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N-PHENYLPYRROLE : A KINETIC, THOUGH NOT THERMODYNAMIC PREFERENCE FOR DILITHIATION [1]

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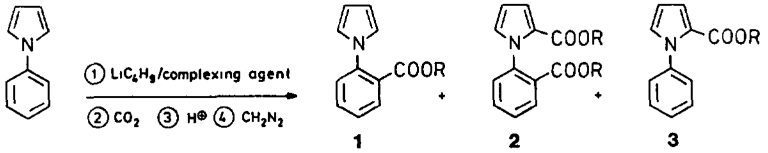
Summary : Under appropriate conditions the clean preparation of either the α-monolithiated or the *o*,α-dilithiated derivative of *N*-phenylpyrrole is possible. In the latter case, the first deprotonation occurs at the α-position. Dimetalation is kinetically but not thermodynamically favored.

While *N*-methylpyrrole [2], *N*-(trimethylsilyl)pyrrole [3] and *N*-(*tert*-butoxycarbonyl)pyrrole [4] efficiently undergo lithiation at the α-position, yields in the range of only 0 - 14% were obtained after metalation and subsequent carboxylation of 1-phenylpyrrole [2, 5]. We wondered what might hamper this reaction. Insufficient stability of the *N*-phenyl-2-pyrryllithium had to be precluded from the outset : neither X-ray [6] nor nmr [6] data revealed any special mode of decomposition for this intermediate. On the other hand, *o*,α-dimetalation of *N*-phenylpyrrole has been reported to occur smoothly when butyllithium activated by *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) is employed leading to doubly substituted derivatives albeit with quite variable yields [7]. Suspecting concomitant mono- and dimetalation to be at the origin of difficulties in generating *N*-phenyl-2-pyrryllithium, we decided to monitor the metalation of *N*-phenylpyrrole as a function of time.

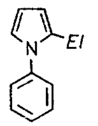
In a first run, *N*-phenylpyrrole was treated with a stoichiometric amount of ethereal butyllithium in the presence of TMEDA. At given intervals, samples were withdrawn and were quenched by reaction with dry ice. After neutralization, an *o*-monocarboxylic acid **1a**, an *o*,α-dicarboxylic acid **2a** and an α-monocarboxylic acid **3a** were obtained. Treatment with diazomethane converted these compounds into the volatile methyl esters **1b**, **2b** and **3b** which were submitted to gas chromatographic analysis using an internal reference ("standard") compound for quantitative evaluation.



a:	OR = OH
b.	OR = OCH$_3$

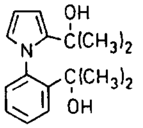
The composition of the product mixture turned out to be strongly time dependent. After 2 h, three products had formed with a total yield of 54% and in the ratio of 7 : 50 : 43, an *o*-monocarboxylate (**1**), an *o*,α-dicarboxylate (**2**) and an α-monocarboxylate (**3**). If the reaction was stopped already after 1 h, the yield was 32% and the product distribution was 0 : 81 : 19. After 32 h, 75% of derivatives **1**, **2** and **3** were detected in the ratio 1 : 4 : 95. The metalation reaction progressed much more slowly in hexane than in diethyl ether. The temperature had to be raised to 65 °C in order to achieve a useful turnover rate. Under these conditions, products **1**, **2** and **3** were formed after 0.2 h with a total yield of 41% and in the ratio 5 : 39 : 56 or after 3 h with 88% yield and a 0 : 2 : 98 ratio. When butyllithium activated with potassium *tert*-butoxide [8] was used, after 2.5 h 78% of esters **1**, **2** and **3** were obtained in the ratio of 0 : 4 : 96.

