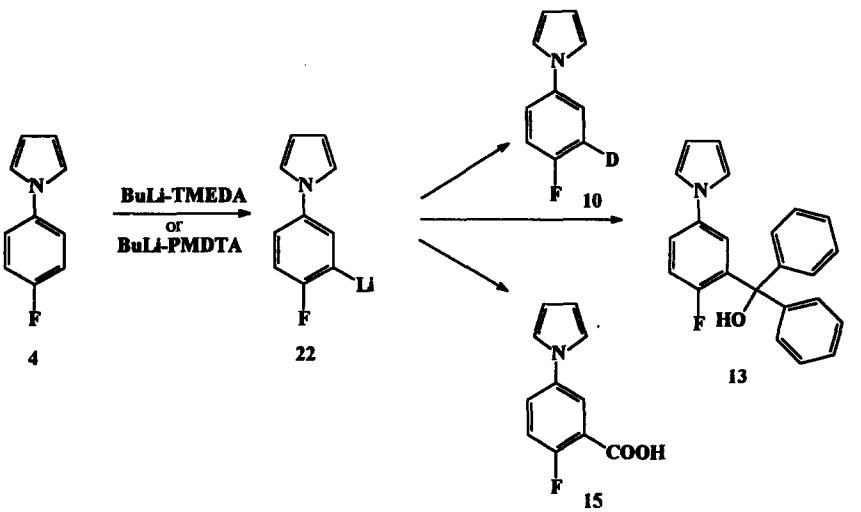
Compounds **11**, **12**, **13**, **14** and **15** were isolated, purified and fully characterised by spectroscopic methods and elemental analyses because they have been unknown until now. However, any attempt to isolate

1-(2-carboxy-3-fluorophenyl)pyrrole has failed because of the fast spontaneous decarboxylation of the product even if citric acid was used for acidification during the workup procedure.



3 19 9 12

Scheme 2. *Electrophilic reagents*: heavy water, benzophenone.



4 22 10 13 15

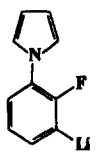
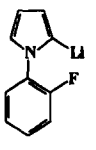
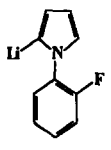
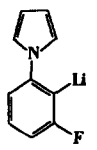
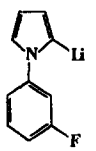
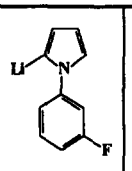
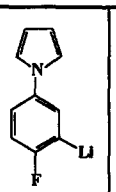
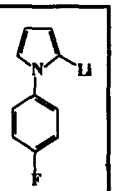
Scheme 3. *Electrophilic reagents*: heavy water, benzophenon or dry ice

In order to rationalise these results we have carried out semiempirical quantum chemical calculations on the lithio derivatives of **2**, **3** and **4** (compounds **16** - **23**), respectively. The energy values show (Table 3) that the α-lithiated derivatives (**17** and **21**) are the most stable among the lithio derivatives of **2** and **3**, while the 1-(3-lithio-4-fluorophenyl)pyrrole (**22**) is more stable than the corresponding α-lithiated derivative (**23**) of compound **4**.

Since these calculations referred to the equilibrium state of the molecules (in vacuo) we can conclude that the observed *ortho* selectivity is due to a kinetic rather than a thermodynamic control. It is known from

the literature that the fluorine atom raises the kinetic acidity of the *ortho* hydrogen atoms in fluorobenzene. The rate of hydrogen/deuterium exchange is 10^6 fold related to that of benzene.[7] At the same time, the lithiation rate of the pyrrole ring in α position may only be ten to hundred times faster than that in the case at benzene (a methoxy group increases the kinetic acidity of the *ortho* position with two orders of magnitude[4] but we were able to accomplish clean α-metallation of 1-(methoxyphenyl)pyrroles with BuLi-PMDTA reagent[1]). In other words, fluorine directs the *ortho* metallation by its especially large effect on the kinetic acidity which is, of course, independent of the tertiary amine type ligand used.

Table 3. Calculated Total Energy Values of the Different Lithiated 1-(Fluorophenyl)pyrroles

	 16	 17	 18	 19	 20	 21	 22	 23
E kcal/mol	-47806.7	-47819.2	-47804.3	-47804.5	-47806.8	-47807.0	-47808.8	-47806.8

An alternative explanation of the observed ligand independent regioselectivity would be a special co-ordination effect of fluorine to lithium. It should develop in a very fast process preceding the hydrogen metal exchange reaction step. Others have recently reported fluorine - metal interactions in crown ether complexes having the fluorine substituent in a special position.[8] However, this co-ordination ability seems to be weak enough that we could see differences between the reactions carried out in the presence of di- and tri-dentate ligands. An experimental evidence of the weakness of such a fluorine-lithium co-ordination is the observation of Schlosser and co-workers.[3] They showed that clean lithiation *ortho* to the methoxy group occurred when fluoroanisoles were treated with butyllithium in tetrahydrofuran at -75 °C for 50 hours (proving to the co-ordination of BuLi to the methoxy oxygen atom).

