SHORT PAPER

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Efficient methods for optional metalation of 1-(methylphenyl)pyrroles in α or benzylic positions

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Novel, selective metalation methods have been described for optional functionalisation of 1-(methylphenyl)pyrroles in α or benzylic positions and an efficient way for dilithiation of the model compounds has also been reported.

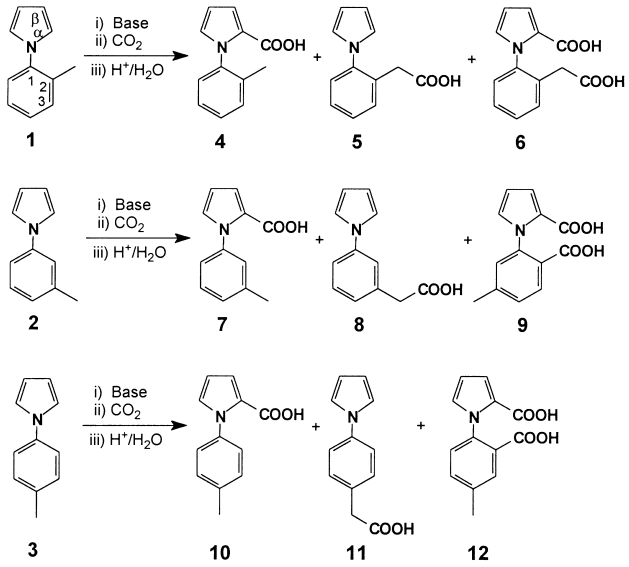
Keywords: regioselectivity, metalation, dimetalation, 1-(methylphenyl)pyrroles

Substituted 1-phenylpyrroles are building blocks for the synthesis of numerous compounds having antibiotic and fungicide,[1] cytostatic[2] effects or CNS activities.[3] In many cases, the standard preparative methods afford these products in low yields because of the sensitivity of the pyrrole ring to acidic conditions.[4] A convenient way for overcoming this problem would be the use of organometallic reactions in the synthesis.[5] However, few papers have dealt with the site selective metalations of substituted 1-phenylpyrroles. Selective α lithiation of 1-phenylpyrrole was described first by Shirley[6] and the α,2 dilithiation of the same molecule was published by Cheeseman.[7] Recently, we have reported on the regiosele ctive methods for the mono- and dilithiation of 1-phenylpyrroles having electron withdrawing substituents in the phenyl ring.[8] Data on the metalation of 1-(methylphenyl)pyrroles (**1**, **2** and **3**) are missing from the literature. Regioselective lithiation of 1-(methylphenyl)pyrrole isomers is a new challenge because the methyl group decreases the reactivity of the neighbouring positions of the phenyl ring for *ortho* metalation but the hydrogen/metal exchange in the benzylic position may compete with the α metalation of the pyrrole moiety. On the other hand, the pyrrole-1-yl group itself may work as an *ortho* directing substituent on the phenyl ring.

In order to find an efficient method for optional α *vs*. benzylic metalation as well as dimetalation of the model compounds systematic investigations have been carried out in our laboratory.

Consecutive treatment of **1**, **2** or **3** with activated organometallic or alkali amide type base and solid carbon dioxide provided mono- and dicarboxylic acids (**4**–**12**) as mixtures or sole products depending on the reaction conditions used. The reactions and the structures of the isolated products are shown in Scheme 1. The reagents, product ratios and yields are summarised in Table 1.

In THF at –75 °C, the position of the metal/hydrogen exchange can be influenced by the quality of the organometallic reagent. The alkali-alkyl type bases (BuLi-PMDTA and BuLi-*t*BuOK) attack selectively the α position of the pyrrole ring (Table 1, entries 1–3, 8–11), while the alkali amide type bases (LiTMP-*t*BuOK, LiDA-*t*BuOK) prefer the benzylic positions of **1**, **2** and **3** (Table entries 4–7). Perfect site selectivity could be achieved in the cases of the *meta* and the *para* methylated 1-phenylpyrroles (**2** and **3**). Moderate α selectivity



Scheme 1

in metalation of **1** can be rationalised if we take into account proximity of the α and the benzylic positions.

Clean α,2 dimetalation of **2** and **3** (products **9** and **12**) with BuLi–TMEDA in diethyl ether at 0 °C indicates that the first lithium/hydrogen exchange occurs probably in the α position and the second lithiation step undergoes within a mixed aggregate formed from the α-metalated species and another activated butyllithium. These observations are in accordance with our earlier findings[9] on the mechanism of dilithiation of unsubstituted 1-phenylpyrrole. In the case of **1**, acidity of the benzylic hydrogens and its proximities to the above mixed aggregate may offer energetically favored hydrogen/metal exchange instead of reaction with the *ortho* hydrogen on the other side of the phenyl ring.

