Lithiation of 1-Benzylimidazole. A Hypothesis on the Regioselectivity of the Electrophilic Attacks on the Lithiated Species

M. Moreno-Mañas*, J. Bassa, N. Lladó and R. Pleixats

Department of Chemistry, Universidad Autónoma de Barcelona, Bellaterra, 08193-Barcelona, Spain.

Received May 26, 1989

Sequential lithiations of 1-benzylimidazole, **1**, and of 1-benzyl-1,2,4-triazole, **2**, followed by treatment with electrophiles others than alkyl halides result in reactions at C-2. However, benzyl halides and, to a certain extent, iodomethane react at the *N*-benzyl carbon atom. An explanatory hypothesis based on steric *ortho* effects is advanced.

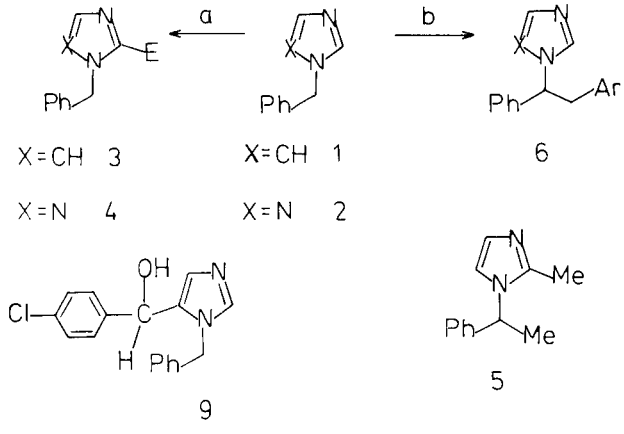
J. Heterocyclic Chem., **27**, 673 (1990).

Introduction.

The lithiation of *N*-protected imidazoles followed by reaction of the conjugate bases with electrophiles is a useful synthetic method leading to imidazoles functionalized at C-2, otherwise difficult to prepare. This subject has been covered in excellent reviews [1,2,3].

Several radicals have been used to protect the N-H bond of the imidazole ring. Among them the benzyl group deserves particular attention. 1-Benzylimidazole, **1**, has been sequentially lithiated with *n*-butyllithium and treated with electrophiles to afford differently functionalized imidazole derivatives **3** (Scheme 1 and Table 1). In general clean regioselective functionalizations at C-2 have been observed. Ogura and Takahashi reported the simultaneous formation of minor amounts of a product arising from condensation at C-5 [8] but this result has been questioned by other authors [2,9]. Also Chadwick and Ngochindo [9] described the formation of product **5** which points out that the benzylic methylene group can also be lithiated. Breslow *et al.* [10] mentioned that in their hands significant benzylic lithiation occurred when **1** was treated with *n*-butyllithium although the electrophile was not revealed. In summary, lithiation of 1-benzylimidazole takes place at C-2 and subsequent reactions with several electrophiles constitute a method to introduce different groups at this position.

Scheme 1



a. - i: *n*-BuLi; ii: Electrophile.

b. - i: *n*-BuLi; ii: $ArCH_2Cl$. Reference [12].

Table 1

Reported Sequential Reactions at C-2 of **1** and at C-5 of **2** with *n*-Buthyllithium and Electrophiles

Y	E^+	E	Reference
CH	CO_2	COOH	[4,5]
CH	Quinoline	2-Quinolinyl	[4]
CH	PhCHO	PHCHOH	[6]
CH	CH_3CHO	CH_3CHOH	[6]
CH	$(CH_3)_2N$-CHO	CHO	[7]
CH	$PhN(CH_3)$-CHO	CHO	[7]
CH	$(CH_3)_2SO_4$	CH_3	[7]
CH	L-Gulono-1,4-lactone derivative	L-Gulonofuranosyl derivative	[8]
CH	CH_3I	CH_3	[9]
N	Ph_2CO	Ph_2CHOH	[11]
N	CD_3OD	D	[11]
N	$(EtO)_2P(O)Cl$	$(EtO)_2P(O)$	[11]
N	*t*-$BuSi(CH_3)_2Cl$	*t*-$BuSi(CH_3)_2$	[11]
N	CH_3I	CH_3	[11]
N	Cl_3C-CCl_3	Cl	[11]
N	CH_3OCOCl	CO_2CH_3	[11]

Similarly, a group from Monsanto reported the synthesis of several triazoles **4** by lithiation of 1-benzyl-1,2,4-triazole, **2**, at the C-5 ring position followed by treatment with electrophiles others than alkyl halides [11].

