Synthesis of Aryl 3-(2-Imidazolyl)propyl Ketones [1]

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The approach to the title compounds was *via* lithiation-substitution of *N*-methyl or *N*-(triphenylmethyl)-imidazole by some iodo ketals. 4-Chloro-4'-halobutyrophenones (halo = F, Cl, Br) were converted by sodium iodide to the corresponding aliphatic iodides which were subsequently ketalized with ethylene glycol to provide the corresponding iodo ketals. Lithiation of either 1-methyl- or 1-(triphenylmethyl)imidazole with *n*-butyllithium generated the corresponding 2-lithioimidazoles, *in situ*, which were then reacted with these iodo ketals to form the corresponding *C*-2 substituted imidazoles. Dilute aqueous acid hydrolysis released the ketone from the ketal. For *N*-triphenylmethyl protected imidazoles, the triphenylmethyl group was also hydrolyzed to give triphenylmethanol and 3-(2-imidazolyl)propyl 4-haloaryl ketones. These *N*-unsubstituted imidazolyl ketones can be alkylated independently with triphenylmethyl chloride to form the corresponding *N*-triphenylmethyl imidazole derivatives.

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In our continuing quest to prepare aryl ω-(*C*-imidazolyl)alkyl ketones [2], we describe the synthesis of compounds in which three methylene groups separate *C*-2 of imidazole from an aromatic ketone. To broaden the scope of these syntheses, one series commenced with imidazole bearing the non-removable *N*-methyl group (**1**, **R** = Me), the other, with the *N*-triphenylmethyl protected imidazoles (**1**, **R** = trityl, CPh_3). It is well-established that lithiation of *N*-substituted imidazoles **1** with *n*-butyllithium (BuLi) takes place quickly at *C*-2 to generate lithio derivatives **2**, which react readily with many reagents, including alkylating agents, to form 1,2-disubstituted imidazoles [3]. We chose the trityl group as the protective group for this project in the light of the many difficulties cited by other investigators in attempting to remove certain "protective" groups smoothly from *N*-1 of 1,2-disubstituted imidazoles [4].

A survey of the literature reveals that, perhaps for very good reasons, relatively few alkyl halides have been employed in these series of lithiation-substitutions. Uncomplicated alkylations of **2** proceed well with methyl and *n*-butyl iodide, as well as dimethyl sulfate. In an earlier study, BuLi lithiated 1-methylimidazole (**1**, **R** = Me) at *C*-2 and subsequent reaction with methyl iodide afforded 1,2-dimethylimidazole (68%) [5]. Relatively straightforward *C*-2 methylation took place when 1-dimethylsulfonamidoimidazole (**1**, **R** = SO_2NMe_2) was lithiated first with BuLi, then reacted with either methyl iodide or sulfate to introduce a 2-methyl group (82 or 63%, respectively) [7].

The more complex lithiation-substitutions of 1-benzylimidazole have been studied in some detail. Initially, the reaction with BuLi, followed by methyl iodide was reported to yield 1-benzyl-2-methylimidazole in 81% yield [5]. It was shown later, that indeed in the first step, H-2 (of imidazole) in 1-benzylimidazole is abstracted quickly as is evidenced by quenching with deuterium oxide and isolating the 2-deuterio analog in 88% yield [6]. However, the reaction of the intermediate lithio derivative **2** (**R** = benzyl) with methyl iodide is slow, and not straightforward. There was isolated **3** (**R** = benzyl) and 2-methyl-(2-phenylethyl)imidazole in varying yields, very much dependent upon reaction conditions [6,7]. Apparently, the *C*-2 anion is in equilibrium with the *N*-benzyl anion, and either anion has the chance to react with methyl iodide, albeit with different rates, resulting in the above-stated mixture.

In contrast, 1-tritylimidazole (**1**, **R** = CPh_3) is lithiated by BuLi only at *C*-2 of imidazole and further reaction with methyl iodide furnished 1-trityl-2-methylimidazole in 95% yield [8]. A cognate series of reactions of 1-tritylimidazole, carried out in the presence of tetramethylethylenediamine (TMEDA) and excess methyl iodide, produced 1-trityl-2-methyl- and 1-trityl-2,5-dimethylimidazole (36 and 64%, respectively) [6].

