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# Competition and Co-operation between *ortho* Directing Groups and Activating Agents: Regioselective Metallation of 1-(Methoxyphenyl)pyrroles

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***Abstract:*** The role of di- and tri-dentate tertiary amine type ligands was studied in regioselective lithiation reactions of 1-(methoxyphenyl)pyrroles with butyllithium (LIC). Clean α-metallation of the pyrrole ring occured when N,N,N',N',N''-pentamethyldiethylenetriamine (PMDTA) was used while the benzene ring was lithiated *ortho* position to the methoxy group in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA). © 1997 Elsevier Science Ltd.

Neighbouring group assisted metallation is one of the most effective methods of modern synthetic chemistry [1]. Relative directing power of the different substituents in aromatic systems have been determined by intra- and intermolecular competition reactions [2]. The outcome of such reactions is usually explained on the basis of electron withdrawal by the heteroatom containing substituents as in the case of anisole lithiation [3] by TMEDA (N,N,N',N'-tetramethylethylenediamine) activated butyllithium (LIC). Other researchers [4] drew their attention to the non-bonding electrons of heteroatoms which can act as electron donor ligands and coordinate lithium atoms. Systematic investigations have shown that the inductive and coordinative effects are operating simultaneously [5]. As a result numerous regioselective metallation processes of compounds bearing two (or more) *ortho* directing groups have been developed by changing reaction conditions and metallation reagents [6].

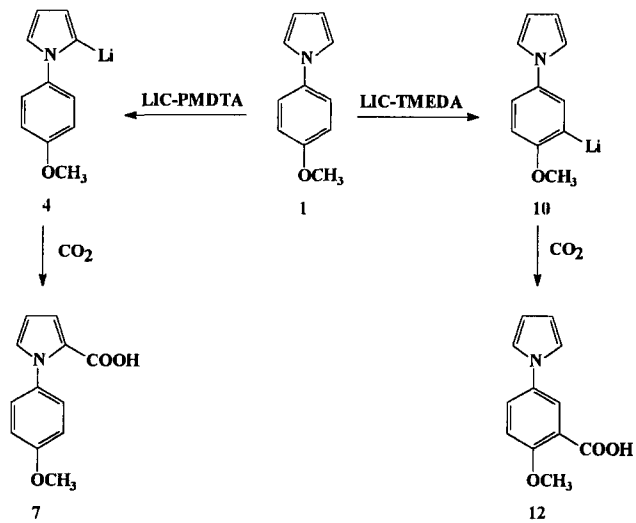
Much less has been published on the role of activating agents in such reactions. Only few examples have demonstrated the special behaviour of PMDTA (N,N,N',N',N''-pentamethyl-diethylenetriamine), the three-dentate ligand [5, 7]. These protocols contain different reaction conditions. In the case of bis(trifluoromethyl)-benzene [7] LICKOR (one to one mixture of butyllithium (LIC) and potassium *tert.*-butoxide (KOR)) and LIC-PMDTA reagents were compared while site selective lithiations of fluoroanisoles [5] were accomplished with simple butyllithium and with LIC-PMDTA. On the other hand, numerous regioselective metallation reactions have been realized in the presence of TMEDA [1, 6]. The ligands are usually taken into account as accelerators of the metallation rate due to their disaggregation effect on butyllithium oligomers [1, 3].

In reality, this is an oversimplification of the role of TMEDA or PMDTA. Nobody has published results of a systematic study on site selective metallation reactions where the effects of two- and three-dentate ligands were compared. In order to shed light on more details of the role of tertiary amine type additives in metallation we have carried out a series of lithiation reactions in the presence of TMEDA and PMDTA, respectively.