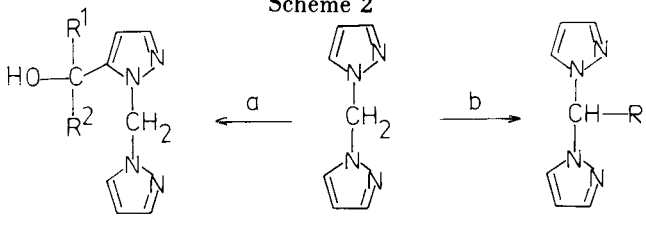
However, our group reported in 1985 completely different results in a general synthesis of 1,2-diaryl-1-(*N*-azolyl)ethanes, **6**, by lithiation of **1** or **2** followed by reaction with benzyl chlorides [12]. In no case products from reaction at C-2 of the imidazole ring or at C-5 of the triazole ring were detected. Therefore, there is an apparent inconsistence between our results and those from other groups.

In general it can be said that reactions of electrophiles at the dipole stabilized side chain N-Cα carbanions [13] are exceptions rather than the rule and attempts to generate the N-Cα carbanions have been performed through an indirect route involving fluoride or alkoxide induced desilylation of 1-[(trimethylsilyl)methyl]azoles [14,15,16].

Nevertheless, the dependence of the regioselectivity on the nature of the electrophile and on the experimental conditions is not exceptional in related systems. Thus,

Katritzky *et al.* have shown that 1-benzylpyrazole is lithiated at -78° at the benzylic methylene group under kinetic control [17]. The organolithium intermediate rearranges to the ring C-5 lithium derivative at higher temperatures. Even more significant is the work by Katritzky *et al.* on the lithiation of bis(pyrazol-1-yl)-methane (Scheme 2) with *n*-butyllithium. When the lithiation is followed by reaction with iodomethane or benzyl chloride the methylene substituted products, **8**, were obtained but reactions with carbonyl electrophiles gave the products **7** from ring lithiation [18]. Again benzyl chloride behaves differently and clearly a general interpretation is needed.

Scheme 2



7 8

a. - i: *n*-BuLi; ii: R^1R^2CO. Reference [18].
b. - i: *n*-BuLi; ii: Benzyl Chloride or Iodomethane. Reference [18].

Results.

Our initial efforts were dedicated to check if the experimental conditions had any influence in the regioselectivity of the reactions of **1** with *n*-butyllithium followed by benzyl halides. As indicated in Table 2 the answer is clearly negative. Indeed, neither the solvent (dimethoxyethane or tetrahydrofuran), the leaving group (Cl, Br or I), the temperature and the presence of additives such as tetramethylethylenediamine or 15-crown-5 had no influence on the regiochemical outcome of the reactions.

The reactions were monitored by gc and pmr. Therefore we needed to assign unambiguously all the proton ring signals of compound **1**. The methylene protons of **1** appear at δ 5.20 in acetone-d_6. The ring proton at C-2 appears at δ 7.65. The other two ring protons resonate at 6.95 and 7.06. A NOEDIFF experiment irradiating at the methylene frequency affected the signals at 7.65 and 7.06. This is a clear evidence for the signal at 7.06 to be due to the proton at C-5.

The reaction crudes of Table 2 were analyzed by pmr. In no case singlets due to the methylene protons of products from attack at C-2 were apparent. The final products **6** (Y = CH) gave signals at *ca.* δ 5.2 and 3.4 for the CH and methylene protons of the chain at N-1.

