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Effect of a Trifluoromethyl Group on Molecular Structure: Competitive Mono- and Dilithiation of 1-[(Trifluoromethyl)phenyl]pyrroles

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Abstract:
Depending on the conditions used during the lithiation and subsequent carboxylation of 1-[(trifluoromethyl)phenyl]pyrroles the mono- and the dicarboxylated derivatives were selectively prepared. The regioselective formation of the monocarboxylic acids could be rationalized in the light of the data collected from the literature. Explanation of the other phenomena, such as regioselective dilithiation and the strong effect of the trifluoromethyl group on the structure and aromaticity of the pyrrole ring in the *ortho* position, has been elucidated by the aid of molecular modelling and single crystal X-Ray measurements.

Keywords: Lithiation; regiocontrol; aromaticity; X-Ray crystal structures.

Introduction

Methyl and trifluoromethyl groups are frequently quoted in the literature as isosteric groups[1] and the latter is used as a building block for mimicking numerous biologically active compounds[2]. Despite the similarity in steric bulk the introduction of a trifluoromethyl group into organic molecules often induces significant changes in their chemical and physical nature, because of the high electronegativity and stability of this unit[3]. In lithiation reactions the trifluoromethyl group is reported as a moderate directing group[4]. However, only a limited amount of experimental data on its special effects have been published. For example, in (trifluoromethyl)benzene the proton mobility in the *ortho* position increases by more than five orders of magnitude compared to the unsubstituted benzene. The same values in the *meta* and *para* positions are around four orders of magnitude[5]. The simultaneous activation of all aromatic sites compromises the regioselective metalation of (trifluoromethyl)benzene as was demonstrated by Schlosser[6]. The situation became more complicated when two trifluoromethyl groups were connected to the benzene ring[7] or other directing groups like halogens were also present[8]. Fine

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tuning on the site selectivity of such reactions required detailed investigation of the reaction conditions and reagent compositions.

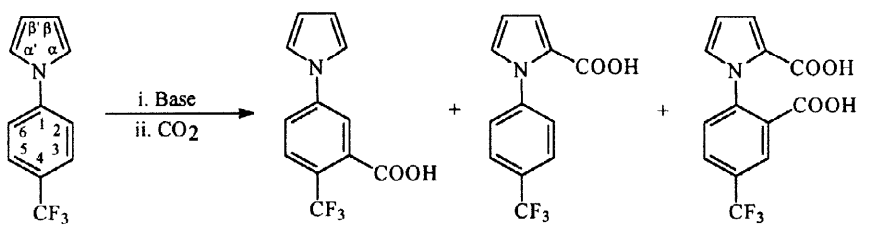
Regioselective lithiation of 1-[(trifluoromethyl)phenyl]pyrroles is a new challenge because of the previously demonstrated[9, 10] α directing power of the pyrrole nitrogen atom. To gain a better insight into the influence of the intriguing trifluoromethyl group, we have decided to collect and compare systematically experimental results, quantum chemical calculations and several sets of X-Ray diffraction data.

Results and Discussion

Lithiation reactions

Consecutive treatment of 1-[4-(trifluoromethyl)phenyl]pyrrole (**1**), 1-[3-(trifluoromethyl)-phenyl]pyrrole (**2**) or 1-[2-(trifluoromethyl)phenyl]pyrrole (**3**) with *n*-butyllithium (in the text butyllithium, BuLi) or tertiary amine activated butyllithium and dry ice provided different products or product mixtures depending on the reaction conditions used. In order to compare efficiency of the activating ligands, every lithiation reaction was interrupted after an hour. Only two exceptions were made (entries 5 and 8 in Table 1) when non-activated butyllithium was used for metalation. As a consequence of the limited reaction time, unreacted starting materials remained in the reaction mixtures. The water soluble lithium salts of the acidic products were easily separated from the residue of **1**, **2** and **3** during the workup procedures. The acidic products were collected from the aqueous solution by acidification. Composition of these crude products was determined by ^{1}H-NMR spectroscopy (these product ratios are listed in Table 1). However, the yields refer to the amount of the products measured after removing the valeric acid contamination by hexane. The recovered starting materials were also indentified by ^{1}H-NMR and accounted in the total material balances. On the basis of these material balances we can say that the amounts and the product distributions of the acidic products represent the efficiency and selectivity of the metalation reactions.

Compound **1** underwent regioselective monolithiation when it was treated with a stoichiometric amount of N,N,N',N'-tetramethylethylenediamine activated butyllithium (BuLi-TMEDA) in tetrahydrofuran, at -75 °C. After quenching with dry ice a 95:5 mixture of the two monocarboxylic acids **4** and **5** was isolated (Scheme 1, Table 1).



1 **4** **5** **6**

Scheme 1.

Lithiation and carboxylation of **1**. (The quantity of base and conditions are shown in Table 1).

The latter could easily be separated from the major product because the minor component precipitated from the ethanol solution after addition of hexane.