From a practical point of view, the use of the "superbasic" butyllithium/potassium *tert*-butoxide mixture is most convenient if α-monometalation of *N*-phenylpyrrole is the objective. After trapping with a variety of electrophiles, the derivatives **3a** (75%), **4** (74%), **5** (52%), **6** (73%), and **7** (81%) were isolated as pure compounds. On the other hand, pure *o*,α-dimetalate can be generated with almost quantitative yield, when simply *two* equivalents of butyllithium are employed in the presence of TMEDA (0.5 h in diethyl ether at 0 °C). Under such conditions, 80% of the diacid **2a** and 58% of the acetone bisadduct **8** were isolated.

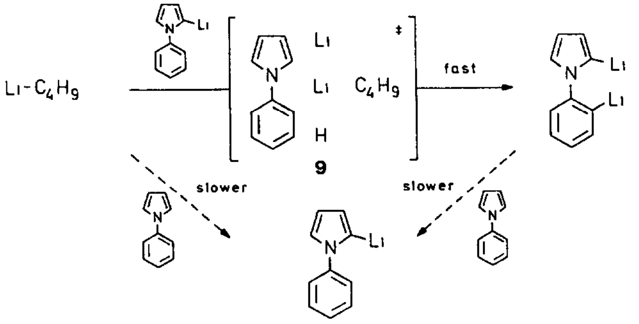


4: *El* = $\overset{\text{OH}}{\text{C}}(C_6H_5)_2$
5: *El* = CH_2CH_2OH
6: *El* = CH_3
7: *El* = SCH_3

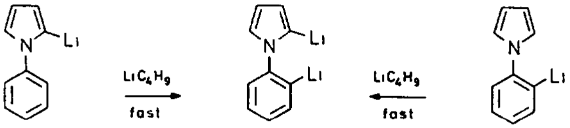
8



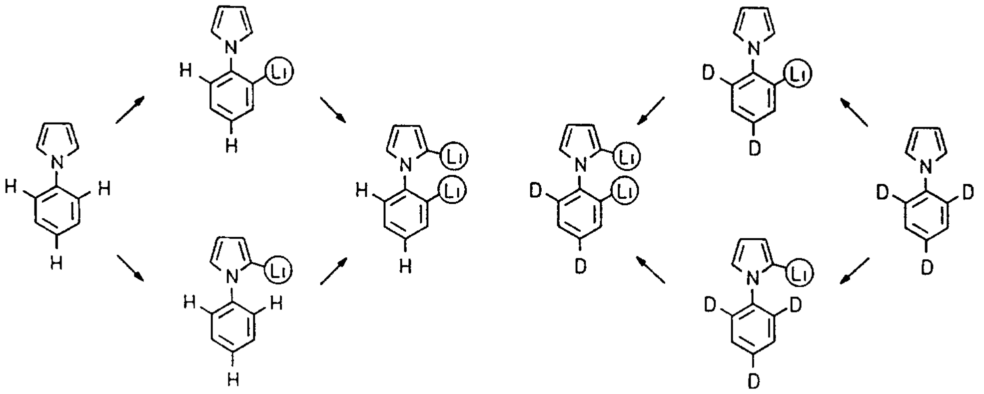
We wanted now to understand why dimetalation was so much preferred with amine activated organolithium reagents. Fresh *N*-phenylpyrrole was added to a moderately concentrated ethereal solution of the *o*,α-dilithio species. Slowly, in the course of more than a full day, the dimetalate was almost completely consumed (8% left after 32 h) in an exchange process producing mainly the α-monolithiated accompanied by a small amount of *o*-monolithiated species (85% and 6%, respectively). Obviously, the formation of the *o*,α-dimetalate (*via* transition state **9**) is only kinetically, not thermodynamically favored.



So far, we have tacitly assumed the *o*,α-dilithio species to be formed through an α-monolithio intermediate. This assumption is plausible but should by no means be taken for granted as long as the inversed order of metalation - first deprotonation at the *ortho* and only subsequently at the alpha position - has not been rigorously ruled out. Actually, not only *N*-phenyl-2-pyrryllithium but also 2-(*N*-pyrryl)phenyllithium rapidly reacts with butyllithium to produce the same *o*,α-dilithio species. This was checked with 2-(*N*-pyrryl)phenyllithium generated from *N*-(2-bromophenyl)pyrrole by halogen/metal exchange with butyllithium [7].