Some other trends emerge from Table 2: a) From run 8 it seems that the anion at C-2 is the thermodynamically more stable (See below). However, it is already formed at -60°, therefore it is possibly also the kinetically preferred, and b) the order of leaving groups ability is Cl > Br > I (Runs 4, 5 and 7).

Once the lack of influence of the experimental conditions on the regioselectivity was clearly established we studied the reactions with several electrophiles. The results are gathered in Scheme 1 and Table 3.

The reaction with iodomethane afforded compound **3a** together with minor amounts of **5**, the product from reaction at both C-2 and the methylene group (Runs 1 and 2). This result is in complete agreement with that previously reported by Chadwick and Ngochindo [9] thus confirming once more that iodomethane can react at the methylene group. Both compounds were isolated and their spectroscopic features compared with those described by the British group.

Reactions with dimethyl disulfide and diphenyl disulfide produced products **3b** and **3c** from reaction at the ring C-2 position (Runs 3 and 4).

Reactions with acyl chlorides took place affording the ketones **3d** and **3e** in low yields (Runs 5 and 6). In no case

Table 2
Sequential Reactions at N-Cα of 1 with *n*-Buthyllithium and Benzyl Halides

Run	Halide	Solvent	T(°C)	Additive	Product	Yield of 6[a]
1	4-ClPhCH_2Cl	DME	-60	--	1+6	29 [b]
2	4-ClPhCH_2Cl	DME	rt	--	1+6	7
3	PhCH_2Br	DME	rt	--	1+6	12
4	PhCH_2Br	THF	-60	--	1+6	(1:5.4)
5	PhCH_2I	THF	-60	--	1+6	(1:0.5)
6	PhCH_2Cl	DME	-60	--	1+6	62 [b]
7	PhCH_2Cl	THF	-60	--	1+6	(1:8.3)
8	PhCH_2Cl	THF	-60→ rt→ -60	--	1+6	(1:4.6)
9	PhCH_2Cl	THF	-60	[c]	1+6	(1:6.2)
10	PhCH_2Cl	THF	-60	[d]	1+6	(1:6.4)

[a] For products **6** in this table X =CH. Figures in parentheses refer to ratios of gc peak areas for compounds **1** and **6**. [b] Reference 12. [c] Tetramethylethylenediamine (1 equivalent). [d] 15-Crown-5 (1 equivalent).

Table 3
Sequential Reactions at C-2 of **1** with *n*-Buthylithium and Electrophiles [a]

Run	E^+	Products	E	Yield (%) [b]
1	CH_3I	**3a**	CH_3	13
		5 [c]		6
2	CH_3I	**3a, 5**		(6.5:1.1)
3 [d]	$(CH_3S)_2$	**3b**	CH_3S	31
4	$(PhS)_2$	**3c**	PhS	38
5	3-ClPhCOCl	**3d**	3-ClPhCO	6
6	4-ClPhCOCl	**3e**	4-ClPhCO	14
7	4-ClPhCHO	**3f**	4-ClPhCHOH	9
		3e	4-ClPhCO	13
		9		13
8	D_2O	**3g**	D	88 [e]
9	2-O_2NPhI	**3h**	I	35 [e]
		3i	2-O_2NPh	9
		Nitrobenzene		45

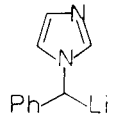
[a] General non optimized conditions: 1 equivalent on *n*-buthyllithium in tetrahydrofuran (in dimethoxyethane for run 3) at -60°. [b] Isolated yields. [c] 2-Methyl-1-(1-phenylethyl) imidazole. See Scheme 1. [d] In dimethoxyethane. Figures in parenthesis refer to ratios of gc peak areas for the indicated products. [e] The temperature was raised to room temperature and lowered again at -60° before addition of the electrophile.

products from attack at the methylene group could be detected.