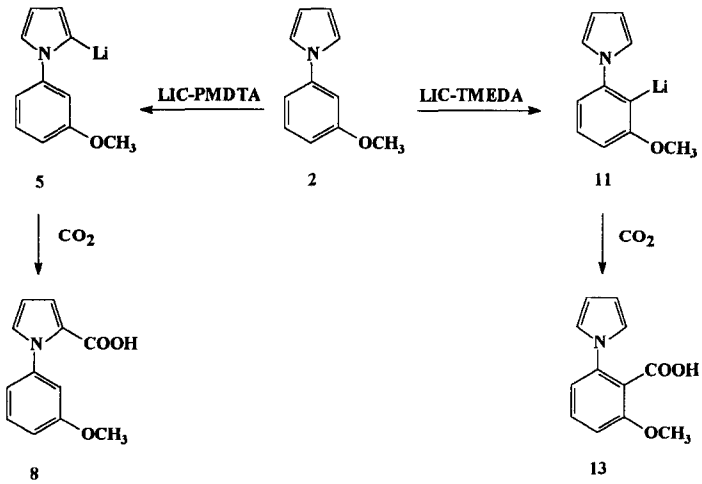
1-(Methoxyphenyl)pyrrole isomers (**1**, **2** and **3**) were chosen as model compounds because the methoxy group is known as a moderately strong *ortho* directing substituent with inductive electron withdrawal as well as electron donor properties. At the same time the nitrogen atom has an α-directing effect in the pyrrole ring.

Molecular mechanics calculations (HiperChem, AM1 programme) showed the α-hydrogen atoms to be the most acidic atoms in the three molecules (**1**, **2** and **3**) in the ground state. Consequently, the α-lithiated compounds (**4**, **5** and **6**) should be the thermodynamically favoured products in the reactions.
Lithiation reactions of **1**, **2** and **3** were accomplished under the same conditions (the solvents, concentrations, temperature and reaction time were kept constant) irrespective of the model compound or activating agent in order to compare the effects of the two ligands.

Consecutive treatment of **1**, **2** or **3** with LIC-PMDTA and dry ice resulted in formation of α-carboxylic acid derivatives (**7**, **8** or **9**), respectively. Compounds **7** and **8** were isolated as the only products while crude **9** contained about 5 % of the isomeric 1-(3-carboxy-2-methoxyphenyl)pyrrole.

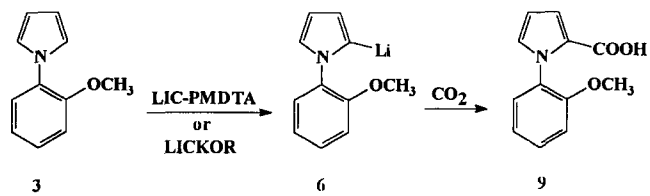



On the other hand, lithiation of **1** or **2** with LIC-TMEDA reagent and quenching the formed organometallic intermediates (**10** or **11**) with dry ice yielded the acids (**12** or **13**) in which the carboxylic groups situated *ortho* position to the methoxy groups. 1-(3-Methoxyphenyl)pyrrole (**2**) underwent hydrogen/lithium exchange at the sterically more hindered *ortho* position between methoxy and pyrryl groups (only 1-(2-carboxy-3-methoxyphenyl)pyrrole (**13**) was formed). The product did not contain even trace amount of the other *ortho* substituted compound (i.e. 1-(4-carboxy-3-methoxyphenyl)pyrrole) at low temperature [8]. The same high regioselectivity was observed when heavy water was used as electrophilic reagent instead of dry ice.




Metallation of compound **3** with LIC-TMEDA reagent did not gave the expected product. Starting material together with some polymeric byproducts were recovered after the usual workup procedure even when methyl iodide or heavy water were used as electrophiles instead of dry ice. Attempts to achieve *ortho* lithiation of **3** by LIC-TMEDA reagent at higher temperature (-50 to -25 $^{o}$C) or prolonged reaction time have also failed. We suppose that a stable mixed aggregate is formed between LIC-TMEDA reagent and **3** in which hydrogen/lithium exchange reaction can not take place in any position.

LICKOR superbase [1] reacted similarly to LIC-PMDTA. Metallation of **3** in tetrahydrofuran - hexane mixture at - 75 $^{o}$C followed by the reaction with dry ice provided 1-(2-methoxyphenyl)pyrrole-2-carboxylic acid (**9**) as the only product.




On the basis of the above mentioned experimental results we can compare the role of the two- and three-dentate ligands in the site selective metallation processes. We have shown recently [9], that 1-phenylpyrrole reacted smoothly with LIC-TMEDA reagent in ether solution at 0 $^{o}$C and the α,*o*-dilithiated compound forms within 10 minutes as kinetically controlled product even when the reagents were used in 1:1 molar ratio. Dilithiated species slowly change into the thermodynamically more stable α-lithio-1-phenylpyrrole by an intermolecular transmetallation process. At the same time α-lithio-1-phenylpyrrole was generated selectively with LIC-PMDTA reagent [10] or with LICKOR superbase [9].