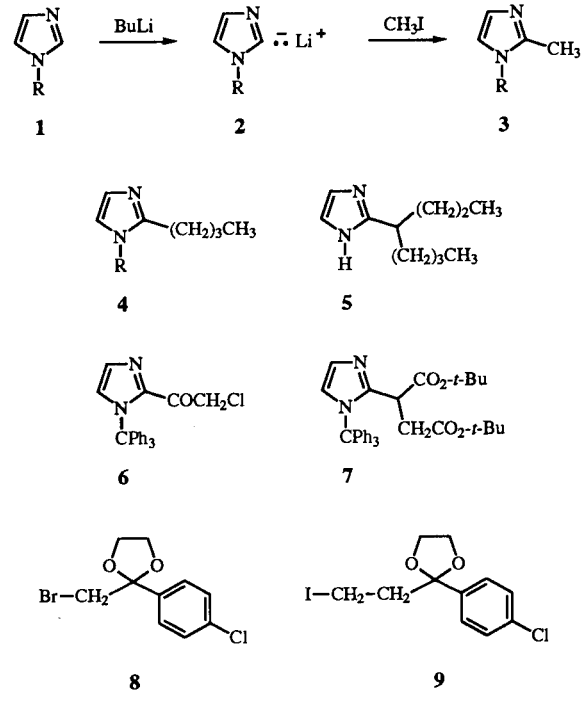
Highly successful lithiation-alkylations at *C*-2 of a number of *N*-[(alkoxy)methyl]imidazoles have been reported. In general, the alkylating agent was methyl iodide. For example, 1-(methoxymethyl)imidazole (**1**, **R** = CH_2OCH_3) reacts with BuLi, and then with methyl iodide to form the 2-methyl derivative in 95% yield [8]. Due to the stubborn resistance to the removal of this protective group under acidic conditions, many other (but related) protective groups have been developed which might be amenable to more facile deprotection with acids. These differently *N*-substituted imidazoles are methylated easily at *C*-2 to form **3** in good yields, where **R** is $CH(CH_3)$-OC_2H_5 (91%) [9], $CH_2OCH_2CH_2OCH_3$ (97%) [10], $CH_2OC(CH_3)_3$ (94%) [10] and $CH_2OCH_2CH_2Si(CH_3)_3$ (94%) [11].

In spite of successes using methyl iodide, few other iodides have been reported to react with 2-lithioimid-

azoles. In one of the few instances when 1-iodobutane was used, alkylation afforded 2-butylimidazole (84%), after hydrolytic removal of a $CH(OC_2H_5)_2$ protective group [12]. Another example of the use of 1-iodobutane is the lithiation-substitution of 1-[(dimethylamino)methyl]-imidazole (**1**, **R** = CH_2NMe_2). After reaction with BuLi, followed by 1-iodobutane, the intermediate aminal was hydrolyzed during an aqueous acidic workup to produce 2-butylimidazole (**4**, **R** = H, 76%) [13a]. In contrast, a similar reaction using 1-bromobutane produced **4** in only 24% yield, accompanied by 4-(2-imidazolyl)octane (**5**, 27%), along with recovered imidazole [13a]. Apparently, the active methylene group of the intermediate 1-[(dimethylamino)methyl]-2-butylimidazole is neutralized and the resultant anion competes with **2** (where **R** = CH_2NMe_2) for alkylation with 1-bromobutane resulting in the formation of the octyl derivative. Metallation of the active methylene group at *C*-2 of 1-substituted imidazoles is well-established [13b].