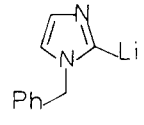
4-Chlorobenzaldehyde (Run 7) produced a complicated mixture of products from which three were isolated: alcohol **3f** arises from the primary reaction at C-2, whereas **3e** arises probably from **3f** by oxidation. A third product has been tentatively assigned structure **9**. It exhibited the characteristic AB system of the diastereotopic methylene protons at δ 5.70, 5.63, 5.55 and 5.47 and a singlet at δ 7.55 attributed to the ring C-2 proton. A second singlet at δ 6.75 could be attributed to both the proton at C-4 or at C-5. However, all the precedents point out that the second favoured position for lithiation in *N*-protected imidazoles is the ring C-5 [2,19,20]. The pmr spectrum of product **3e** was uninformative with respect to the ring reaction position. However, it was reduced to the alcohol **3f** with sodium borohydride in methanol. Alcohol **3f** exhibited singlets at δ 6.70 and 6.88 safely attributed to the protons at C-4 and C-5.

Reaction with deuterium oxide afforded 88% yield of the C-2 deuterated starting material **3g**. This experiment was performed driving the reaction mixture to room temperature and cooling again at -60° before quenching. Otherwise deuteration was not complete. This seems to indicate that the carbanionic species **11** is thermodynamically more stable as already suggested from experiment 8 of Table 1. However, this fact does not imply that the carbanionic species **10** is kinetically preferred and indeed the result from reactions at -60° rather suggest the opposite.

Formulae



10



11

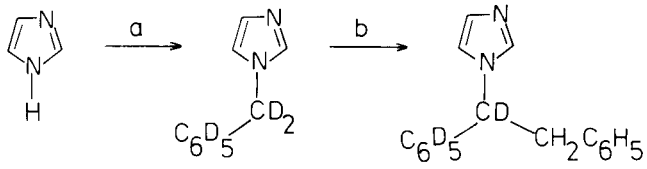
It has been described that 2-nitroiodobenzene can react with nucleophiles through a non chain radical mechanism by collapse of a radical pair in the solvent cage [21]. We wondered if such an electrophile could give rise to a change in the regiochemistry. The corresponding reaction (Run 9) produced two products from reaction at C-2, **3h** and **3i**, The first one comes from attack at the iodine atom. Correspondingly, nitrobenzene was also isolated in significant yields.

At this point it seemed clear from our own work and that of others [9,11,18] that benzyl halides and, up to a certain point, iodomethane possess structural features that differentiate their behaviour from those of other electrophiles.

Recently Monsanto chemists have shown that groups at the C-5 position of 1-alkyl-1,2,4-triazoles can migrate to the *N*-alkyl chain under basic conditions [22]. In order to check the possibility of the hydrogen atom migration from the methylene group to the ring C-2 position we prepared 1-(D_7)benzylimidazole, **12**, by reaction of imidazole with (D_7)benzyl bromide (Scheme 3). The deuterated **12** showed singlets at δ 7.50, 6.85 and 7.10, an infrared absorption at 2265 cm^{-1} and the base peak in the mass spectrum at m/e

98 (perdeuterated benzyl fragment). Compound **12** was sequentially treated in the usual way with *n*-butyllithium and benzyl chloride. The resulting product **13** and the recovered **12** were analyzed with respect to deuterium distribution. The recovered **12** was identical to the starting material within the limits of the pmr integration and ms detection possibilities. The condensation product **13** showed only signals of equal intensity at δ 7.60, 6.85, and 7.25 plus the AB signals of the diastereotopic methylene protons (3.64, 3.61, 3.58, 3.55). Its cmr spectrum showed the absence of the signal at δ 63.5 corresponding to the C-1 of the side chain due to the deuterium effect. The mass spectrum did not show evidences of deuterium scrambling neither.

Scheme 3



12

a. - i: HNa, DME; ii: (D_7)Benzyl Bromide.
b. - i: *n*-BuLi; THF, -60°C; ii: Benzyl Chloride.

Concluding Remarks.

The results of our work point out that the species **11** is thermodinamically more stable than **10** and possibly also kinetically favoured. Both species must be simultaneously present at low temperature since products from one and the other are formed depending on the electrophile. However, the mechanisms through which they equilibrate are still puzzling as the experiment with deuterium labelled compounds indicates.