On the basis of our experimental observations and theoretical calculations we have concluded that since the *-I* effect of the fluorine atom can not increase the equilibrium acidity value of the *ortho* hydrogen atoms above the acidity of the α hydrogen atoms of the pyrrole ring, the kinetic acidity of the hydrogen atom adjacent to the fluorine plays an important role. It seems to be three or four orders of magnitude higher than that of the α hydrogen atoms, thus *ortho* lithiation is preferred in these systems.

Comparison of these results with our findings for 1-phenylpyrrole[14] and 1-(methoxyphenyl)pyrrole series has also confirmed that the dual character of the methoxy group is responsible for the ligand dependent site-selective metallation of those compounds. The fast co-ordination between the methoxy oxygen atom and butyllithium is the crucial step in cases of the reactions with BuLi-TMEDA reagent but it can be avoided by

the use of a tri-dentate ligand (PMDTA) at low temperature. The special (kinetic acidity increasing) effect together with the weak co-ordinating ability of the fluorine substituent result in the ligand independent clean *ortho* lithiation of the fluorinated model compounds with both BuLi-TMEDA and BuLi-PMDTA reagents.

EXPERIMENTAL PART

Generalities:

All commercial starting materials were purchased from FLUKA AG and Merck-Schuchardt and were used without further purification. Butyllithium was supplied by Chemetall GmbH Lithium Division, Frankfurt.

Diethyl ether and terahydrofuran were obtained anhydrous by distillation from sodium wire after the characteristic blue colour of in situ generated sodium diphenylketyl had been found to persist. TMEDA and PMDTA were also distilled from sodium wire before use. The concentration of the butyllithium solution was determined by double titration method.[9] All experiments were carried out in Schlenk-flasks under dry nitrogen atmosphere. Dry ice - acetone baths were used to achieve -75°C during metallation reactions.

^{1}H-NMR spectra were recorded in deuteriochloroform solution at 250 MHz (BRUKER WM 250). Chemical shifts refer to tetramethylsilane (δ = 0 ppm). Assignments for the proton signals are given in all cases, the numbers in parentheses refer to the numbering of the carbon skeleton (Table 1). The signal of COOH group is absent because its place and form are strongly concentration dependent. IR spectra were recorded on an appliance type PERKIN ELMER 1600 with a Fourier Transformer. Data are given in cm^{-1}.

Preparation of 1-(fluorophenyl)pyrroles:

Compounds **2**, **3** and **4** were prepared from the corresponding fluoroanilines and *cis,trans*-2,5-dimethoxytetrahydrofuran in glacial acetic acid according to the literature procedure[10].

1-(2-fluorophenyl)pyrrole (2) [11]: 78 %; bp 74-76 °C/0.4 mmHg. - ^{1}H-NMR: δ 7.38 (1H, ddd, J_{HH} 7.5, 2.1, J_{HF} 7.5, H(6)), 7.2 (3H, m, H(3+4+5)), 7.02 (2H, sym.m, H(α+α`)), 6.34 (2H, t like m, $J_{HH}$ 2.3, H($\beta$+$\beta$`)).

1-(3-fluorophenyl)pyrrole (3)[12]: 67 %; bp 108-110 °C/13 mmHg. - ^{1}H-NMR: δ 7.40 (1H, dt, J_{HH} 8.2, J_{HF} 6.3, H(5)), 7.20 (2H, ddd, J_{HH} 8.2, 2.0, 1.0, H(6)), 7.13 (1H, dt, J_{HH} 2.1, J_{HF} 10.1, H(2)), 7.09 (2H, t like m, J_{HH} 2.2, H(α+α`)), 6.95 (1H, dddd, $J_{HH}$ 8.2, 2.1, 1.0, $J_{HF}$ 8.4, H(4)), 6.35 (2H, t like m, $J_{HH}$ 2.2, H($\beta$+$\beta$`)).

1-(4-fluorophenyl)pyrrole (4)[13]: 63 % (16 g); mp 50-52 °C. - ^{1}H-NMR: δ 7.3 (2H, m, H(2+6)), 7.10 (2H, dd, J_{HH} 8.2, J_{HF} 9.0, H(3+5)), 7.00 (2H, t like m, J_{HH} 2.2, H(α+α`)), 6.35 (2H, t like m, $J_{HH}$ 2.2, H($\beta$+$\beta$`)).