In order to clarify this ambiguity we have prepared *N*-[*o*,*o'*,*p*-$^{2}H_{3}$]phenylpyrrole. An equimolar mixture of the trideuterated substrate and the unlabelled parent compound was treated with a stoichiometrically unsufficient amount (1.0 mole-equivalent) of butyllithium. After carboxylation and esterification, unconsumed starting material was recovered and submitted to mass spectrometric analysis. The isotopomeric composition of 50 : 50 was found to be unchanged.



The absence of a kinetic isotope effect after labelling the crucial aromatic sites estabalishes unequivocal evidence in favor of initial proton abstraction at the alpha (rather than the *ortho*) position followed by an even faster second metalation, this time taking place at the *ortho* position. The relative rate of the second *o*-metalation step *vs.* the first α-metalation step appears to be concentration dependent (approximating perhaps a value of 2 at 1.0 M and of 5 at 0.15 M concentrations).

Already quite a while ago, double metalation was recognized to be widespread and intriguing phenomenon [9]. The rate enhancement of the second deprotonation step with respect to the first one was ascribed to mixed aggregate formation between the monometalated intermediate and unconsumed reagent. Thus, the second metal transfer occurring as an intracomplex process can be substantially accelerated. The present study of the *N*-

phenylpyrrole lithiation confirms this view. Although one may feel tempted, it would be premature to generalize the conclusions drawn from our findings and to postulate that most if not all double metalation reactions are kinetically, rather than thermodynamically, controlled. Further investigations are warranted.

EXPERIMENTAL PART

1. Generalities

Starting materials have been purchased from Fluka AG, Buchs, Aldrich-Chemie, Steinheim, or Merck-Schuchardt, Darmstadt, unless literature sources or details for the preparation are given. *Butyllithium* and *potassium* tert-*butoxide* were supplied by CheMetall, Frankfurt, and Hüls-Troisdorf. All commercial reagents were used without further purification.

Air and moisture sensitive compounds were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of 99.995% pure nitrogen.

Diethyl ether and *tetrahydrofuran* were obtained anhydrous by distillation from sodium wire after the characteristic blue color of in situ generated sodium diphenylketyl [10] had been found to persist.

Ethereal extracts were dried with sodium sulfate. Before distillation of compounds prone to radical polymerisation or sensitive to acids a spatula tip of *hydroquinone* or, respectively, *potassium carbonate* was added.

The temperature of dry ice-methanol baths is consistently indicated as -75°C, "room temperature" (22 - 26°C) as 25°C. If reduced pressure is not specified, *boiling ranges* were determined under ordinary atmospheric conditions (720 ± 25 mmHg).

Whenever reaction products were not isolated, their yields were determined by *gas chromatography* comparing their peak areas with that of an internal standard and correcting the ratios by response factors. The purity of distilled compounds was checked on at least two columns loaded with stationary phases of different polarity. Chromosorb G-AW of 80 - 100 and, respectively, 60 - 80 mesh particle size were chosen as the support for packed analytical or preparative columns (2 or 3 m long, 2 mm inner diameter and 3 or 6 m long, 1 cm inner diameter, respectively). Packed columns were made of glass, while quartz was chosen as the material for coated, SCOT-type capillary columns (≥ 10 m long). The type of the stationary phase used is abbreviated as SE-30 (silicone rubber) and Ap-L (Apiezon L hydrocarbon).

Nuclear magnetic resonance spectra of hydrogen nuclei were recorded at 250 MHz in deuterochloroform. Chemical shifts refer to the signal of tetramethylsilane (δ = 0 ppm). The shift numbers of silylated compounds were determined relataive to the residual solvent peak ($CHCl_3$: δ = 7.27 ppm). Coupling constants (J) are measured in Hz. Coupling patterns are described by abbreviations : s (singulet), d (doublet), t (triplet), q (quadruplet), td (triplet of a doublet) and m (multiplet).