Dramatic changes were observed when the N,N,N',N'',N''-pentamethyldiethylenetriamine activated butyllithium (BuLi-PMDTA) was used as the lithiating agent. Beside the two monocarboxylic acids **4** and **5** dicarboxylic acid **6** was also formed; a 75:19:6 ratio of the three components was detected in the crude product. Furthermore, clean *α,2*-dimetalation occured, when **1** was treated with butyllithium or with BuLi-TMEDA reagent at 0 °C in diethyl ether solution. These reactions yielded the dicarboxylic acid (**6**) as the sole product independent of the amount of butyllithium used (Table 1, entries 3-5).

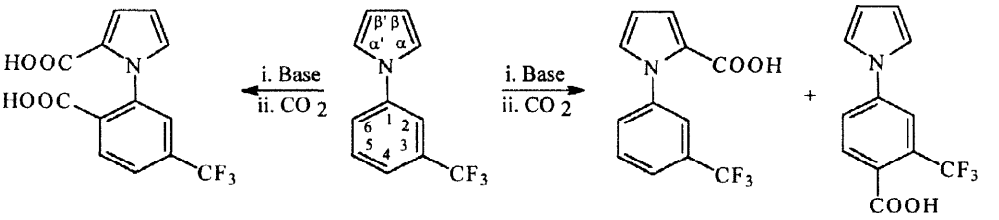
Table 1
Lithiation reactions of **1**, **2** and **3**; conditions and results

Entry	Compound	Solvent[a]	Base (equivalent)	Conditions	Products (ratio)	Yield[b]
1	**1**	THF	BuLi-TMEDA (1)	-75 °C, 1 h	**4** + **5** (95 : 5)	50 %
2	**1**	THF	BuLi-PMDTA (1)	-75 °C, 1 h	**4** + **5** + **6** (75 : 19 : 6)	30 %
3	**1**	Et_2O	BuLi-TMEDA (1)	0 °C, 1 h	**6**	28 %
4	**1**	Et_2O	BuLi-TMEDA (2)	0 °C, 1 h	**6**	79 %
5	**1**	Et_2O	BuLi (1)	0 °C, 2 h	**6**	33 %
6	**2**	THF	BuLi-TMEDA (1)	-75 °C, 1 h	**7** +**8** + **9** (25 : 50 : 25)	41 %
7	**2**	THF	BuLi-PMDTA (1)	-75 °C, 1 h	**7** + **8** (50 : 50)	63 %
8	**2**	Et_2O	BuLi (1)	0 °C, 2 h	**9**	39 %
9	**2**	Et_2O	Bu:Li-TMEDA (2)	0 °C, 1 h	**9**	57 %
10	**3**	THF	BuLi-PMDTA (1)	-75 °C, 1 h	**11** + **12** (50 : 50)	56 %
11	**3**	THF	LITMP-KOBu^t (1)	-75 °C, 1 h	**11** + **12** (22 : 78)	26 %
12	**3**	Et_2O	BuLi-TMEDA (1)	0 °C, 1 h	**11** + **12** (52 : 48)	65 %
13	**3**	Et_2O	BuLi-TMEDA (2)	0 °C, 1 h	**11** + **12** (48 : 52)	72 %

[a] THF: tetrahydrofuran; Et_2O: diethyl ether. [b] The yields are calculated on the basis of the amount of **1** or **2** or **3**.

Lithiation of **2** occured similar way (Scheme 2, Table 1, entries 6-10). Mainly the monocarboxylic acids were formed in tetrahydrofuran, at -75 °C. A 1:1 mixture of **7** and **8** was detected in the crude product by ^{1}H-NMR measurements when the BuLi-PMDTA reagent was used. On the other hand, lithiation with BuLi-TMEDA followed by dry ice quenching effected formation of **7**, **8** and the dicarboxylic acid **9** in a 1:2:1 ratio. The well separated ^{1}H-NMR signals of the different monocarboxylic acid isomers (**7** and **8**) helped us to determine the product distributions, but attempts to

separate them from each other failed. Dicarboxylic acid was the product regardless of the amount of the base when the reactions were carried out in diethyl ether at 0 °C. Thus, both butyllithium and BuLi-TMEDA effected *α',6* dilithiation providing **9**.

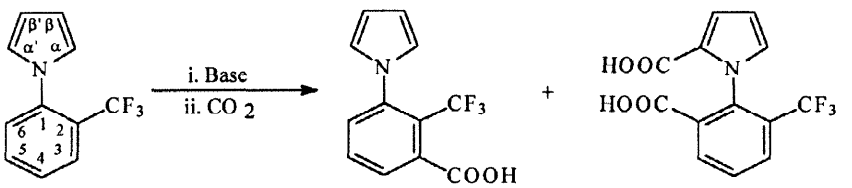


9 **2** **7** **8**

Scheme 2.

Lithiation and carboxylation of **2**. (The quantity of base and conditions are shown in Table 1).