The regioselectivity deserves some attention. Hardness and softness of the quenching reagent have been invoked to explain the observed regioselectivities in the lithiation of 1,2-dimethylimidazole and subsequent reaction with electrophiles [23]; this system is different from ours in that the active points are the methyl group at C-2 and the ring C-5 position. It is hard to accept that reactions protagonized by highly charged species such as **10** and **11** are controlled by frontier orbitals. It is also difficult to understand why charge controlled reactions of the same competing charged species with neutral electrophiles give rise to different regioselectivities. Therefore, we would like to introduce the steric factor which has seldom, not to say never, been considered in discussing the lithiations of *N*-protected imidazoles. Indeed, the only electrophiles which escape to the rule are benzyl halides and iodomethane to some extent. These electrophiles also present a peculiar behaviour towards bis(1-pyrazolyl)methane [18] as previously remembered. They are the only electrophiles for which pentacoordination is required in the transition state and therefore they are the most sterically demanding. *Ortho* steric interactions, although not so important as in six membered rings are commonplace in imidazole rings [24]. These steric interactions in the transition state of attack at C-2, between the benzyl group at *N*-1 and the substituents of the electrophilic pentacoordinated carbon atom, can not be easily relieved. For other electrophiles the situation in the transition state is different since lower coordination numbers are required and the angles around the electrophilic center permit longer distances between the interacting groups.

In summary and as a matter of fact, electrophiles prefer in general to react at the ring C-2 position in lithiated 1-benzylimidazole. Only those that can not do so for steric reasons react at the benzylic center.

EXPERIMENTAL

Reactions of 1-Benzylimidazole (**1**) with Benzyl Halides.

The general method has been described elsewhere [12]. The modifications introduced in this paper have been defined in Table 1. Gc analyses were performed with a "Crosslinked Methyl Silicone Gum HP Ultra 1" capillar column.

1-Benzyl-2-methylthioimidazole (**3b**) (General Procedure).

n-Butyllithium 1.6*M* in hexane (6.7 ml, 10.7 mmoles) was slowly added under argon to a stirred solution of 1-benzylimidazole, **1**, (1.58 g, 10 mmoles) in anhydrous dimethoxyethane (30 ml) cooled at -60°. The stirring was continued for 10 minutes. Dimethyl disulfide (2.96 g, 30 mmoles) in dimethoxyethane (5 ml) was slowly added. The mixture was kept at -60° for 1.5 hours and then allowed to warm to room temperature. The solvent was evaporated and the residue was partitioned between water and dichloromethane. The organic layer was washed with water, dried and evaporated. The residue was chromatographed through silica gel (70-230 mesh). Product **3b** (0.64 g, 31%) was eluted with dichloromethane-chloroform (1:3) and the starting material **1** (0.45 g, 28%) was recovered with chloroform as eluent. The imidazole **3b** was an oil (bp 138-152° (oven temperature)/0.1 mm Hg); pmr (acetone-d_6): δ 2.52 (s, 3H), 5.17 (s, 2H), 6.95 (d, J = *ca.* 2 Hz), 7.15-7.40 (m, 6H); cmr (acetone-d_6): δ 15.4, 49.3, 121.4, 127.1, 127.4, 128.5, 128.9, 137.1, 142.0; ms: m/e 204 (M, 13), 91 (100).

1,5-Naphthalenedisulfonate of **3b**.

The imidazole **3b** (0.206 g 1.01 mmoles) and a 75% aqueous suspension of 1,5-naphthalenedisulfonic acid (195.7 mg, 0.50 mmole) were dissolved in ethanol (14 ml). The salt (0.224 g, 63%) crystallized spontaneously, mp 222-224° (from ethanol-chloroform).

Anal. Calcd. for $C_{32}H_{32}N_4O_6S_4$: C, 55.18; H, 4.59; N, 8.04. Found: C, 55.08; H, 4.60; N, 7.84.

The same general method was used for all the reaction of Table 2.

1-Benzyl-2-methylimidazole (**3a**).

This compound was obtained as an oil; pmr (deuteriochloroform): δ 2.27 (s, 3H), 5.00 (s, 2H), 6.7-7.3 (m, 7H), coincident with the described spectrum [9]; ms: m/e 172 (M, 42), 105 (19), 91 (100), 77 (19), 65 (33).