Mass spectra were obtained at a 70 eV ionisation potential. Whenever no molecular peak was observed under standard conditions, chemical ionization ("c.i.") in ammonia atmosphere was applied. - *Elementary analyses* were performed in the laboratory of I. Beetz, D-96317 Kronach.

2. Metalation Reactions : Evolution of Product Ratios with Time

a) 1-Phenylpyrrole (1.43 g, 10.0 mmol), *N,N,N',N'*-tetramethylethylenediamine (1.50 mL, 1.16 g, 10.0 mmol) and a small amount of an "internal standard" for gas chromatograpic analysis (0.2 g of tetradecane) were added to a solution of butyllithium (10.0 mmol) in diethyl ether (40 mL) and hexane (6.7 mL) kept in an ice bath. Samples were withdrawn at given intervals and were poured on freshly crushed dry ice covered with diethyl ether. After acidification with 5% hydrochloric acid to pH 3, the organic phases were decanted and treated with ethereal diazomethane until the yellow color of the latter reagent persisted. The concentrations of 1-(2-methoxycarbonylphenyl)pyrrole [11] (**1b**), dimethyl 1-phenylpyrrole-2,2'-dicarboxylate [12] (**2b**) and methyl 1-phenylpyrrole-2-carboxylate (**3b**) were quantified by gas chromatography (2 m, 10% Apiezon-L, 180 °C [5 min] with 20 °C/min to 200 °C [30 min]) relative to the internal standard, calibration factors having been determined beforehand using pure authentic materials. The results are listed in Table 1.

Analogous runs were carried out in the presence of *N,N,N',N'*-tetramethylethylenediamine in hexane at 65 °C, in the presence of potassium *tert*-butoxide in 7 : 1 (v/v) mixture of tetrahydrofuran and hexane at -75 °C (using 0.22 M concentrations) and in the presence of potassium *tert*-butoxide in neat hexane at 25 °C (using 0.22 M concentrations). The data found are again compiled in Table 1.

Table 1. Metalation of 1-phenylpyrrole with butyllithium under various reaction conditions : yields of 1-(2-methoxycarbonylphenyl)pyrrole (**1**), dimethyl 1-phenylpyrrole-2,2'-dicarboxylate (**2**) and methyl 1-phenylpyrrole-2-carboxylate (**3**) as a function of the metalation time.

Complex. a)	*Sv* b)	temp.	t [h] c)	**1**	**2**	**3**
TMEDA	DEE/HEX	0 °C	1.0	-	26%	6%
			2.0	4%	27%	23%
			5.0	2%	22%	18%
			10.0	3%	13%	32%
			32.0	1%	3%	71%
TMEDA	HEX	65 °C	0.2	2%	16%	23%
			0.5	2%	11%	45%
			1.0	1%	5%	71%
			2.0	-	3%	79%
			3.0	-	2%	86%
$KOC(CH_3)_3$	THF	-75 °C	0.2	-	3%	67%
			0.5	-	2%	69%
			2.5	-	3%	75%
$KOC(CH_3)_3$	HEX	25 °C	0.2	-	12%	23%
			1.0	-	11%	29%
			5.0	-	11%	24%

a) Complexands : TMEDA = *N,N,N',N'*-tetramethylethylenediamine; b) Solvents (*Sv*) : THF = tetrahydrofuran, DEE = diethyl ether, HEX = hexane, DEE/HEX = 6 : 1 (v/v) mixture; c) t = metalation time before quenching with dry ice.

Two more runs were performed in neat ether at 0.15 M and 1.0 M concentrations. In the latter case the proportions of the α-monosubstituted product (**3**) increased rapidly at the expense of the *o*,α-disubstituted derivative (**2**). At low concentration the product composition changed much more slowly (Table 2).