Now, we have a methoxy group in the molecule and it completely changes the direction of metallation in the case of reaction with LIC-TMEDA while the same selective α-lithiation occurs with LIC-PMDTA reagent.

The phenomenon can not be explained simply by the presence of an "overriding base" as suggested by others in the case of metallation of anisole [3] since both of our metallating agents are strong enough bases to fulfil such requirement. If LIC-TMEDA could react in such a way we should get the same products independently from the structure of the activating agent (e.g. α-lithiation in all cases).

LIC-TMEDA complex exists as a dimer [11] in tetrahydrofuran solution because the lithium atom would be coordinatively unsaturated in the monomer. We propose that during addition of 1-(methoxyphenyl)pyrrole to the reagent fast coordinative bond formation has to take place between the methoxy oxygen atom and the lithium atom (if it were slow, α-deprotonation should occur). The *ortho*-hydrogen/lithium exchange reaction takes place within the substrate-butyllithium-TMEDA complex (similar to the process reported by Bauer [11] in other cases).

In the LIC-PMDTA reagent the nonbonding electron pairs of the three nitrogen atoms "saturate" the coordination sites of lithium (LIC-PMDTA can even exist in monomeric form in tetrahydrofuran [12]). Nitrogen atoms being more effective donors than the methoxy oxygen atom the latter has no chance to compete with the former for lithium coordination. Thus the reagent has the possibility to attack the most acidic α-position and PMDTA precludes the directed metallation.

## 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. Concentration of the buthyllithium solution was determined by double titration method [13].

All experiments were carried out in Schlenk-flasks under dry nitrogen atmosphere. Dry ice - acetone bath was used to achieve -75°C during metallation reactions.

$^1$H-NMR spectra were recorded in deuteriochloroform solution at 250 MHz (BRUKER WP 250). Chemical shifts refer to the signal of tetramethylsilane (δ = 0 ppm). 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 $cm^{-1}$.

Microanalyses were performed at Department of Chemical Technology, Technical University of Budapest.

***Preparation of 1-(methoxyphenyl)pyrroles:***

Compounds **1**, **2** and **3** were prepared from the corresponding methoxyanilines and *cis,trans*-2,5-dimethoxytetrahydrofuran in glacial acetic acid according to the literature procedures [14, 15]. The protocol was slightly modified in the case of compound **3** because of its high tendency of polymerisation under acidic conditions.

**1-(4-methoxyphenyl)pyrrole (1)** [14, 15]: 65 %; mp 111-113 °C (from methanol). - $^1$H-NMR: δ 7.31 (2H, ddd, *J* 9.0, 3.2, 2.5), 7.00 (2H, t like m, *J* 2.4), 6.94 (2H, ddd, *J* 9.0, 3.2, 2.5), 6.33 (2H, t like m, *J* 2.4), 3.82 (3H,s).
**1-(3-methoxyphenyl)pyrrole (2)** [15]: 62 %; bp 98-100 °C/0.4 mmHg. - $^1$H-NMR: δ 7.33 (1H, t, *J* 8.1), 7.10 (2H, t like m, *J* 2.3), 6.99 (1H, ddd, *J* 8.0, 2.0 1.0), 6.93 (1H, t, *J* 2.2), 6.80 (1H, ddd, *J* 8.0, 2.0, 1.0), 6.36 (2H, t like m, *J* 2.1), 3.84 (3H,s).
**1-(2-methoxyphenyl)pyrrole (3)** [15, 16]: After 15 minutes refluxing a mixture of 2-methoxyaniline (150 mmol, 18.6 g), *cis,trans*-2,5-dimethoxytetrahydrofuran (166 mmol, 21.9 g) and 20 mL of glacial acetic acid was cooled down to 25 °C and diluted with 150 mL of distilled water (instead of concentration by distillation). The aqueous solution was extracted with dichloromethane (3 x 50 mL). The organic phase was treated with sodium carbonate while the solution remained alkaline. The dried dichloromethane solution was concentrated and the dark oily residue was distilled under vacuum to yield pure **3**: 61.5 % (16 g); bp 88-94 °C/0.5 mmHg. - $^1$H-NMR: δ 7.2 (2H, m), 7.00 (4H, m), 6.30 (2H, t like m, *J* 4.0), 3.81 (3H,s).