2-Methyl-1-(1-phenylethyl)imidazole (**5**).

This compound was obtained as an oil; pmr (deuteriochloroform): δ 1.8 (d, J = 7 Hz, 3H), 2.25 (s, 3H), 5.25 (q, J = 7 Hz, 1H), 6.8-7.45 (m, 7H), coincident with the described spectrum [9]; ms: m/e 186 (M, 21), 105 (100), 103 (22), 91 (21), 79 (31), 77 (31).

1-Benzyl-2-phenylthioimidazole (**3c**).

This compound was obtained as an oil; pmr (deuteriochloroform): δ 5.21 (s, 2H), 6.90-7.42 (m, 12H); ms: m/e 267 (M + 1, 20), 266 (M, 56), 265 (32), 167 (23), 91 (100).

1,5-Naphthalenedisulfonate of **3c**.

This compound was a solid, mp 220-222°.

Anal. Calcd. for $C_{42}H_{36}N_4O_6S_4$: C, 61.44; H, 4.42; N, 6.82. Found: C, 61.46; H, 4.31; N, 6.68.

1-Benzyl-2-(3-chlorobenzoyl)imidazole (**3d**).

This compound was a solid, mp 77-78°; ir (potassium bromide): 1650 cm^{-1}; pmr (deuteriochloroform): δ 5.70 (s, 2H), 7.20 (d, J *ca.* 1 Hz, 1H), 7.1-7.8 (m, 8H), 8.1-8.3 (m, 2H); cmr (deuteriochloroform): δ 51.9, 126.0, 127.4, 128.0, 128.7, 128.9, 129.2, 129.7, 130.7, 132.4, 134.0, 136.2, 138.8, 142.2, 182.3; ms: m/e 299 (5), 298 (20), 297 (29), 296 (M, 56), 295 (47), 267 (57), 201 (22), 111 (29), 91 (100), 65 (30).

Anal. Calcd. for $C_{17}H_{13}ClN_2O$: C, 68.80; H, 4.41; N, 9.44. Found: C, 68.83; H, 4.27; N, 9.21.

1-Benzyl-2-(4-chlorobenzoyl)imidazole (**3e**).

This compound was a solid, mp 82-83°; ir (potassium bromide): 1640 cm^{-1}; pmr (acetone-d_6): δ 5.75 (s, 2H), 7.25-7.35 (m, 6H), 7.5-7.7 (m, 3H), AA' part of the AA'BB' system 8.32, 8.43 (2H); cmr (acetone-d_6): δ 52.4, 127.8, 128.3, 128.6, 128.9, 129.5, 130.3, 133.5, 137.0, 138.5, 139.3, 205.9; ms: m/e 298 (6), 296 (M, 17), 201 (21), 111 (26), 91 (100), 75 (24), 65 (40).

Anal. Calcd. for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.41; N, 9.44; Cl, 11.95. Found: C, 68.97; H, 4.47; N, 9.39; Cl, 11.96.

1-Benzyl-2-((4-chlorophenyl)(hydroxy)methyl)imidazole (**3f**).

This compound was a solid, mp 116-117°; ir (potassium bromide): 3200-3300 (broad) cm^{-1}; pmr (deuteriochloroform): δ 4.25 (broad s), AB system at 4.60, 4.75, 4.90, 5.12 (2H), 5.90 (s, 1H), 6.70 (s, 1H), 6.8-7.4 (m, 10H); cmr (acetone-d_6): δ 49.0, 68.4, 121.0, 126.7, 127.2, 127.3, 127.8, 128.3, 132.2, 137.1, 140.9; ms: m/e 300 (2), 298 (M, 4), 91 (100).

Anal. Calcd. for $C_{17}H_{15}ClN_2O$: C, 68.73; H, 5.02; N, 9.38. Found: C, 68.24; H, 5.09; N, 9.35.

1-Benzyl-5-((4-chlorophenyl)(hydroxy)methyl)imidazole (**9**).

