2-SUBSTITUTED IMIDAZOLES. 3.* METALLATION OF 1-METHYL-2-PHENYL- AND 1-METHYL-2-(FURYL-2)IMIDAZOLES

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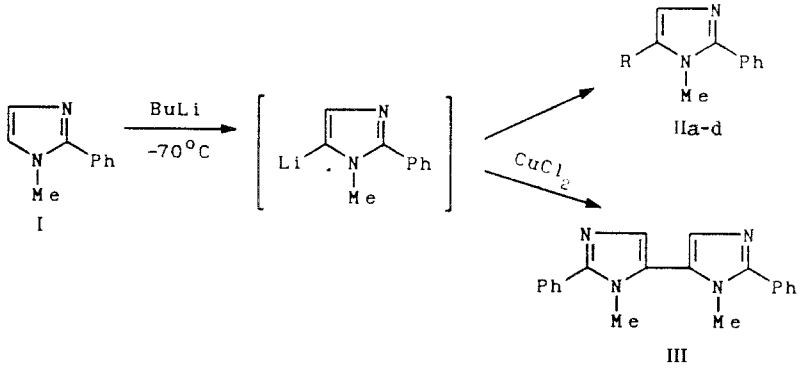
1-Methyl-2-phenylimidazole reacts with butyllithium to give 5-lithium substituted products. On the other hand, 1-methyl-2-(furyl-2)imidazole is metallated under the same conditions exclusively on the furan ring and primarily in the 3 position. The introduction of triethylamine into the reaction mixture, or replacement of butyllithium by lithium 2,2,6,6-tetramethylpiperidide leads to the formation of a lithium derivative substituted at the 5-position of the furan ring exclusively.

Metallation of imidazoles [2-4] and furans [5] is an important synthetic procedure in the chemistry of these heterocycles. Generally, 1-R-imidazoles are metallated at position 2 but when this is occupied the reaction leads to the formation of the 5-lithio-derivative. Metallation at the α-position is characteristic for furan although in recent years a series of derivatives of furan metallated mainly in the β-position have been isolated. This is peculiar to furans with substituents which, on account of specific coordination, facilitate a change in the direction of the reaction [6, 7].

In this connection it was of interest to examine the metallation of 1-methyl-2-(furyl-2)imidazole [8] in parallel with the metallation of 1-methyl-2-phenylimidazole (I).

Compound I, like 1-ethoxymethyl-2-phenylimidazole [9], is metallated by butyllithium in dry ether at —70°C. Treatment of the anion with DMF, dry ice, benzaldehyde, and benzonitrile gives the corresponding 1-methyl-5-R-phenylimidazoles (II) in 27-53% yield and reaction with anhydrous copper chloride gives the 5,5'-biimidazole III in 20% yield.



IIa R = CHO, b R = COOH, c R = $CHOHC_6H_5$, d R = COC_6H_5

On the other hand, 1-methyl-2-(furyl-2)imidazole (IV) is metallated exclusively on the furan ring. Thus the action of butyllithium on compound IV in 9:1 ether—hexane at —70°C followed by treatment with DMF results in the formation of a mixture of 1-methyl-2-(3-formylfuryl-2)imidazole (V) and 1-methyl-2-(5-formylfuryl-2)imidazole (VI) in 3:1 ratio with an overall yield of 48% (the experimental conditions have not been optimized). Isomers V and VI were separated by column chromatography on acidic alumina and their structure established from their PMR spectra. The PMR spectrum of the aldehyde V showed, in the aromatic region, doublets of the two protons of the furan ring (7.1 and 8.07 ppm) with $J_{4,5}$ = 1.75 Hz which is characteristic for a 2,3-substituted furan [10], together with a scarcely separated doublet ($J_{4,5}$ = 0.94 Hz) from the imidazole protons at 7.3 and 7.62 ppm (Table 1). The aldehyde VI was identical to a sample which we prepared earlier by the formylation of compound IV by the Vilsmeier complex [8].

*For Communication 2, see [1].