The experimental results let us to conclude, that 1-(methylphenyl)pyrroles can be mono- or difunctionalised regioselectively by the use of tailor made metalation conditions and reagents.

The only exception is the mono metalation of **1** in α position: the monocarboxylic acid **4** formed as a minor product (Table 1, entry 1). However, **5** and **6** were obtained in 93 and 88 % excess (Table 1, entries 4 and 9) and the corresponding mono- or dicarboxylic acids were obtained in 95-100 % selectivities via consecutive mono- or dimetalation and carboxylation of **2** and **3**, respectively. These new methods can serve as convenient routes to multisubstituted 1-phenylpyrrole derivatives.

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Table 1 Metalation and consecutive carboxylation of 1-(methylphenyl)pyrroles

Entry	Base[a] (equivalent)	Conditions[b]	Starting material	Products (ratio)[c]	Yield[d]
1	BuLi–PMDTA (1)	THF, –75 °C, 1h	**1**	**4** + **5** (60:40)	39 %
2	BuLi–PMDTA (1)	THF, –75 °C, 1h	**2**	**7** + **8** (99:1)	73 %
3	BuLi–PMDTA (1)	THF, –75 °C, 1h	**3**	**10** (100:0)	70 %
4	LITMP–*t*BuOK (1)	THF, –75 °C, 1h	**1**	**4** + **5** (7:93)	53 %
5	LITMP–*t*BuOK (1)	THF, –75 °C, 1h	**2**	**7** + **8** (5:95)	69 %
6	LITMP–*t*BuOK (1)	THF, –75 °C, 1h	**3**	**10** + **11** (44:56)	54 %
7	LIDA–*t*BuOK (1)	THF, –75 °C, 3h	**3**	**11** (100:0)	45 %
8	BuLi–*t*BuOK (1)	THF, –75 °C, 1h	**1**	**4** + **5** + **6** (17:58:25)	78 %
9	BuLi–*t*BuOK (2)	THF, –75 °C, 1h	**1**	**4** + **5** + **6** (2:10:88)	52 %
10	BuLi–*t*BuOK (1)	THF, –75 °C, 1h	**2**	**7**+ **8** (91:9)	70 %
11	BuLi–*t*BuOK (1)	THF, –75 °C, 1h	**3**	**10**+ **12** (95:5)	63 %
12	BuLi–TMEDA (2)	Et_2O, 0 °C, 1h	**1**	**4** + **6** (30:70)	66 %
13	BuLi–TMEDA (2)	Et_2O, 0 °C, 1h	**2**	**9** (100:0)	86%
14	BuLi–TMEDA (2)	Et_2O, 0 °C, 1h	**3**	**12** (100:0)	85%
15	BuLi–PMDTA (2)	Et_2O, 0 °C, 1h	**1**	**4** + **5** + **6** (7:40:53)	85%
16	BuLi–PMDTA (2)	Et_2O, 0 °C, 1h	**2**	**8** + **9** (12:88)	85%
17	BuLi–PMDTA (2)	Et_2O, 0 °C, 1h	**3**	**10** + **12** (6:94)	79%

[a]BuLi: butyllithium; PMDTA: N,N,N′,N″,N″-pentamethylethylenetriamine; TMEDA: N,N,N′N′-tetramethylethylenediamine; LiTMP: lithium 2,2,6,6-tetramethylpiperidide; LiDA: lithium diisopropylamide; *t*BuOK: potassium *tert*-butoxide.
[b]THF: tetrahydrofuran; Et_2O: diethyl ether.
[c]The product ratios were determined from the ^{1}H NMR spectra of the crude products.
[d]The overall yield of the crude acidic products.

Experimental

The starting materials **1**[10], **2**[10] and **3**[11] were syntheised from the corresponding toluidine and *cis*,*trans*-2,5-dimethoxytetrahydrofuran according to the procedure of Gross.[11]