The recent paper by Coutts and coworkers [14] is a true indication of the potential complexity of these lithiation-substitutions, where changing the nature of the halo group to be displaced can dramatically alter the nature of the product. Standard lithiation of 1-tritylimidazole with BuLi at -60° generates **2** (**R** = CPh_3) and was followed by the addition of either *t*-butyl 2-chloro- or 2-bromo- or 2-iodoacetate (X-CH_2-CO_2-*t*-Bu). It appears that in the 2-chloro ester, the carbonyl carbon is more electrophilic than the methylene carbon bearing the chloro group and the only product was 1-trityl-2-(chloroacetyl)imidazole (**6**, 54%, based on 50% isolation of starting imidazole). The bromo ester fared better in terms of alkylation when **2** (**R** = CPh_3) is initially substituted by the CH_2-CO_2-*t*-Bu group. But, in the presence of base, the active methylene anion (of the CH_2 at *C*-2) is generated which, in turn, reacts faster than **2**, (**R** = CPh_3) with the starting bromo ester to furnish di-*t*-butyl 2-(1-trityl-2-imidazolyl)succinate, **7**, 88%). In sharp contrast, the iodine atom in *t*-butyl 2-iodoacetate is sufficiently electrophilic to react with the anionic center (*C*-2) of **2** to furnish 1-trityl-2-iodoimidazole (62%). In a related reaction, 1,2-diiodoethane underwent halogen-metal interchange with 3-lithiothiophene to produce 3-iodothiophene in 63% yield [15]. Lithiation of 1-(dimethylsulfamoyl)-2-(*tert*-butyldimethylsilyl)imidazole with *n*-butyllithium afforded the 5-lithio derivative which was alkylated by an ω-chloro-1-iodoalkane to introduce the (ω-chloro)alkyl side chain at C-5 of the imidazole [16].

While methyl and *n*-butyl iodide behave as anticipated during lithiation-alkylations, there was no guarantee that other alkyl iodides would follow suit. We wanted to explore alkylations of *N*-protected 2-lithioimidazoles **2**



with ω-haloalkyl aryl ketones, where the ketone is protected as an acetal to prevent attack by **2** on the ketone function. From the above literature, it became apparent

Scheme 1

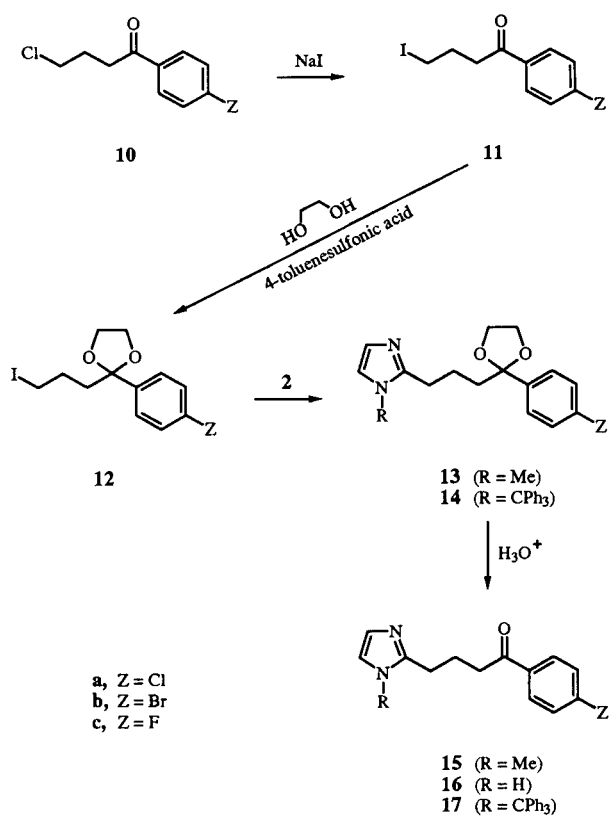


Table 1

Selected ^{1}H Chemical Shifts, δ (in ppm) of **10** to **17** (in Deuteriochloroform), Downfield from Tetramethylsilane

X-CH_2-CH_2-CH_2-CY_2-Ar-(4-Z)