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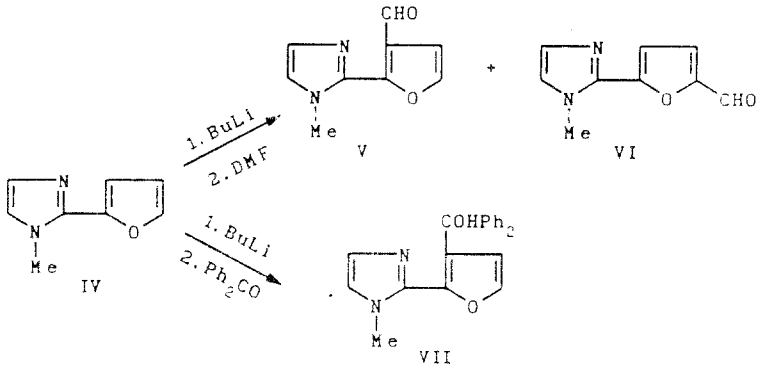
TABLE 1. PMR Spectra of Compounds V-VII and IX-XI (DMSO-D_6)

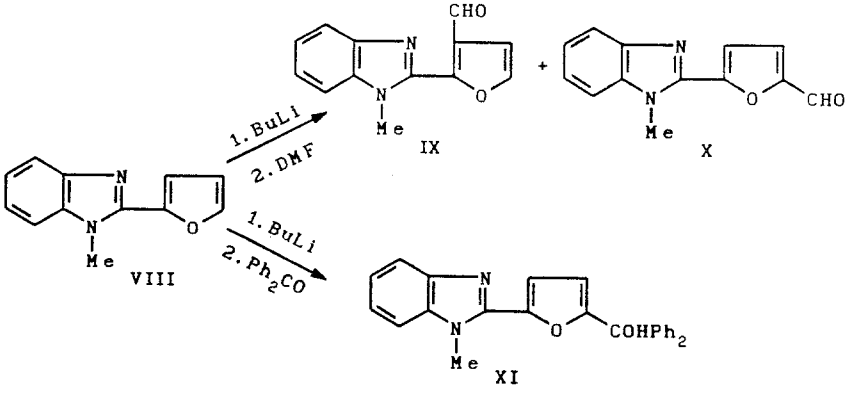
Compound	Chemical shift, δ, ppm							J, Hz		
	imidazole (benzimidazole) ring			furan ring			CHO [$(C_6H_5)_2$], s	4, 5	3', 4'	4', 5'
	N-CH_3, s	4-H, d (4,7-H)	5-H, d (5,6-H)	3'-H, d	4'-H, d	5'-H, d				
V	4,07	7,62	7,3	—	7,1	8,7	10,6	—*	—	1,75
VI	4,05	7,47	7,17	7,17	7,77	—	9,72	—*	3,8	—
VII	3,8	7,15	6,85	—	5,74	7,66	(7,18)	0,94	—	1,88
IX	4,3	(7,95 m)	(7,6 m)	—	7,25	8,3	10,85	—	—	1,75
X	4,27	(7,9 m)	(7,5 m)	7,65	7,85	—	9,93	—	3,8	—
XI	3,8	(7,57 m)	(7,3 m)	7,16	6,28	—	(7,3 s)	—	3,66	—

*$J_{4,5}$ could not be measured on account of inadequate resolution of the instrument.

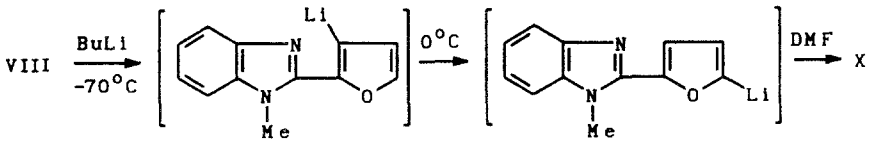


The direction of the metallation of compound IV is strongly influenced by the nature of the solvent. Thus, in toluene the aldehydes V and VI are formed in approximately equal quantities whereas in tetrahydrofuran compound V is formed with only traces of VI. The high regioselectivity of the metallation reaction in THF was confirmed by the preparation of 1-methyl-2-[3-(α-hydroxybenzhydryl)furyl-2]imidazole (VII), in which none of the isomeric 1-methyl-2-[5-(α-hydroxybenzhydryl)furyl-2]imidazole was detected.