Metallation (General procedure):

1-(Fluorophenyl)-pyrrole (**2**, **3** or **4**) (10.0 mmol, 1.61 g) and an equivalent quantity of activating agent (TMEDA, 10.0 mmol, 1.16 g; or PMDTA, 10.0 mmol, 1.73 g) were dissolved in dry terahydrofuran (25.0 ml)

and cooled down to -75 °C. A 15 % hexane solution of butyllithium (11.0 mmol, 7.3 ml) was added dropwise to the solution. After 60 minutes stirring at -75 °C the electrophilic reagent (D_2O or benzophenone) was added or the mixture was poured into a dry ice - diethyl ether slurry. At + 20 °C 20 ml of distilled water was added, the phases were separated and the aqueous solution was washed with diethyl ether (3 x 15 ml). The collected organic solutions were dried over sodium sulfate and concentrated in vacuo. The residue contained the deuterated 1-(fluorophenyl)pyrroles (**8**, **9** or **10**) or the benzophenone adducts (**11**, **12** or **13**) as crude products. The pure carbinols were isolated by column chromathography (eluent: hexane/acetone = 8/1).

The carboxylic acid derivatives were isolated from the aqueous solution by acidification with 15 % citric acid solution. The products (**14** or **15**) precipitated from the solution in the form of an oil or crystals. In the case of oil the aqueous phase was extracted with dichloromethane (3x25ml). The collected dichloromethane solutions were dried over sodium sulfate and concentrated in vacuo. The residue was treated with hexane to obtain crystalline material. The products were recrystallised from hexane.

1-(2-Fluoro-[3-^{2}H]phenyl)pyrrole (8): 100 %; - ^{1}H-NMR: 7.38 (1H, ddd, J_{HH} 7.5, 2.1, J_{HF} 7.5, H(6)), 7.22 (1H, ddd, J_{HH} 7.5, 2.1, J_{HF} 7.5, H(4)), 7.18 (1H, t, J_{HH} 7.5, H(5)), 7.02 (2H, sym.m, H(α+α`)), 6.34 (2H, t like m, $J_{HH}$ 2.3, H(β+β`)).

1-(3-Fluoro-[2-^{2}H]phenyl)pyrrole (9): 94 %; - ^{1}H-NMR: δ 7.40 (1H, dt, J_{HH} 8.2, J_{HF} 6.3, H(5)), 7.19 (1H, d, J_{HH} 8.3, H(6)), 7.09 (2H, t like m, J_{HH} 2.2, H(α+α`)), 6.95 (1H, br. t, $J_{HH} \cong J_{HF}$ 8.4, H(4)), 6.35 (2H, t like m, $J_{HH}$ 2.2, H(β+β`)).

1-(4-Fluoro-[3-^{2}H]phenyl)pyrrole (10): 100 %; - ^{1}H-NMR: δ 7.3 (2H, m, H(2+6)), 7.10 (1H, dd, J_{HH} 8.2, J_{HF} 9.0, H(5)), 7.00 (2H, t like m, J_{HH} 2.2, H(α+α`)), 6.35 (2H, t like m, $J_{HH}$ 2.2, H(β+β`)).

1-(3-diphenylhydroxymethyl-2-fluorophenyl)pyrrole (11): 41 %; mp 99-101 °C (from hexane). - ^{1}H-NMR: δ 7.3 (10H, m, 8xH(Ph)+H(5+6)), 7.06 (2H, td, J_{HH} 8.0, 1.1, 2xH(Ph)), 6.95 (2H, sym.m, H(α+α`)), 6.74 (1H, td, $J_{HH}$ 7.6, 2.1, $J_{HF}$ 7.6, H(4)), 6.31 (2H, t like m, $J_{HH}$ 2.2, H(β+β`)), 3.48 (1H, d, J_{HH} 8.0, OH). - IR (KBr): 3603, 3474 (ν_{O-H}). - Analysis: calc. for $C_{23}H_{18}FNO$ (343.40) C 80.45, H 5.28, N 4.08; found C 80.31, H 5.40, N 4.13 %.

1-(2-diphenylhydroxymethyl-3-fluorophenyl)pyrrole (12): 52 %; mp 129-131 °C (from hexane). - ^{1}H-NMR: δ 7.3 (12H, m, 10xH(Ph)+H(5+6)), 7.03 (1H, ddd, J_{HH} 8.3, 1.6, J_{HF} 11.1, H(4)), 6.43 (2H, t like m, J_{HH} 2.1, H(α+α`)), 6.19 (2H, t like m, $J_{HH}$ 2.1, H(β+β`)), 2.75 (1H, s, OH). - IR (KBr): 3506 (ν_{O-H}). - Analysis: calc. for $C_{23}H_{18}FNO$ (343.40) C 80.45, H 5.28, N 4.08; found C 80.60, H 5.32, N 4.19 %.