Compound	X [a]	*N*-Me	Im-H-4 [b]	Im-H-5 [b]	X-CH_2 [c]	C-CH_2-C [c]	CH_2-CY_2 [c]	$(OCH_2)_2$ [d]	Z	Ar [d,e]
10a	Cl	—	—	—	3.68	2.21	3.16	—	Cl	7.43, 7.91
10b	Cl	—	—	—	3.68	2.22	3.15	—	Br	7.61, 7.84
10c	Cl	—	—	—	3.68	2.23	3.16	—	F	7.14, 8.01
11a	I	—	—	—	3.32	2.24	3.10	—	Cl	7.44, 7.91
11b	I	—	—	—	3.32	2.25	3.10	—	Br	7.62, 7.85
11c	I	—	—	—	3.33	2.25	3.12	—	F	7.14, 8.01
12a	I	—	—	—	3.17	1.94 [f]	1.94 [f]	3.75, 4.01	Cl	7.31, 7.38
12b	I	—	—	—	3.17	1.93 [f]	1.93 [f]	3.74, 4.00	Br	7.31, 7.47
12c	I	—	—	—	3.16	1.96 [f]	1.96 [f]	3.75, 4.00	F	7.01, 7.40
13a	1-Me-2-Im	3.52	6.88	6.75	2.63	1.80 [f]	1.95 [f]	3.73, 4.00	Cl	7.28, 7.37
13b	1-Me-2-Im	3.52	6.87	6.74	2.63	1.80 [f]	1.95 [f]	3.73, 3.99	Br	7.31, 7.44
13c	1-Me-2-Im	3.51	6.86	6.74	2.64	1.81 [f]	1.97 [f]	3.73, 3.99	F	6.98, 7.40
14a	1-Tr-2-Im	—	6.93	6.65	1.84	1.36 [f]	1.42 [f]	3.63, 3.88	Cl	7.08, 7.27 [g]; 7.27
15a	1-Me-2-Im	3.59	6.90	6.79	2.78	2.18	3.10	—	Cl	7.41, 7.89
15b	1-Me-2-Im	3.58	6.88	6.79	2.76	2.16	3.08	—	Br	7.55, 7.79
15c	1-Me-2-Im	3.58	6.89	6.79	2.77	2.17	3.09	—	F	7.09, 7.97
16a	2-Im [h]	—	6.96	6.96	2.83	2.16	3.03	—	Cl	7.42, 7.87
16a	2-Im [i]	—	6.86	6.86	2.67	1.97	3.10	—	Cl	7.59, 7.96
17a	1-Tr-2-Im	—	6.97	6.73	2.02	1.70	2.65	—	Cl	7.12, 7.29 [g]; 7.39, 7.78

[a] Im represents the imidazolyl group, Me is methyl, Tr is trityl. [b] The apparent coupling constant, $J_{H\text{-}4,H\text{-}5}$ is about 1.2 Hz. [c] The spin-spin coupling constants are in the order of 6.0-8.0 Hz. [d] The centers of the AA'BB' complex multiplets are recorded. [e] No attempt was made to measure long-range F-H coupling constants. [f] Overlapping signals, as part of complex multiplets. [g] For the trityl ^{1}H nmr signals. [h] In "regular" deuteriochloroform, no NH signal was observed, which is quite common for imidazoles. But, in a dilute solution of deuteriochloroform which had been passed through a short column of basic alumina [17], the NH proton nmr signal was a broad signal at 1.76 ppm (exchangeable with deuterium oxide). [i] In extra dry deuteriodimethyl sulfoxide, the NH signal was observed at 11.72 ppm.

that one should employ the iodo compound to ensure success. Since ω-chloro-acetophenones, propiophenones and butyrophenones are readily available it was easy to explore this concept.

We chose to transform the aliphatic chloro to an iodo group, and protect the ketone as the ethylene glycol acetal. Theoretically, these steps can be carried out in either order, that is, with displacement of the halo group, first, followed by ketalization with ethylene glycol, or by reversing these two steps. After several trials, it was found that the more desirable sequence was to displace the halo group by iodo, then ketalize. The reason is that in the alternate sequence, where the ketal was formed first and then subsequently reacted with iodide ion, the ketal was opened quantitatively, along with the formation of the iodide.