A 1:1 mixture of 1-[3-carboxy-2-(trifluoromethyl)phenyl]pyrrole (**11**) and 1-[3-carboxy-2-(trifluoromethyl)phenyl]pyrrole-2-carboxylic acid (**12**) formed during lithiation and carboxylation of compound **3** in tetrahydrofuran at -75 °C (Scheme 3, Table 1). The relative amount of the dicarboxylic acid **12** increased to 78 % when potassium *tert.*-butoxide activated lithium 2,2,6,6-tetramethylpiperidide (LITMP-KOBu^t) was choosen as metalating agent.



3 **11** **12**

Scheme 3.

Lithiation and carboxylation of **3**. (The quantity of base and conditions are shown in Table 1).

The same competition was observed between CF_3 group directed monolithiation and the pyrrole governed *α',6* dilithiation in diethyl ether at 0 °C. Without activating agent, butyllithium was not able to deprotonate compound **3** but the BuLi-TMEDA reagent was strong enough to replace hydrogen atoms with lithium in the *α'* and *6* positions and a mixture of the two carboxylic acids (**11** and **12**) formed again. Fortunately, we could separate the two acids by treatment of the crude product with chloroform. The monocarboxylic acid proved to be soluble in this solvent while **12** remained in the solid phase. Both products were recrystallised from ethyl acetate.

The experimental results demonstrated that the presence of a trifluoromethyl group in the molecule causes special effects during metalation reactions. It is worthwhile to mention that in diethyl ether **1**, **2** and **3**, similarly to 1-phenylpyrrole[11, 12] (**10**), underwent *α',6*-dilithiation.

Molecular modelling

In order to rationalise the observed phenomena semiempirical quantum-chemical calculations were carried out. Conformational analysis of **1**, **2**, **3**, **11** and, for comparison, of **10** and 1-(2-

methylphenyl)pyrrole (**13**) was performed at the AM1 semiempirical level[13]. Due to the few rotational degrees of freedom their conformational space was explored by the straightforward grid search technique utilising the torsional increment of 10° for the systematic rotation of the C(2)-C(1)-N-C(α) torsion between 0° and 360°.

Table 2.
Results of the semiempirical quantum chemical calculations: charge distribution values of the carbon atoms, changes in the geometries and aromaticities of the pyrrole rings

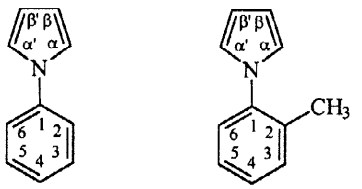
Charge distribution values	Compounds					
	10[a]	**1**	**2**	**3**	**11**	**13**
C(α)	-0.13	-0.13	-0.14	-0.07	-0.06	-0.13
C(α')	-0.13	-0.15	-0.13	-0.11	-0.11	-0.13
C(β)	-0.18	-0.18	-0.17	-0.19	-0.19	-0.18
C(β')	-0.18	-0.15	-0.18	-0.16	-0.16	-0.19
C(2)	-0.15	-0.19	-0.06	-0.34	-0.21	0.00
C(3)	-0.07	-0.03	-0.24	0.01	-0.16	-0.12
C(4)	-0.13	-0.29	-0.03	-0.12	-0.06	-0.10
C(5)	-0.06	0.02	-0.09	-0.05	-0.06	-0.09
C(6)	-0.16	-0.19	-0.09	-0.15	-0.11	-0.13
Formation heats (kcal/mol)	77.118	-78.837	-78.062	-74.183	-154.064	71.456
Angle of benzene ring to the C(α)-C(β)-C(α') plane	27°	23°	26°	56°	61°	43°
Deviation of N-C(1) bond to the C(α)-C(β)-C(α') plane	0.1°	0.1°	0.1°	9.2°	10.9°	2.3°
N atom position above the C(1)-C(α)-C(α') plane	0.0 Å	0.0 Å	0.0 Å	0.11 Å	0.13 Å	0.0 Å
Bird's aromaticity index of the pyrrole	60.3	57.9	58.9	57.7	56.7	61.1

[a]The ^{13}C-NMR peaks of **10** in $CDCl_3$: δ 140.68, 129.43,125.49, 120.41, 119.20, 110.34 [14].

Electrostatically fitted (ESP) atomic charges were calculated on structures corresponding the global minima. Only charges on carbon atoms were considered (Table 2) because these data are more sensitive to the structural and electronic changes than that of the hydrogen atoms. Calibration of our calculation method was easily made by comparison of the order of the ^{13}C chemical shift values[14] of **10** with the charge distribution order since calculated ESP charges correlate well with ^{13}C-NMR chemical shifts[15]. According to the strong electron withdrawing effect of the trifluoromethyl group, the neighbouring *ortho* carbons have the smallest electron densities in the basic forms of **1**, **2** and **3**, respectively (Table 2). Thus, proton abstraction should occur from these positions most readily when a strong base attacks the molecules.