This compound was a solid, mp 102-103°; ir (potassium bromide): 3400 cm^{-1}; pmr (acetone-d_6): δ 4.25 (broad s), AB system at 5.47, 5.55, 5.63, 5.70 (2H), 5.75 (s, 1H), 6.75 (d, J *ca.* 1 Hz, 1H), 7.0-7.4 (m, 9H), 7.55 (d, J *ca.* 1 Hz, 1H); ms: m/e 300 (1.5), 298 (M, 5), 158 (76), 157 (35), 141 (21), 130 (25), 103 (31), 97 (32), 91 (83), 77 (100), 65 (20), 51 (27).

1-Benzyl-2((4-chlorophenyl)(hydroxy)methyl)imidazole (**3f**) by Reduction of **3e**.

Sodium borohydride (0.044 g, 1.16 mmoles) was added portionwise to a solution of **3e** (0.40 g, 1.35 mmoles) in methanol (6 ml) stirred at 5-10°. The mixture was refluxed for 1 hour and the solvent was evaporated. The residue was acidified upon addition of water (6 ml) and 3*N* hydrochloric acid and the mixture was refluxed for 15 minutes and finally partitioned between aqueous sodium hydrogenocarbonate and dichloromethane. The organic layer was washed with water, dried and evaporated to afford **3f** (55%), mp 113-115°.

1-Benzyl-2-deuterioimidazole (**3g**).

This compound was a solid, mp 68-69°; pmr (acetone-d_6): 5.25 (s, 2H), 6.90 (s, 1H), 7.10 (s, 1H), 7.3 (m, 5H); cmr (acetone-d_6): δ 50.7, 120.0, 128.2, 128.6, 129.5, 129.9, 138.6; ms: m/e 160 (M + 1, 7), 159 (M, 23), 91 (100), 65 (27).

1-Benzyl-2-iodoimidazole (**3h**).

This compound was a solid, mp 99-101°; pmr (acetone-d_6): δ 5.21 (s, 2H), 7.03 (s, 1H), 7.15-7.45 (m, 6H); ms: m/e 284 (M, 21), 157 (14), 127 (17), 91 (100), 65 (30).

Anal. Calcd. for $C_{10}H_7IN_2$: H, 3.19; N, 9.86. Found: H, 3.32; N, 9.62.

1-Benzyl-2-(2-nitrophenyl)imidazole (**3i**).

This compound was a solid, mp 91-92°; ir (potassium bromide): 1536, 1362 cm^{-1}; pmr (acetone-d_6): δ 5.36 (s, 2H), 7.02 (s, 1H), 7.20 (s, 1H), 7.13-8.1 (m, 9H); ms: m/e 279 (M, 2), 130 (24), 91 (100).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.04. Found: C, 68.57; H, 4.45; N, 14.88.

(D_7) Benzyl Bromide.

A mixture of (D_8) toluene (5.62 g, 0.056 mole), *N*-bromosuccinimide (8.00 g, 0.045 mole), a catalytic amount of azobisisobutyronitrile and dichloromethane (80 ml) was refluxed for 30 minutes under irradiation with a 500W bulb. The solid was filtered off and the filtrate was washed with an aqueous solution of sodium carbonate, dried and evaporated. The residue was distilled (bp 97°/15 mm Hg) to afford 5.33 g (55% yield) of (D_7) benzyl bromide.

1-((D_7)Benzyl)imidazole (**12**).

A solution of imidazole (2.04 g, 0.030 mole) in anhydrous dimethoxyethane (15 ml) was added dropwise into a stirred and ice-cooled suspension of sodium hydride (0.864 g, 0.036 mole) in the same solvent (25 ml). The stirring was maintained for 45 minutes at room temperature. A solution of (D_7)benzyl bromide (5.30 g, 0.030 mole) in anhydrous dimethoxyethane (15 ml) was then added. The mixture was stirred for 2 hours at room temperature and partitioned between ether and water. The organic layer was washed with water, dried and evaporated. The residue was recrystallized from ether to afford **12** (51%), mp 72-73°; ir (potassium bromide): 2280 cm^{-1}; pmr (deuteriochloroform): δ 6.85 (s, 1H), 7.10 (s, 1H), 7.50 (s, 1H); cmr (deuteriochloroform): δ 119.1, 129.6, 137.2; ms: m/e 165 (M, 16), 98 (100), 70 (41).