Several preliminary experiments were performed to test the feasibility of using some halo ketals in alkylations. 4-Chlorophenacyl bromide was readily converted to the ethylene glycol ketal **8**. Attempts to alkylate the active methylene anion of 1,2-dimethylimidazole [13b] with **8** produced a mixture of unidentifiable products. Also, when the iodo ketal **9** (readily made from 3,4'-dichloropropiophenone) was used in lithiation-alkylation of **2** (**R** = Me), an intractable mixture of products was obtained.

However, lithiation-substitution of **2** with iodo ketals derived from ω,4'-dihalobutyrophenones **10** (Scheme 1) was successful. In the first step, the aliphatic chloro group of **10** was converted to an iodide **11** in excellent yield. Ketalization with ethylene glycol afforded **12**, also in excellent yield. Both **11** and **12** were deemed pure in terms of their ^{1}H nmr spectra (Table 1), and were colorless once purified, but readily turned reddish-purple upon standing. Purification of these iodides was possible by washing with mild base (*e.g.*, sodium bicarbonate or bisulfite) and/or column chromatography on silica gel. However, elemental analyses (C, H) were invariably well off acceptable values.

When used immediately, these iodo ketals readily substituted **2** (**R** = methyl or trityl) at *C*-2, successfully. The resultant ketals **13** and **14** were then hydrolyzed to the target ketones **15** and **16**. During such acid-catalyzed hydrolyses of **14**, besides liberating the ketone, the trityl group was also hydrolyzed to produce an unsubstituted imidazole (on *N*). In an independent alkylation, such an unsubstituted imidazole **16a** was readily alkylated to the trityl derivative **17a**.

Pertinent ^{1}H nmr spectral data on all of the compounds is assembled in Table 1. With close proximity of

the chemical shifts of imidazole ring protons, it was important to gather further information for definitive assignments. In that vein, nuclear Overhauser effects (nOe) were used to distinguish between the chemical shifts of H-4 and H-5 in **13a**. Irradiation of the *N*-methyl proton signal at 3.52 ppm caused enhancement of the H-5 signal of **13a** at 6.75 ppm (8.8%). Interesting anisotropic effects of the trityl group on some neighboring methylene proton resonances were observed (Table 1). Considerable upfield shifts are noted of these proton nmr signals when the *N*-methyl compounds were compared with their *N*-trityl counterparts.

EXPERIMENTAL

Melting points were determined on a MEL-TEMP or Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra (at 300 and 75.4 MHz, respectively) were obtained in deuteriochloroform using a Varian XL-300 spectrometer. Chemical shifts were recorded in ppm (δ) downfield from tetramethylsilane. For AA'BB' spin systems, the chemical shifis of A and B are reported as the centers of the two sets of complex multiplets. Pertinent ^1H nmr spectral data are listed in Table 1. Mass spectra were recorded on a Finnigan MAT 90 spectrometer at 150 eV and 190° source temperature.

All research chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, and were used as supplied, except 4,4'-dichlorobutyrophenone which was obtained from Lancaster Synthesis Inc., Windham, NH. In working up mixtures containing acetals (particularly when formed in anhydrous acidic media), the reaction is always poured into aqueous solutions of sodium bicarbonate (saturated) or carbonate solution (1 *M*) so as to maintain a *p*H of 8, or higher. The "usual" work-up procedure implies that the organic product is extracted into dichloromethane (unless stated otherwise), the extract washed with aqueous sodium bicarbonate or carbonate solution, then with brine, dried (sodium sulfate) and solvent(s) removed, *in vacuo* (20-30 Torr). For more complete drying, the sample was placed in high vacuum (<1 Torr, until a constant weight was obtained). Petroleum ether refers to that fraction boiling between 30-60°. Thin layer chromatograms (tlc) were run on silica gel coated aluminum plates with a fluorescent indicator purchased from Aldrich, or on "Baker" Si-HPF TLC plates from J. T. Baker Chemical Co., Phillipsburg, NJ. Aldrich grade 60 Å silica gel (200-400 mesh) was used for column chromatography. Whenever tlc indicated good separation of components, flash chromatography was used for separation. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN.