We characterised the most stable conformers of **1**, **2** and **3** by their formation heats and also the torsion angles of the phenyl and the pyrrole rings (Table 2). The C(α)-C(β)-C(α') triangle was used for

definition of the plane of the heterocyclic ring while the phenyl moiety was considered as a planar ring. The results are summarised in Table 2. While the pyrrole ring turns away from the phenyl ring by 27° in the parent compound (**10**), the same angle is more than twice the size in the case of the *ortho* trifluoromethyl derivatives **3** (56°) and **11** (61°) but 43° in the case of **13**. Furthermore, the C(1)-N bond is not situated in the same plane as the C(α)-C(β)-C(α') triangle in the pyrrole ring, deviation angles being 9.2°, 10.9° and 2.3° in **3**, **11** and **13**, respectively.



10 **13**

The calculations showed that the geometry of the nitrogen bonds is also perturbed in these molecules. The nitrogen atom emerges from the C(1)-C(α)-C(α') plane by 0.11 Å (**3**) and 0.13 Å (**11**) but the same value is only 0.03 Å in the case of **13** and practically zero in **1** and **2**. The out-of-plane bending observed at the pyrrole nitrogen effects significant degradation of the aromaticity (see the *Bird's index* [16] values in Table 2). Steric bulkiness alone can not explain these effects of the *ortho* trifluoromethyl group because the "isosteric" methyl group (in **13**) does not significantly influence the planarity of the pyrrole ring or the other, above mentioned properties of the molecule. We propose that a strong electronic repulsion effect between the π electrons of the ring and the electron-rich CF_3 group has also to be taken into consideration.

This unprecedented effect of the *ortho* trifluoromethyl group on the pyrrole aromaticity which we have found during the analysis of our computation results turned our attention to the behaviour of the 1-[2-(trifluoromethyl)phenyl]pyrrole derivatives. We wished to find experimental evidence of these structure deformations. Since compound **3** is liquid at ambient temperature we prepared compounds **11** and **12** in pure crystalline form for X-Ray diffraction analysis.

Single Crystal X-Ray Diffraction Measurements

Continuous numbering of the atoms has been used during elucidation of the X-Ray structures. The numbering schemes are shown in Figures 1 and 3, respectively.

The monocarboxylic acid **11** forms orthorhombic crystals having two conformationally independent molecules (**11A** and **11B** in Figure 1) in the asymmetric unit which are connected to each other with strong hydrogen bonds (Table 3). These bidentate carboxylic acid dimers form layers parallel with the *ac* plane of the crystal, with their phenyl rings perpendicular to the layers. The main packing interactions in the layers are the edge-to-face π-π interactions of the phenyl and the pyrrole moieties, while those between the layers are the hydrophobic interactions between the trifluoromethyl and phenyl groups (Figure 2).

On the basis of the atomic co-ordinates determined from the single crystal X-Ray measurements we calculated the least squares planes of the phenyl and the pyrrole rings and their interplanar angle. These