1-(3-diphenylhydroxymethyl-4-fluorophenyl)pyrrole (13): 49 %; mp 133-136 °C (from hexane). - ^{1}H-NMR: δ 7.3 (11H, m, 10xH(Ph)+H(6)), 7.10 (1H, dd, J_{HH} 9.0, J_{HF} 11.2, H(5)), 6.93 (1H, dd, J_{HH} 2.5, J_{HF} 7.1, H(2)), 6.85 (2H, t like m, J_{HH} 2.2, H(α+α`)), 6.26 (2H, t like m, $J_{HH}$ 2.2, H(β+β`)), 3.45 (1H, d, J_{HH} 8.2, OH).

- IR (KBr): 3551 (ν_{O-H}). - Analysis: calc. for $C_{23}H_{18}FNO$ (343.40) C 80.45, H 5.28, N 4.08; found C 80.37, H 5.40, N 4.07 %.

1-(3-carboxy-2-fluorophenyl)pyrrole (14): 87 %; mp 204-206 °C. - ^{1}H-NMR: δ 7.79 (1H, ddd, J_{HH} 7.6, 1.6, J_{HF} 7.6, H(4)), 7.75 (1H, ddd, J_{HH} 7.1, 1.6, J_{HF} 7.1, H(6)), 7.35 (1H, td, J_{HH} 7.6, J_{HF} 1.8, H(5)), 7.15 (2H, sym. m, H(α+α')), 6.30 (2H, t like m, J_{HH} 2.0 H(β+β')). - IR (KBr): 3434 (ν_{O-H}), 1692 ($\nu_{C=O}$). - Analysis: calc. for $C_{11}H_8FNO_2$ (205.19) C 64.39, H 3.93, N 6.82; found C 64.42, H 4.03, N 6.91 %.

1-(3-carboxy-4-fluorophenyl)pyrrole (15): 87 %; mp 183-185 °C. - ^{1}H-NMR: δ 7.93 (1H, dd, J_{HH} 2.7, J_{HF} 6.0, H(2)), 7.8 (1H, m, H(6)), 7.42 (1H, dd, J_{HH} 9.0, J_{HF} 10.0, H(5)), 7.37 (2H, t like m, J_{HH} 2.1, H(α+α')), 6.28 (2H, t like m, J_{HH} 2.1, H(β+β')). - IR (KBr): 3439 (ν_{O-H}), 1693 ($\nu_{C=O}$). - Analysis: calc. for $C_{11}H_8FNO_2$ (205.19) C 64.39, H 3.93, N 6.82; found C 64.50, H 3.96, N 6.83 %.

Acknowledgement: This work was supported by the National Research Foundation of Hungary, Budapest (OTKA grant T-014397) and the Varga József Foundation, Hungary.

REFERENCES

1. Faigl, F.; Fogassy, K.; Thurner, A.; Tőke, L. *Tetrahedron* **1997**, *53*, 4883-4888.
2. Schlosser, M. Organoalkali Reagents. In *Organometallics in Synthesis: A Manual;* Schlosser, M., Editor; Wiley: Chichester, 1994; pp. 1-166.; Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.
3. Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett* **1991**, 731-732.
4. Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids,* Pergamon Press, London, 1976; pp 51-76 & 85-86.
5. Takagishi, S.; Schlosser, M. *Synlett* **1991**, 119.
6. HyperChem for Windows, Release 4.5, 1995, Hypercube Inc., 1115 NW 4th Street, Gainesville, Fl 32601, U.S.A.
7. Hall, G.E.; Piccolini, R.; Roberts, J.D. *J. Am. Chem. Soc.* **1955**, 77, 4540-4543.
8. Plenio, H.; Diodone, R. *Chem. Ber.* **1997**, 130, 963-968.
9. Wakefield, B.J. Organolithium Methods. In *Best Synthetic Methods*; Katritzky, A.R.; Meth-Cohn, O.; Rees, C.W., Ser. Eds.; Academic Press: London, 1988; pp. 18-19.
10. Gross, H. *Chem.Ber.* **1962**, *95*, 2270-2275.
11. Nacci, V.; Campiani, G.; Garofalo, A. *Synth. Commun.* **1991**, 20, 3019-3029.
12. Chakrabarti,J.K.; Tupper, D. *J. Heterocyclic Chem.* **1974**, 417-421.
13. Elguero, J.; Estopá, C.; Ilavsky, D. *J. Chem. Res. (M)* **1981**, 4237-4252.
14. Faigl, F.; Schlosser, M. *Tetrahedron* **1993**, *49*, 10271-10278.