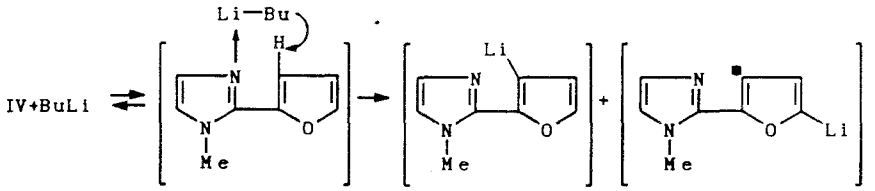
Metallation of 1-methyl-2-(furyl-2)benzimidazole (VIII) by butyllithium in ether with subsequent treatment with DMF yielded, as in the case of compound IV, 1-methyl-2-(3-formylfuryl-2)benzimidazole (IX) and the previously reported [11] 1-methyl-2-(5-formylfuryl-2)benzimidazole (X) in 3:1 ratio (from PMR results).



However, when DMF was replaced by benzophenone, unexpectedly only the 5-substituted furylbenzimidazole XI was isolated. Evidently, the reaction in this case is controlled largely by thermodynamic factors, i.e., in the course of the slower addition of benzophenone to the molecule of organometallic compound, the latter has time to rearrange to the 5-lithioderivative. This suggestion is confirmed by experiment. If the 3-lithioderivative which is formed at —70°C is warmed to 0°C and then treated with DMF, only the aldehyde X is formed.



We suggest that metallation of the furan ring in compounds IV and VIII at position 3 becomes possible as a result of the preferential coordination of butyllithium with the pyridine nitrogen of the imidazole ring. In the complex XII which is formed, the activation barrier to a β-metallation reaction must of course be somewhat lower than in the uncoordinated base IV.



XII

Indirect confirmation of such an explanation is provided by the fact that lithium 2,2,6,6-tetramethylpiperidide, which will obviously coordinate with compound IV only with difficulty, metallizes it exclusively at the 5-position of the furan ring. The formation of the aldehyde VI alone is evidence of this. Compound IV is similarly metallized by butyllithium in the presence of triethylamine.

EXPERIMENTAL

PMR spectra of compounds IIa-d, V, VI, IX, and X were run on a Tesla BS 487 (80 MHz) instrument and of compounds III, VII, and XI on an FX-90 (90 MHz). Monitoring of the course of the reactions and of the purity of the compounds was effected by TLC on Silufol UV-254 plates in methylene chloride.

The results of elemental analyses on C and H for compounds IIa-d, III, V, VII, and IX corresponded to the calculated.

Metallation of 1-Methyl-2-phenylimidazole. To a suspension of 1 g (6.33 mmoles) 1-methyl-2-phenylimidazole (I) [12] in 30 ml dry ether was added, dropwise with stirring in a current of nitrogen at —70 to —60°C, 4.5 ml (7.56 mmoles) 1.68 M butyllithium in hexane. The reaction mixture was stirred for 1 h at —70°C. The suspension of 5-lithio-1-methyl-2-phenylimidazole so formed was used in the preparation of compounds IIa-d.

1-Methyl-2-phenyl-5-aldehyde (IIa, $C_{11}H_{10}N_2O$). To a suspension of 5-lithio-1-methyl-2-phenylimidazole at —70°C was added, dropwise, 1.06 ml (13.7 mmoles) DMF in 4 ml dry ether and after 15 min cooling was discontinued. The reaction mixture was left to warm to room temperature and then poured into 150 ml water and the ether layer separated and dried over anhydrous $CaCl_2$. The ether was distilled off and the oily residue dissolved in 100 ml 5% CH_3COOH. The crystals which deposited were filtered off and recrystallized from 5:1 hexane—benzene. Mp 87-88°C, PMR spectrum (CF_3COOH) (δ, ppm): 3.8 (s, 3H, N—CH_3), 7.34 (s, 5H, arom.), 8.07 (s, 1H, 4-H), 9.6 (s, 1H, CHO). Yield 0.27 g (23%).