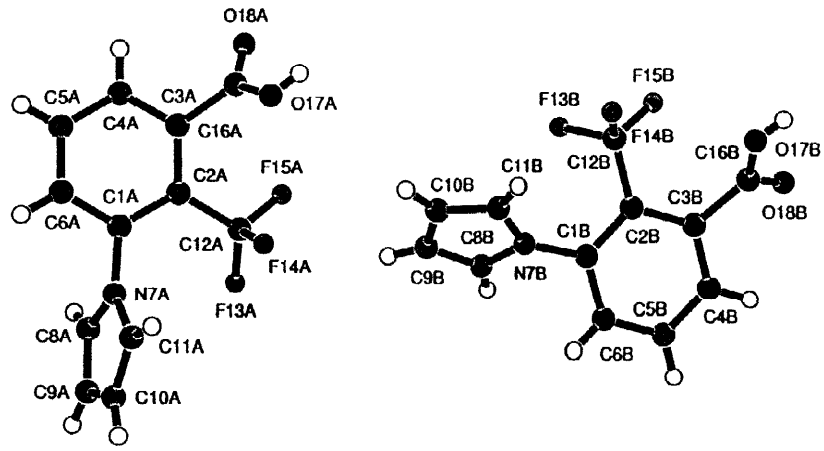


Figure 1.
Structure of **11A** and **11B** in the single crystal

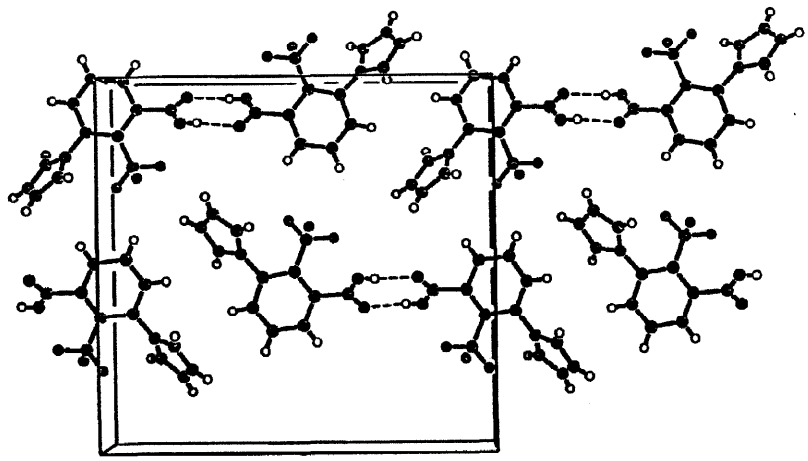


Figure 2.
Packing of **11A** and **11B** in their crystal. The view is along the *b* axis with the *a* axis vertical and the *c* axis horizontal

angles in the two conformers are 61.97(±0.29)° and 50.69(±0.28)° in **11A** and **11B**, respectively and they are in accordance with that calculated by quantum-chemical methods (61.4°, Table 2). The measured deviation of the nitrogen atom position from the C(1)-C(α)-C(α') plane is 0.0337 Å in **11A** and 0.0078 Å in **11B**. This value of the **11A** conformer is significantly larger than the experimental error. In the same time the experimentally determined deviation of the C(α)-C(β)-C(α') or C(α)-C(β')-C(α') planes and the N-C(1) bond are 1.3° and 0.95° in **11A** while 3.7° and 4.0° in **11B**, respectively. These values show again the deformation of the pyrrole plane in accordance with the prediction. Furthermore, the *Bird's index* of the pyrrole ring in **11** recalculated from the experimental data is 55.3 which is smaller than the estimated value (56.7). These data have confirmed the results of our semiempirical quantum chemical calculations on the perturbation effect of the *ortho* trifluoromethyl group on the geometry and aromaticity of the pyrrole ring.

Single crystal diffraction measurements on the dicarboxylic acid **12** gave further evidence of the above mentioned intriguing effect. Compound **12** forms triclinic crystals in which two enantiomers connected with each other by strong hydrogen bonds (Table 3) build up a unit cell (Figure 3).

Table 3.
Hydrogen bonds in the crystals of **11** and **12**

D-H....A	Symmetry	d(D-H) (Å)	d(H...A) (Å)	d(D...A) (Å)	∠(D-H..A) (°)
in compound **11**					
O(17)-H(17)...O(36)	[x-½, -y+½, -z+1]	0.750	1.908	2.655	174.02
O(35)-H(35)...O(18)	[x+½, -y+½, -z+1]	0.750	1.931	2.679	176.92
in compound **12**					
O(13)-H(13)...O(14)	[-x+1, -y+1, -z]	0.820	1.837	2.651	172.25
O(21)-H(21)...O(20)	[-x+2, -y,-z]	0.820	1.845	2.658	170.95

In the crystal the molecules form chains that are parallel to the diagonal between the ends of *a* and *b* edges of the unit cell. The chains are packed together by hydrophobic interactions between each pair of the three hydrophobic groups.

In our point of view, the most important question was again the angle between the phenyl ring and the heterocyclic ring and the plane deformation of the pyrrole. The torsion angle increased to 77.50 (±0.15)° which is due to the bulkiness of the two carboxylic groups in the *α'* and *6* positions. The deviation of the nitrogen atom from the C(1)-C(α)-C(α') plane is 0.0844(37) Å which is even larger than that was in the crystal of **11**.

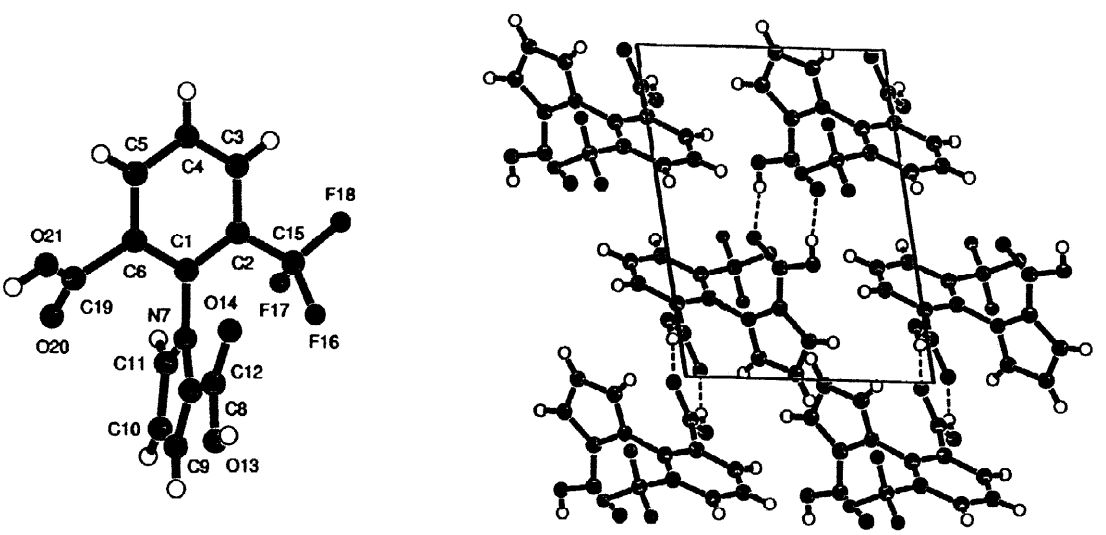


Figure 3.
Structure of **12** and packing of its dimers in the crystal. The view is along the *c* axis with the *b* axis vertical and the *a* axis horizontal