Metallation of 1-(methylphenyl)pyrroles (general procedure): 1-(Methylphenyl)pyrrole (**1**, **2** or **3**) (1 g, 6.36 mmol) was added at the desired temperature to a solution of the activating agent [TMEDA (6.36 mmol, 0.75 g or 12.7 mmol, 1.5 g), or PMDTA (6.36 mmol, 1.1 g or 12.7 mmol, 2.2 g), or potassium *tert*-butoxide (6.36 mmol, 0.7 g or 12.7 mmol, 1.4 g)] or TMP (7.0 mmol, 1.0 g) and potassium *tert*-butoxide (6.36 mmol, 0.7 g), or diisopropylamine (6.36 mmol, 0.6 g) and potassium *tert*-butoxide (6.36 mmol, 0.7 g) and a hexane solution of butyllitium (c: 1.3 mol/l, 7.0 mmol, 5.4 ml or 14 mmol, 10.8 ml) in dry THF (15 ml) or dry Et_2O (15 ml). After stirring for 1 h at the desired temperature the reaction mixture was quenched with dry ice. At 20 °C 20 ml of distilled water and Et_2O (20 ml) were added, the phases were separated and the aqueous solution was washed with Et_2O (3 × 15 ml), The aqueous solution was acidified with 15 % citric acid solution. The product precipitated as an oil or as crystals. In the case of an oil the aqueous phase was extracted with ethyl acetate (3 × 20 ml). The collected organic solutions were dried over sodium sulfate and concentrated *in vacuo*. The crystalline product was filtered, washed with water (2 × 5 ml) and dried. To obtain the pure compounds the crude products were recrystallised from hexane or ethyl acetate, respectively. Products **4** [m.p. 158–159°C (from hexane); lit.: 100–102°C (from water)[12], **5** [m.p. 77–79°C (from hexane); lit.: 78–79˚C (from water),[13a] 40˚C (from diethyl ether) [13b], **8** [m.p. 148–149°C (from hexane); lit.: 142–145°C (from water),[14], **10** [m.p. 166–167°C (from hexane); lit.: 182–183°C (from water), lit.: 182–184°C (from water)[15] and **11** [m.p. 180–181°C (from water), 180–182°C (from water),[16] are known from the literature. The structures were established by measuring the melting points, the IR and the ^{1}H NMR spectra. Yields given below in parenthesis refer to the efficiency of the recrystallisations of the new products.

Compound **6**: white crystals, m.p. 178–179 °C (29 % from ethyl acetate). IR (KBr) ν/cm^{-1}: 3446 (OH), 1690, 1652 (CO).^{1}H NMR (250 MHz, acetone-d_6), δ 3.26 (1H, d, *J*=16.3 Hz, HCH), 3.42 (1H, d, *J*=16.3 Hz, HCH), 6.29 (1H, m, $H_{\beta'}$), 6.91 (1H, t like m, *J* 1.9, H_β), 7.1 (1H, m, $H_{\alpha'}$), 7.2 (1H, m, Ph), 7.4 (3H, m, Ph). Anal. calc. for $C_{13}H_{11}NO_4$, C, 63.67; H, 4.52; N, 5.71. Found C, 63.50; H, 4.81; N, 5.75.

Compound **7**: white crystals , m.p. 148–149 °C (52 % from hexane). IR (KBr) ν/cm^{-1}: 3446 (OH), 1678 (CO). ^{1}H NMR (250 MHz, DMSO-d_6), δ 2.33 (3H, s, Me), 6.25 (1H, t like m, *J*=1.9 Hz, $H_{\beta'}$), 6.96 (1H, t like m, *J*=1.9 Hz, H_β), 7.1 (4H, m, $H_{\alpha'}$ + Ph), 7.3 (1H, m, Ph). Anal. calc. for $C_{12}H_{11}NO_2$ C, 71.63; H, 5.51; N, 6.96. Found C, 71.67; H, 5.89; N, 7.08.

Compound **9**: white crystals, m.p. 196–198°C (62 % from ethyl acetate). IR (KBr) ν/cm^{-1}: 3447 (OH), 1694 (CO). ^{1}H NMR (250 MHz, DMSO-d_6), δ 2.36 (3H, s, Me), 6.21 (1H, t like m *J*=2.1 Hz, $H_{\beta'}$), 6.9 (1H, m, H_β), 7.0 (1H, m, $H_{\alpha'}$), 7.12 (1H, s, Ph), 7.30 (1H, d, *J*=7.9 Hz, Ph), 7.79 (1H, d, *J*=7.9 Hz, Ph). Anal. calc. for $C_{13}H_{11}NO_4$ C, 63.67; H, 4.52; N, 5.71. Found C, 63.66; H, 4.81; N, 5.75.

Compound **12**: white crystals, m.p. 182–183 °C (56 % from ethyl acetate). IR (KBr) ν/cm^{-1}: 3447 (OH), 1694 (CO). ^{1}H NMR (250 MHz, DMSO-d_6), δ 2.38 (3H, s, Me), 6.2 (1H, m, $H_{\beta'}$), 6.9 (1H, m, H_β), 7.0 (1H, m, $H_{\alpha'}$), 7.17 (1H, d, *J*=7.9 Hz, Ph), 7.39 (1H, d, *J*=7.9 Hz, Ph), 7.68 (1H, s, Ph). Anal. calc. for $C_{13}H_{11}NO_4$ C, 63.67; H, 4.52; N, 5.71. Found C, 63.39; H, 4.51; N, 5.91.

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