1-Methyl-2-phenylimidazole-5-carboxylic Acid (IIb, $C_{11}H_{10}N_2O_2$). A suspension of 5-lithio-1-methyl-2-phenylimidazole was poured onto 50 g dry ice. After evaporating off the CO_2 the lithium salt of the acid IIb was filtered off, dissolved in 5 ml water, and carefully neutralized with 1:1 hydrochloric acid to pH 6. The crystals which deposited were filtered off and recrystallized from water. Mp 209-210°C. PMR spectrum (CF_3COOH) (δ, ppm): 3.8 (s, 3H, N-CH_3), 7.35 (s, 5H, arom.), 7.95 (s, 1H, 4-H). Yield 0.68 g (53%).

1-Methyl-5-(α-hydroxybenzyl)-2-phenylimidazole (IIc, $C_{17}H_{16}N_2O$). To a suspension of 5-lithio-1-methyl-2-phenylimidazole was added, dropwise with stirring at —70°C, 1.25 ml (12.66 mmoles) freshly distilled benzaldehyde in 5 ml dry ether. The mixture was stirred 15 min at —70°C and then allowed to warm to room temperature. The reaction mixture was poured into 100 ml 5% CH_3COOH, the ether removed in a current of nitrogen, and the crystals which deposited filtered off and recrystallized from benzene. Mp 174-175°C. PMR spectrum [$(CD_3)_2CO$] (δ, ppm): 3.78 (s, 3H, N—CH_3), 6.03 (s, 1H, CHOH), 6.6 (s, 1H, 4-H), 7.55 (m, 10H, arom.). Yield 0.6 g (36%).

1-Methyl-5-benzoyl-2-phenylimidazole (IId, $C_{17}H_{14}N_2O$). To a suspension of 5-lithio-1-methyl-2-phenylimidazole was added, dropwise at —70°C, 0.72 ml (7 mmoles) benzonitrile in 5 ml dry ether. The mixture was warmed to room temperature, stirred 30 min, and poured into 150 ml water. The ether layer was separated and the water layer extracted with 2 × 50 ml methylene chloride and the combined extracts dried over Na_2SO_4 and evaporated at atmospheric pressure. The residue was stirred with 50 ml 5% CH_3COOH and the crystals which deposited were filtered off and recrystallized from 5:1 hexane—benzene. Mp 160-161°C. PMR spectrum (CF_3COOH) (δ, ppm): 3.84 (s, 3H, N—CH_3), 7.2 (m, 10H, arom.), 7.7 (s, 1H, 4-H). Yield 0.45 g (27%).

1,1′-Dimethyl-2,2′-diphenyl-5,5′-biimidazole (III, $C_{20}H_{18}N_4$). A solution of 0.79 g (5 mmoles) compound I in 30 ml dry THF was cooled to —74°C and, while stirring in a current of nitrogen, 3.3 ml (5.28 mmoles) 1.6 M butyllithium in pentane was added dropwise with stirring. The reaction mixture was stirred for 1 h at —74°C and a solution of 0.67 g (5 mmoles) $CuCl_2$ in 5 ml dry DMF added dropwise. This mixture was stirred 30 min at —70°C, warmed to room temperature, and poured into 50 ml 3% hydrochloric acid. The solution was evaporated in a water pump vacuum to a volume of 10 ml, cooled, and neutralized with concentrated ammonia solution to pH 9. The crystals which deposited were filtered off and crystallized from 3:2 toluene—heptane. Mp 218-219°C. PMR spectrum (DMSO—D_6) (δ, ppm): 3.62 (s, 6H, 2N-CH_3), 7.2 (s, 2H, 4-H, 4-H), 7.55 (m, 10H, arom.). Yield 0.16 g (20%).

1-Methyl-2-(3-formylfuryl-2)imidazole (V, $C_9H_8N_2O_2$). A. To a solution of 0.74 g (5 mmoles) compound IV in 30 ml dry ether was added, dropwise in a current of nitrogen at —72 to —68°C, 3 ml (5.04 mmoles) 1.68 M butyllithum in hexane. The reaction mixture was stirred 1 h at —70°C, treated with 0.38 ml (5 mmoles) DMF, warmed to room temperature, and poured into 50 ml 5% CH_3COOH. The mixture was neutralized with concentrated ammonia solution to pH 7, the ether layer separated, and the aqueous layer extracted with methylene chloride (30 ml). The combined extracts were dried over $CaCl_2$ and the solvent evaporated. The residue was chromatographed on a column (2.5 × 20 cm) of acidic Al_2O_3 with methylene chloride eluent. The eluent was evaporated and the residue recrystallized from hexane. Mp 142-143°C. Yield 0.32 g (36%).