Conclusions

Comparison of the experimental results, the semiempirical quantumchemical calculations and the crystallographic data allow us to rationalize the behaviour of the trifluoromethyl group in lithiation reactions. We suppose that its strong electron-withdrawing effect is responsible for the activation of the neighbouring *ortho* positions effecting preferential formation of compounds **4**, **8** and **9** from **1**, **2** or **3** at low temperature in tetrahydrofuran, respectively.

Another mechanism has to compete with the above mentioned one when α' lithiation of the pyrrole ring or α',*6* dilithiations occur (formation of **5**, **6** or **7**, **9** or **12**, respectively). In these cases one should suppose that metalation at the pyrrole α' position has to proceed first which then directs the second lithiation step at C(6). The above mentioned bulkiness and high electron-density of the trifluoromethyl group in **1**, **2** and **3** can also account for this phenomenon;

a) Under the conditions leading to dilithiation (e.g. in diethyl ether which has smaller solvating ability than that of tetrahydrofuran) the alkalialkyl reagents (existing as bulky aggregates) are shifted toward the pyrrole moiety because of the dipole-dipole repulsion and steric interference between the reagent and the trifluoromethyl group.

b) At the same time, the heteroatom polarisation effect[17] which may be assisted with an interaction between the π+n electrons of the pyrrole and the lithium in the alkalialkyl reagent activate the pyrrole α' position for metal hydrogen exchange. The rate of α' lithiation may overcompensate the directing effect of the trifluoromethyl group and (within a mixed aggregate with butyllithium[17]) it can induce the second lithiation in the C(6) position of the benzene moiety yielding the dicarboxylic acids **6**, **9** or **12**, respectively. Similar dilithiation processes operated in the case of **10** as we demonstrated earlier by detailed kinetic and mechanistic investigations[12].

In the case of **3**, the special repulsive effect of the trifluoromethyl group on the neighbouring pyrrole ring was also recognised and confirmed by single crystal X-Ray measurements. We suppose that formation of the mixture of **11** and **12** in diethyl ether at 0 °C is due to the decreased pyrrole aromaticity which reduces the rate of α' lithiation and consequently the rate of dilithiation of **3** related to **1** and **2** (under the same conditions **1** and **2** served the dicarboxylic acids **6** and **9** as the sole products, respectively).

Among the prepared new carboxylic acids **12** has special importance because of its chirality. Separation of the enantiomers may furnish us with new chiral ligands.

Experimental Part

General:

All commercial starting materials were purchased from FLUKA AG and Merck-Schuchardt and were used without further purification. *n*-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[18]. 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.

NMR spectra were recorded in deuteriochloroform or hexadeuteriodimethylsufoxide solution at 250 MHz (BRUKER AC 250). Chemical shifts refer to tetramethylsilane (δ = 0 ppm), coupling constants are given in Hz. Assignments for the proton signals are given in all cases, the numbers in parentheses refer to the numbering of the carbon skeleton (Scemes 1, 2 and 3). The signal of the COOH group is

absent because its place and form are strongly concentration dependent. Infrared (IR) spectra were recorded on a PerkinElmer FT-IR spectrometer.

Semiempirical quantum-chemical calculations were carried out using the SPARTAN 3.1 program package[19]. The electrostatically fitted atomic charges were calculated by the Mertz-Kollman scheme as implemented in SPARTAN. Electrostatic potential maps were calculated as -10 kcal/mol contour plots.

Single crystal X-Ray diffraction measurements were accomplished by a RIGAKU R-axis IIC imaging plate detector for **11** and a RIGAKU AFC6S diffractometer for **12**. All data on the single crystsals are deposited at the Cambridge Crystallographic Data Centre; deposition numbers: CCDC 113927 (for **11**) and CCDC 113928 (for **12**).

Preparation of 1-[(trifluoromethyl)phenyl]pyrroles:

Compounds **1**, **2** and **3** were prepared from the corresponding (trifluoromethyl)anilines and *cis,trans*-2,5-dimethoxytetrahydrofuran in glacial acetic acid according to the literature procedure[20].