Table 2. Metalation of 1-phenylpyrrole (1 eq.) with butyllithium (1 eq.) in the presence of *N,N,N',N'*-tetramethylethylenediamine (1 eq.) at various concentrations : total yields and, in parentheses, ratios of dimethyl 1-phenylpyrrole-2,2'-dicarboxylate (**2**) and methyl 1-phenylpyrrole-2-carboxylate (**3**) as a function of the metalation time.

Concentr. a)	*Sv* b)	temp.	t [h] c)	yield	(**2** : **3**)
0.15	DEE d)	0 °C	1.0	36%	(78 : 22)
			3.5	29%	(82 : 18)
			22.5	35%	(69 : 31)
			54.0	41%	(46 : 54)
1.0	DEE e)	0 °C	0.10	34%	(59 : 41)
			1.0	32%	(66 : 43)
			3.5	49%	(31 : 69)
			22.5	49%	(16 : 84)
			54.0	83%	(6 : 94)

a) Concentration in mol/L; b) Solvent (*Sv*) = diethyl ether; c) metalation time (t) before quenching with dry ice; d) Actually a 9 : 1 (v/v) mixture of diethyl ether and hexane; e) neat diethyl ether.

At 0 °C, an equimolar amount of 1-phenylpyrrole was added to a 1.19 M ethereal solution of the *o*,α-dimetalate prepared by treatment of 1-phenylpyrrole with two equivalents of butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine. Samples were withdrawn in regular intervals and consecutively treated with carbon dioxide, acid and diazomethane. The product compositions (see Table 3) were analyzed by gas chromatography as described above.

Table 3. Transmetalation between *o*,α-dilithio-1-phenylpyrrole and 1-phenylpyrrole in a 3 : 1 (v/v) mixture of diethyl ether and hexane at 0 °C and in the presence of *N,N,N',N'*-tetramethylethylenediamine : yields a) of 1-(2-methoxycarbonylphenyl)pyrrole (**1**), dimethyl 1-phenylpyrrole-2,2'-dicarboxylate (**2**) and methyl 1-phenylpyrrole-2-carboxylate (**3**) as a function of the reaction time.

t [h] b)	**1**	**2**	**3**	total yield c)
0.0	-	100%	-	100%
0.2	12%	65%	18%	86%
4.0	4%	68%	27%	99%
22.0	4%	26%	63%	93%
32.0	6%	8%	85%	99%

a) The calculation takes into account that each reaction between the dimetalate and unmetalated 1-phenylpyrrole produces *two* monometalated species; b) reaction time before quenching with dry ice; c) sum of the individual yields (**1b** + **2b** + **3b**).

3. Monosubstitution : Preparative Scale Reactions

Under vigorous stirring and at -75 °C, potassium *tert*-butoxide (2.8 g, 25 mmol) and butyllithium (25 mmol) in hexane (15 mL) were added to a solution of 1-phenylpyrrole (3.6 g, 25 mmol) in tetrahydrofuran (30 mL). After 90 min at -75 °C, the electrophilic reagent (in general 25 mmol, however, carbon dioxide being applied in excess) was added. The product was isolated by extraction and purified by crystallization.

1-Phenylpyrrole-2-carboxylic acid [2] **(3a)** : 75%; mp 182 - 184 °C (dec.; recryst. from ethyl acetate). - ^{1}H-NMR : δ 7.5 (3 H, m), 7.4 (2 H, m), 7.18 (1 H, dd, *J* 3.8, 1.8), 7.09 (1 H, dd, *J* 2.5, 1.8), 6.36 (1 H, dd, *J* 3.8, 2.5).