B. Metallation of 0.74 g (5 mmoles) compound IV was carried out under conditions similar to those described above, except that THF was used as solvent. After treating the organometallic compound with 0.38 ml (5 mmoles) DMF, the reaction mixture was allowed to warm to room temperature and poured into 50 ml 5% CH_3COOH. The mixture was neutralized with concentrated ammonia and extracted with 3 × 30 ml methylene chloride. Isolation and purification were as in method **A**. Yield 0.49 g (56%).

1-Methyl-2-(5-formylfuryl-2)imidazole (VI). A. The chromatograph column from which compound V (method **A**) had been removed was washed down with 200 ml 9:1 methylene chloride—methanol. The solvent was evaporated and the residue recrystallized from hexane. Mp 107-108°C, agreeing with literature data [8]. Yield 0.11 g (12%).

B. To a solution of 0.7 g (5 mmoles) compound IV in 30 ml dry THF was added, with stirring at —70°C in a current of nitrogen, a separately prepared solution of lithium 2,2,6,6-tetramethylpiperidide made from 3 ml (5.04 mmoles) 1.68 M butyllithium in hexane and 0.77 g (5.5 mmoles) 2,2,6,6-tetramethylpiperidine at —30°C in nitrogen. The reaction mixture was stirred for 30 min at —70°C to —65°C and 0.38 ml (5 mmoles) DMF added dropwise. The imidazole VI was isolated in a similar way to compound V (method **B**), but chromatography was effected on neutral alumina. Yield 0.49 g (51%).

C. Metallation of 0.74 g (5 mmoles) compound IV was carried out under the conditions used for compound V (method **A**) in the presence of 1.4 ml (10 mmoles) freshly distilled triethylamine. After adding 0.38 ml (5 mmoles) DMF the product was isolated as for compound V (method **B**) but neutral alumina was used for chromatography. Yield 0.38 g (43%).

1-Methyl-2-[3-(α-hydroxybenzhydryl)furyl-2]imidazole (VII, $C_{21}H_{18}N_2O_2$). Compound IV [0.74 g (5 mmoles)] was metallated under the conditions used for compound V (method **B**). A solution of 0.91 g (5 mmoles) benzophenone in 10 ml dry THF was then added dropwise. The reaction mixture was warmed to room temperature, stirred for 30 min, and poured into 150 ml water. The crystals which deposited were filtered off, dried, and chromatographed on a column of the same dimensions as above, charged with 50 g neutral alumina using methylene chloride as eluent. The fraction with R_f 0.2-0.3 was separated, evaporated, and crystallized from octane. Mp 167-168°C. Yield 0.51 g (31%).

1-Methyl-2-(3-formylfuryl-2)benzimidazole (IX, $C_{13}H_{10}N_2O$) was prepared under the same conditions as compound V (method **A**) from 1 g (5.05 mmoles) compound VIII. The isomeric aldehydes were separated by column chromatography on acidic alumina. Mp 132-133°C (aqueous alcohol). Yield of aldehyde IX 0.47 g (41%).

1-Methyl-2-(5-formylfuryl-2)benzimidazole (X). A. The chromatograph column after removing compound IX was washed down with 200 ml of 9:1 methylene chloride—methanol. The eluent was evaporated and the residue recrystallized from aqueous alcohol. Mp 148-149°C. Yield 0.11 g (10%).

B. Compound VIII (1 g, 5.05 mmoles) was metallated under the same conditions as compound V (method **A**) but before treatment with DMF the reaction mixture was kept at 0°C for 15 min. Isolation and purification were carried out as for method **A** but neutral alumina was used for chromatography. Mp 148-149°C. Yield 0.15 g (13%).

1-Methyl-2-[5-(α-hydroxybenzhydryl)furyl-2]benzimidazole (XI) was prepared in a similar way to compound VII from 1 g (5.05 mmoles) compound VIII. Mp 213-215°C (toluene); from [13], mp 204-205°C (from aqueous alcohol). Yield 0.76 g (40%).

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