2-(4-Chlorophenyl)-2-(3-iodopropyl)-1,3-dioxolane (**12a**).

To a solution of 4,4'-dichlorobutyrophenone (**10a**, 9.5 g, 0.044 mole) in butanone (50 ml) was added sodium iodide (19.6 g, 0.13 mole). The stirred suspension was refluxed 3 hours, at which time the reaction was deemed to be complete (followed by ^1H nmr). The mixture was cooled and filtered. The filtrate was evaporated, *in vacuo*, and the residue partitioned between 1 *M* sodium carbonate (100 ml) and dichloromethane (100 ml). The dichloromethane layer was separated, treated with 1 *M* sodium carbonate (3 x 100 ml, until colorless), washed with brine (100 ml) and dried (sodium sulfate). The solvent was evaporated, *in vacuo*, to yield 4'-chloro-4-iodobutryophenone (**11a**) as an olive-tan solid, mp 67-69° (12.2 g, 90%); ms: CI (CH_4) m/z (relative intensity) 311 (34), 309 (100) [M+1], 181 (59) [M-I]. This product was immediately used in the next step.

A stirred mixture of **11a** (6.2 g, 0.02 mole), ethylene glycol (12.0 g, 0.19 mole) and 4-toluenesulfonic acid monohydrate (1.0 g, 0.005 mole) in benzene (125 ml) was refluxed (6 hours), with azeotropic removal of water. After cooling, the mixture was transferred to a separatory funnel and the lower acidic polar layer drawn. This polar fraction was washed several times with benzene and the combined benzene extract washed with 1 *M* sodium carbonate (2 x 100 ml), then with brine (100 ml) and was dried (sodium sulfate). The solvent was removed, *in vacuo*, to yield **12a** as an amber oil, (6.8 g, 97%). This unstable product was used immediately for lithiation-substitution.

1-(4-Chlorophenyl)-4-(1-methyl-2-imidazolyl)-1-butanone (**15a**).

A solution of 1-methylimidazole (1.64 g, 1.6 ml, 0.02 mole) in dry tetrahydrofuran (20 ml) was cooled to -40° under dry nitrogen. The imidazole was lithiated by slowly adding (10 minutes) a solution of butyllithium in hexane (8.0 ml, 2.5 *M*, 0.02 mole). The yellow solution was stirred at -40° for 15 minutes, and a solution of **12a** (6.8 g, 0.02 mole) in anhydrous tetrahydrofuran (20 ml) added dropwise, followed by an additional 2 hours of stirring at -40°. The solution was allowed to warm to room temperature and was quenched with 10 ml of saturated sodium bicarbonate. Solvents were removed, *in vacuo*, and the residue partitioned between dichloromethane (100 ml) and 1 *M* sodium carbonate (100 ml). The dichloromethane layer was separated, and washed with 1 *M* sodium carbonate (2 x 100 ml), brine (100 ml), dried (sodium sulfate) and removed. There was isolated 2-(4-chlorophenyl)-2-[3-(1-methyl-2-imidazolyl)propyl]-1,3-dioxolane (**13a**) as an amber oil, (6.2 g, 98%); tlc, R_f = 0.3 (dichloromethane-2-propanol saturated with ammonium hydroxide, 90:5:2). The ketal was hydrolyzed immediately to the ketone.

A stirred solution of **13a** (5.8 g, 0.019 mole) in 2 *N* hydrochloric acid (50 ml) and methanol (50 ml) was refluxed for 4.5 hours. Sufficient solid sodium carbonate was added to make the solution basic (*p*H 9.5) and the volume reduced by half, *in vacuo* (at 5 Torr). The mixture was filtered and was extracted with dichloromethane (3 x 100 ml). This extract was washed with brine (100 ml), dried (sodium sulfate) and the solvent removed, *in vacuo*, to yield an oil (4.9 g, 99%); tlc, R_f = 0.3 (ethyl acetate-methanol, 9:1).