1-[(4-Trifluoromethyl)phenyl]pyrrole (1)[21]: 76%, mp 106-108 °C. ^{1}H-NMR ($CDCl_3$): δ 7.57 (2H, d, *J* 8.2, H(3+5)), 7.48 (2H, d, *J* 8.2, H(2+6)), 7.12 (2H, t, *J* 2.2, H(α+α')), 6.40 (2H, t, *J* 2.2, H(β+β')).

1-[(3-Trifluoromethyl)phenyl]pyrrole (2)[22]: 70%, bp 86-88°C/0.7 mmHg, (lit.[22] bp 106-110 °C/12 mmHg). ^{1}H-NMR ($CDCl_3$): δ 7.51 (1H, s, H(2)), 7.42 (3H, m, H(4+5+6)), 6.98 (2H, t, *J* 2.1, H(α+α')), 6.27 (2H, t, *J* 2.1, H(β+β')).

1-(2-Trifluoromethyl-phenyl)pyrrole (3)[23]: 84%, bp 64°C/0.3 mmHg. ^{1}H-NMR ($CDCl_3$): δ 7.79 (1H, dd, *J* 7.6, 1.0, H(3)), 7.61 (1H, td, *J* 7.6, 1.0, H(4)), 7.50 (1H, t, *J* 7.8, H(5)), 7.40 (1H, d, *J* 7.8, H(6)), 6.84 (2H, sym. m, H(α+α')), 6.33 (2H, t, *J* 2.1, H(β+β')).

Metalation (General procedure):

1-(Trifluorophenyl)-pyrrole (**1**, **2** or **3**) (10.0 mmol, 2.11 g) and, if it was necessary, the activating agent (TMEDA, 10.0 mmol, 1.16 g, or double this amount; or PMDTA, 10.0 mmol, 1.73 g) were dissolved in dry tetrahydrofuran or diethyl ether (25.0 ml) and cooled to -75 °C or 0 °C, respectively. A 15 % hexane solution of butyllithium (11.0 mmol, 7.3 ml or 22.0 mmol, 14.6 ml) was added dropwise to the solution. After 60 minutes stirring at the given temperature 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 (3x15 ml). The collected ether solutions were dried over sodium sulfate and concentrated in vacuo. The amount of the residue and its ^{1}H-NMR data corresponded to the unreacted starting material **1**, **2** or **3**, respectively. The carboxylic acid derivatives were isolated from the aqueous solution by acidification with 15 % citric acid solution. The products either oiled out or precipitated from the solution as crystals. The crystals were filtered, the oils were separated by extraction with dichloromethane (25ml). In boths cases the aqueous phases were extracted with dichloromethane (3x25 ml). The collected dichloromethane solutions were dried over sodium sulfate and concentrated in vacuo. The residues and the solids were used together for determination of the product distribution by ^{1}H-NMR spectroscopy. Then these crude products were treated with hexane to remove the valeric acid side product. In order to separate pure products from their mixtures the solid materials were treated with or recrystallised from an appropriate solvent according to their different

solubility. The type of solvents are given. In the cases of isolating regioisomeric mixtures the results of the microanalysis corresponded to the calculated values.

1-[3-Carboxy-4-(trifluoromethyl)phenyl]pyrrole (**4**, from ethanol-hexane mixture), mp 111-113 °C. IR(KBr): 3430(ν_{O-H}), 1703($\nu_{C=O}$) cm^{-1}. ^{1}H-NMR (in $CDCl_3$): δ 8.21 (1H, d, *J* 2.1, H(2)), 7.86 (1H, dd, *J* 8.2, 2.1 H(6)), 7.53 (1H, d, *J* 8.2, H(5)), 6.89 (2H, t, *J* 2.0 , H(α+α')), 6.39 (2H, t, *J* 2.0, H(β+β')). Analysis: calc. for $C_{12}H_8F_3NO_2$ (255.19) C 56.48%, H 3.16%, N 5.49%; found: C 56.46 %, H 3.07 %, N 5.52 %.

1-[4-(Trifluoromethyl)phenyl]pyrrole-2-carboxylic acid (**5**, from ethanol-hexane mixture), mp 182-184 °C. IR(KBr): 3448(ν_{O-H}), 1676 ($\nu_{C=O}$) cm^{-1}. ^{1}H-NMR (in $CDCl_3$): δ 7.69 (2H, d, *J* 8.4, H(2+6)), 7.44 (2H, d, *J* 8.4, H(5+3)), 7.24 (1H, t, *J* 2.2, H(α')), 6.99 (1H, t, *J* 2.2, H(β)), 6.35 (1H, dd, *J* 3.9, 2.2, H(β')). Analysis: calc. for $C_{12}H_8F_3NO_2$ (255.19) C 56.48%, H 3.16%, N 5.49%; found: C 56.46 %, H 3.07 %, N 5.52 %.