2-(Diphenylhydroxymethyl)-1-phenylpyrrole (4) : 74%; mp 108 - 109 °C (dec.; recryst. from hexane). - ^{1}H-NMR : 7.25 (10 H, s), δ 7.2 (3 H, m), 7.0 (2 H, m), 6.71 (1 H, dd, *J* 2.8, 2.0), 6.11 (1 H, dd, *J* 3.8, 2.9), 5.62 (1 H, dd, *J* 3.6, 1.8), 2.50 (1 H, s). - MS (c.i.) : 327 (7%, M^+ + 2), 326 (25%, M^+ + 1), 325 (71%, M^+), 309 (70%), 308 (61%), 248 (100%). - Analysis : calc. for $C_{23}H_{19}NO$ (325.41) C 84.89, H 5.88; found C 85.12, H 5.88%.

2-(2-Hydroxyethyl)-1-phenylpyrrole (5) : 52%; bp 122 - 124 °C/0.5 mmHg; n_D^{20} 1.5893. - ^{1}H-NMR : δ 7.4 (5 H, m), 6.78 (1 H, dd, *J* 2.9, 1.8), 6.23 (1 H, t, *J* 3.2), 6.14 (1 H, ddt, *J* 1.9, 1.7, 0.7), 3.68 (2 H, q, *J* 6.2), 2.83 (2 H, td, *J* 6.5, 0.6), 1.57 (1 H, t, *J* 6.0). - MS : 187 (21%, M^+), 156 (100%). - Analysis : calc. for $C_{12}H_{13}NO$ (187.24) C 76.98, H 7.00; found C 76.94, H 6.97%.

2-Methyl-1-phenylpyrrole [13] **(6)** : 73%; bp 136 - 138 °C/35 mmHg. - ^{1}H-NMR : δ 7.3 (5 H, m), 6.75 (1 H, dd, *J* 2.1, 1.8), 6.19 (1 H, t, *J* 3.0), 6.03 (1 H, s-like m), 2.19 (3 H, s).

2-Methylthio-1-phenylpyrrole (7) : 81%; bp 94 - 96 °C/0.35 mmHg; n_D^{20} 1.6130. - ^{1}H-NMR : δ 7.4 (5 H, m), 6.95 (1 H, dd, *J* 2.8, 1.8), 6.48 (1 H, dd, *J* 3.6, 1.7), 6.28 (1 H, t, *J* 3.3), 2.08 (3 H, s). - MS : 189 (80%, M^+), 174 (100%). - Analysis: calc. for $C_{11}H_{11}NS$ (189.27) C 69.81, H 5.86; found C 69.83, H 5.83%.

4. Disubstitution : Preparative Scale Reactions

1-Phenylpyrrole-2,2'-dicarboxylic acid (2a) : At 0 °C, butyllithium (55 mmol) in hexane (40 mL) and *N,N,N',N'*-tetramethylethylenediamine (8.3 mL, 6.4 g, 55 mmol) were added to a solution of 1-phenylpyrrole (3.6 g, 25 mmol) in diethyl ether (40 mL). After 30 min, the mixture was poured onto an excess of freshly crushed dry ice. Water (0.1 L) was added and the organic layer was discarded. The aqueous phase was washed with diethyl ether (2 × 25 mL) before being acidified with hydrochloric acid to pH 3. The precipitate was collected, dried and recrystallized from ethyl acetate; 80%; mp 194 - 196 °C (dec.). - ^{1}H-NMR (D_3COD) : δ 8.08 (1 H, dd, *J* 7.8, 1.8), 7.70 (1 H, td, *J* 7.5, 1.8), 7.59 (1 H, td, *J* 7.6, 1.4), 7.39 (1 H, dd, *J* 7.8, 1.5), 7.13 (1 H, dd, *J* 3.9, 1.6), 7.01 (1 H, dd, *J* 2.8, 1.8), 6.35 (1 H, dd, *J* 3.9, 2.8). - Analysis : calc. for $C_{12}H_9NO_4$ (231.21) C 62.34, H 3.92; found C 62.14, H 3.88%. - **Dimethyl 1-phenylpyrrole-2,2'-dicarboxylate (2b)** : By treatment of **2a** with diazomethane; 82%; mp 86 - 87 °C (dec.; recryst. from hexane). - ^{1}H-NMR : δ 8.06 (1 H, dd, *J* 7.5, 1.9), 7.61 (1 H, dt, *J* 7.7, 1.7), 7.51 (1 H, dt, *J* 7.7, 1.5), 7.36 (1 H, dd, *J* 7.5, 1.4), 7.10 (1 H, dd, *J* 3.9, 1.8), 6.89 (1 H, dd, *J* 2.5, 1.8), 6.33 (1 H, dd, *J* 3.9, 2.6), 3.69 (3 H, s), 3.68 (3 H, s). - MS (c.i.) : 259 (100%, M^+), 228 (10%), 200 (22%). - Analysis : calc. for $C_{14}H_{13}NO_4$ (259.26) C 64.86, H 5.05; found C 64.97, H 4.91%.