1-((1-Deuterio-1-(D_5)phenyl-2-phenyl)ethyl)imidazole (**13**).

This compound was obtained by the general procedure as an oil; ir (film): 2265 cm^{-1}; pmr (acetone-d_6): δ AB system at 3.55, 3.58, 3.61 and 3.64 (2H), 6.85 (s, 1H), 7.10-7.25 (m, 5H), 7.25 (s, 1H), 7.60 (s, 1H); cmr (acetone-d_6): δ 41.9, 117.8, 127.0, 128.8, 129.3, 136.6, 136.8, 139.3; ms: m/e 255 (M + 1, 15), 254 (M, 30),

164 (27), 163 (100), 136 (39), 109 (25).

Acknowledgements.

Financial support from DGICYT (Ministry of Education and Science of Spain) through grant 0030/87 is gratefully acknowledged.

REFERENCES AND NOTES

[1] H. W. Gschwend and H. R. Rodríguez, *Org. React.*, **26**, 1 (1979).

[2] B. Iddon, *Heterocycles*, **23**, 417 (1985).

[3] B. A. Tertov and Yu. V. Koshchienko, *Chem. Heterocyclic Compd.*, **24**, 117 (1988).

[4] D. A. Shirley and P. W. Alley, *J. Am. Chem. Soc.*, **79**, 4922 (1957).

[5] D. Owen, R. G. Plevey and J. C. Tatlow, *J. Fluorine Chem.*, **17**, 179 (1981).

[6] A. M. Roe, *J. Chem. Soc.*, 2195 (1963).

[7] P. E. Iversen and H. Lund, *Acta Chem. Scand.*, **20**, 2649 (1966).

[8] H. Ogura and H. Takahashi, *J. Org. Chem.*, **39**, 1374 (1974).

[9] D. J. Chadwick and R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. I*, 481 (1984).

[10] C. C. Tang, D. Davalian, P. Huang and R. Breslow, *J. Am. Chem. Soc.*, **100**, 3918 (1978).

[11] D. K. Anderson, J. A. Sikorski, D. B. Reitz and L. T. Pilla, *J. Heterocyclic Chem.*, **23**, 1257 (1986).

[12] M. R. Cuberes, M. Moreno-Mañas and A. Trius, *Synthesis*, 302 (1985).

[13] P. Beak and D. Reitz, *Chem. Rev.*, **78**, 275 (1978).

[14] S. Shimizu and M. Ogata, *J. Org. Chem.*, **51**, 3897 (1986).

[15] S. Shimizu and M. Ogata, *J. Org. Chem.*, **52**, 2314 (1987).

[16] S. Shimizu and M. Ogata, *Tetrahedron*, **45**, 637 (1989).

[17] A. R. Katritzky, C. Jarayam and S. N. Vassilatos; *Tetrahedron*, **39**, 2023 (1983).

[18] A. R. Katritzky, A. E. Abdel-Rahman, D. E. Leahy and O. A. Schwarz; *Tetrahedron*, **39**, 4133 (1983).

[19] A. J. Carpenter, D. J. Chadwick and R. I. Ngochindo; *J. Chem. Res. (M)*, 1913 (1983); *J. Chem. Res. (S)*, 196 (1983).

[20] A. J. Carpenter and D. J. Chadwick, *Tetrahedron*, **42**, 2351 (1986).

[21] C. Galli, *Tetrahedron*, **44**, 5205 (1988).

[22] J. A. Sikorski, D. K. Anderson and J. M. Curtis, XIIIth European Colloquium on Heterocyclic Chemistry, communication P47. Fribourg, Switzerland, 1988.

[23] B. Iddon and B. L. Lim, *J. Chem. Soc., Perkin Trans. I*, 271 (1983).

[24] M. R. Grimmett, *Adv. Heterocyclic Chem.*, **27**, 241 (1980).