1-[2-Carboxy-4-(trifluoromethyl)phenyl]pyrrole-2-carboxylic acid (**6**, from ethanol-hexane mixture), mp 158-159°C. IR(KBr): 3446(ν_{O-H}), 1711, 1660($\nu_{C=O}$) cm^{-1}. ^{1}H-NMR (in DMSO-d_6): δ 8.13 (1H, d, *J* 8.2, H(3)), 7.99 (1H, d, *J* 8.2, 1.7, H(5)), 7.56 (1H, d, *J* 8.2, H(6)), 7.12 (1H, dd, *J* 2.6, 1.8, H(α')), 6.93 (1H, dd, *J* 3.7, 1.8, H(β)), 6.28 (1H, dd, *J* 3.7, 2.6, H(β')). Analysis: calc. for $C_{13}H_8F_3NO_4$ (299.2) C 52.19%, H 2.70%, N 4.68%; found: C 52.19 %, H 2.74%, N 4.71 %.

Mixture of **7** *and* **8** *(precipitated from hexane):*

1-[3-(Trifluoromethyl)phenyl]pyrrole-2-carboxylic acid (**7**) ^{1}H-NMR (in $CDCl_3$): δ 7.70 (2H, d, *J* 7.9, H(4+6)), 7.58 (1H, s, H(2)), 7.54 (1H, t, *J* 7.9, H(5)), 7.26 (1H, dd, *J* 4.1, 2.0 H(β)), 6.99 (1H, dd, *J* 2.5, 2.0, H(α)), 6.35 (1H, dd, *J* 4.1, 2.5 H(β')).

1-[4-Carboxy-3-(trifluoromethyl)phenyl]pyrrole (**8**) ^{1}H-NMR (in $CDCl_3$): δ 7.99 (1H, d, *J* 8.1, H(5)), 7.64 (1H, s, H(2)), 7.51 (1H, d, *J* 8.1 H(6)), 6.86 (2H, t, *J* 2.1, H(α+α')) 6.35 (2H, t, *J* 2.1 H(β+β')).

1-[2-Carboxy-5-(trifluoromethyl)phenyl]pyrrole-2-carboxylic acid (**9**, from ethanol-hexane mixture), mp 160-162°C. IR(KBr): 3448(ν_{O-H}), 1706, 1677($\nu_{C=O}$) cm^{-1}. ^{1}H-NMR (in DMSO-d_6): δ 8.05 (1H, d, *J* 8.1, H(5)), 7.90 (1H, dd, *J* 8.1,1.0, H(4)), 7.71 (1H, s, H(2)), 7.14 (1H, dd, *J* 2.9, 1.6, H(α)), 6.93 (1H, dd, *J* 3.7, 1.6, H(β')), 6.27 (1H, dd, *J* 3.7, 2.9, H(β)). Analysis: calc. for $C_{13}H_8F_3NO_4$ (299.2) C 52.19%, H 2.70%, N 4.68%; found: C 52.24%, H 2.76 %, N 4.74%.

1-[3-Carboxy-2-(trifluoromethyl)phenyl]pyrrole (**11**, from ethyl acetate), mp 144-146°C. IR(KBr): 3446(ν_{O-H}), 1718 ($\nu_{C=O}$) cm^{-1}. ^{1}H-NMR (in $CDCl_3$): δ 7.73 (1H, dd, *J* 8.0, 1.6, H(4)), 7.66 (1H, t, *J* 7.7, H(5)), 7.53 (1H, dd, *J* 7.5, 1.6, H(6)), 6.88 (2H, t, *J* 2.0, H(α+α')), 6.35 (2H, t, *J* 2.0, H(β+β')); (in DMSO-d_6): δ 7.82 (1H, t, *J* 7.7, H(5)), 7.72 (1H, d, *J* 7.6, H(4)), 7.59 (1H, d, *J* 7.6, H(6)), 6.96 (2H, t, *J* 2.0, H(α+α')), 6.24 (2H, t, *J* 2.0, H(β+β')). Analysis: calc. for $C_{12}H_8F_3NO_2$ (255.19) C 56.48%, H 3.14%,N 5.49%; found: C 56.55 %, H 3.07%, N 5.55%.

1-[6-Carboxy-2-(trifluoromethyl)phenyl]pyrrole-2-carboxylic acid (**12**, from ethyl acetate), mp 216-217°C. IR(KBr): 3446(ν_{O-H}), 1705, 1674($\nu_{C=O}$) cm^{-1}. ^{1}H-NMR (in DMSO-d_6): δ 8.09 (1H, d, *J* 7.7, H(5)), 8.01 (1H, d, *J* 7.7, H(3)), 7.75 (1H, t, *J* 7.7, H(4)), 7.01 (1H, sym.m, H(α)), 6.88 (1H,dd, *J*

3.8,1,8 , H(β')), 6.23 (1H, dd 3.8, 2.9, *J* 2.0, H(β)). Analysis: calc. for $C_{13}H_8F_3NO_4$ (299.20) C 52.19%, H 2.70%, N 4.68%; found: C 52.14%, H 2.72%, N 4.73 %.

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