1-Phenylpyrrole-2,2'-bis[1-methyl-1-ethanol] (8) : With acetone (4.1 mL, 3.1 g, 52 mmol); 90% (crude); mp 33 - 38 °C (from hexane). - ^{1}H-NMR : δ 7.5 (1 H, m), 7.4 (2 H, m), 7.3 (1 H, m), 7.04 (1 H, dd, *J* 3.0, 1.9), 6.20 (1 H, dd, *J* 3.4, 3.0), 6.14 (1 H, dd, *J* 3.4, 1.9), 3.48 (1 H, s, broad), 2.26 (1 H, s, broad), 1.65 (3 H, s), 1.60 (3 H, s), 1.48 (3 H, s), 1.39 (3 H, s). - Crude diol **8** was submitted to silica gel mediated dehydration [14]; the resulting **4,4,6,6-tetramethyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine** was purified and fully characterized; 58% (relative to 1-phenylpyrrole); bp 123 - 125 °C/0.4 mmHg; mp 48 - 49 °C (by column chromatography). - ^{1}H-NMR : d 7.49 (1 H, d, broad, *J* 7.6), 7.4 (2 H, m), 7.3 (1 H, m), 6.92 (1 H, dd, *J* 2.8, 1.8), 6.25 (1 H, t, *J* 3.2), 6.18 (1 H, dd, *J* 3.5, 1.8), 1.61 (6 H, s, broad), 1.07 (3 H, s, broad), 0.86 (3 H, s, broad). - MS : 242 (4%, *M* +1), 241 (26%, M^+), 226 (100%), 184 (84%). - Analysis : calc. for $C_{16}H_{19}NO$ (241.33) C 79.63, H 7.93; found C 79.65, H 7.89%.

5. Isotope Effect Determination

At 0 °C, butyllithium (5.26 mmol) in hexane [15] (3.5 mL) was added to a solution of 1-phenylpyrrole (0.368 g, 2.57 mmol) and 1-(2,4,6-[$^2H_3$]phenyl)pyrrole (0.392 g, 2.68 mmol) in *N,N,N',N'*-tetramethylethylenediamine

(0.800 mL, 0.620 g, 5.34 mmol) and diethyl ether (21.5 mL). After 1 h at 0 °C, the mixture was poured on dry ice. Water (10 mL) was added. The aqueous and the ethereal phase were separated. The latter was submitted to analysis by means of a mass spectrometer coupled to a gas chromatograph. Beforehand artificial mixtures of the non-deuterated and trideuterated starting materials had been prepared and used to calibrate the *m/e* 146 *vs.* 143 response intensity. On this basis, the recovered 1-phenylpyrrole (55% of the original quantity) had an isotopomer distribution of 50 : 50 (± 5). Integration of the nmr spectrum led to the same result within 10% accuracy margins. - The alkaline layer was acidified and an aliquot was treated with diazomethane. As gas chromatography revealed, the solution contained the esters **1b**, **2b** and **3b** in the ratio of 2 : 33 : 65.

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