***Metallation (General procedure):***
N-(Methoxyphenyl)-pyrrole (**1**, **2** or **3**) (10.0 mmol, 1.73 g) and an equivalent quantity of activating agent (TMEDA, 10.0 mmol, 1.16 g; or PMDTA, 10 mmol, 1.73 g) was 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 mixture was pured 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 was impure recovered starting material. (The amount of it was always in good accordance with the yield of the product.)
The aqueous solution was acidified with 10 % hydrochloric acid solution. The product precipitated from the solution in the form of oil or crystal. 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 get crystalline material. The products were recrystallised from hexane.
**1-(4-Methoxyphenyl)pyrrole-2-carboxylic acid (7)** [17]: 46 %; mp 150-152 °C. - $^1$H-NMR: δ 7.20 (2H, d like m, *J* 9.0), 7.12 (1H, dd, *J* 3.2, 1.9), 6.91 (1H, t like m, *J* 4.2), 6.90 (2H, d like m, *J* 9.0), 6.23 (1H, dd, *J* 3.2, 2.3), 3.81 (3H,s). - IR (KBr): 1662 ($\nu_{C=O}$), 3447 ($\nu_{O-H}$).
**1-(3-Carboxy-4-methoxyphenyl)pyrrole (12)** [18]:18 %; mp 146-148 °C. - $^1$H-NMR: δ 8.15 (1H, d, *J* 2.9), 7.52 (1H, dd, *J* 9.1, 2.9), 7.09 (1H, d, *J* 9.1), 7.03 (2H, t like m, *J* 2.2), 6.31 (2H, t like m, *J* 2.2), 4.09 (3H,s). IR (KBr): 1699, 1724 ($\nu_{C=O}$), 3437 ($\nu_{O-H}$).
**1-(2-Methoxyphenyl)pyrrole-2-carboxylic acid (9):** 30 %; mp 116-118 °C. - $^1$H-NMR: δ 7.34 (1H, dd, *J* 8.0, 1.8), 7.22 (1H, dd, *J* 8.0, 1.8), 7.13 (1H, dd, *J* 3.8,1.8), 6.98 (2H, t like m, *J* 7.5), 6.85 (1H, dd, *J* 2.5, 1.8), 6.29 (1H, dd, *J* 3.8, 2.5), 3.83 (3H,s). - IR (KBr): 1662 ($\nu_{C=O}$), 3446 ($\nu_{O-H}$).
Analysis: calc. for $C_{12}H_{11}NO_3$ (217.09) C 66.33, H 5.11, N 6.45; found C 66.09, H 5.21, N 6.42 %.
**1-(3-Methoxyphenyl)pyrrole-2-carboxylic acid (8):** 68 %; mp 137-138 °C. - $^1$H-NMR: δ 7.28 (1H, t, *J* 8.0), 7.18 (1H, dd, *J* 3.9, 1.8), 6.96 (1H, t like m, *J* 2.2), 6.89 (2H, sym. m), 6.83 (1H, t, *J* 2.1), 6.27 (1H, dd, *J* 3.9, 2.7), 3.81 (3H,s). - IR (KBr): 1667 ($\nu_{C=O}$), 3426 ($\nu_{O-H}$).
Analysis: calc. for $C_{12}H_{11}NO_3$ (217.09) C 66.33, H 5.11, N 6.45; found C 66.76, H 5.21, N 6.57 %.

**1-(2-Carboxy-3-methoxyphenyl)pyrrole (13):** 68 %; mp 117-119 °C. - $^1$H-NMR: δ 7.38 (1H, t, *J* 7.8), 6.93 (1H, dd, *J* 7.8, 1.0), 6.90 (3H, m), 6.29 (2H, t like m, *J* 2.0), 3.88 (3H,s). - IR (KBr): 1702 ($\nu_{C=O}$), 3433 ($\nu_{O-H}$).
Analysis: calc. for $C_{12}H_{11}NO_3$ (217.09) C 66.33, H 5.11, N 6.45; found C 66.40, H 5.10, N 6.46 %.

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