Anal. Calcd. for $C_{14}H_{15}ClN_2O \cdot 0.25H_2O$: C, 62.92; H, 5.85; N, 10.48. Found: C, 63.00; H, 5.94; N, 10.51.

2-(4-Bromophenyl)-2-(3-iodopropyl)-1,3-dioxolane (**12b**).

A solution of 4'-bromo-4-chlorobutyrophenone (**10b**, 10.5 g, 0.04 mole) in butanone (100 ml) was reacted with sodium iodide (18.0 g, 0.12 mole) for 22 hours, as described above for the preparation of **11a**. There was isolated 4'-bromo-4-iodobutryophenone (**11b**, 14.3 g, 100%), mp 70°. This unstable iodide was immediately used for the next step.

A stirred mixture of **11b** (14.2 g, 0.04 mole), ethylene glycol (12.5 g, 0.20 mole), and 4-toluenesulfonic acid monohydrate

(2.5 g, 0.012 mole) in benzene (125 ml) was refluxed (5 hours), with water being removed as the azeotrope. After a similar work-up as for **12a**, there was isolated **12b** as a thick tan oil (14.3 g, 90%). This unstable iodide was immediately used for the next step.

1-(4-Bromophenyl)-4-(1-methyl-2-imidazolyl)-1-butanone (**15b**).

To a cold (-40°) solution of 1-methylimidazole (3.7 g, 0.045 mole) in dry tetrahydrofuran (40 ml), under a blanket of dry nitrogen was added, dropwise (10 minutes), a solution of 2.4 *M* butyllithium in hexane (16.7 ml, 0.042 mole). After the addition, the yellow solution was stirred at -40° for 15 minutes. A solution of **12b** (14.3 g, 0.036 mole) in anhydrous tetrahydrofuran (20 ml) was added dropwise. After stirring at -40° an additional 15 minutes, the solution was allowed to warm to room temperature and was quenched with saturated sodium bicarbonate (20 ml). The solvent was evaporated, *in vacuo*, and the residue worked up as for **13a** to furnish **13b** as an oil, (11.5 g, 92%); tlc R_f = 0.25 (dichloromethane-2-propanol saturated with ammonium hydroxide, 90:5:2).

Anal. Calcd. for $C_{16}H_{19}BrN_2O_2$: C, 54.71; H, 5.45; N, 7.98. Found: C, 54.96; H, 5.48; N, 7.92.

A solution of **13b** (11.5 g, 0.033 mole) in concentrated hydrochloric acid (10 ml), water (100 ml) and methanol (100 ml) was refluxed (3.5 hours). Sufficient 0.5 *M* sodium carbonate was added to adjust the *p*H of the solution to 9.5. The volume of the solution was reduced by one fourth, *in vacuo*. The aqueous phase was extracted with dichloromethane (3 x 100 ml), the extract washed with brine (100 ml), dried (sodium sulfate) and the solvent evaporated, *in vacuo*, to yield **15b** (oil, 9.1 g, 90%). Column chromatography of a sample (1.5 g) on silica gel (30 g), eluting with ethyl acetate-ethanol (23:2), provided an analytical sample of **15b** (1.2 g) which was recrystallized from ether-petroleum ether (2:1), mp 57-58°.

Anal. Calcd. for $C_{14}H_{15}BrN_2O$: C, 54.74; H, 4.92; N, 9.12. Found: C, 54.53; H, 4.88; N, 9.00.

2-(4-Fluorophenyl)-2-(3-iodopropyl)-1,3-dioxolane (**12c**).

4'-Fluoro-4-chlorobutyrophenone (**10c**, 10.0 g, 0.05 mole) was reacted (17 hours) with sodium iodide (22.5 g, 0.12 mole) in butanone (100 ml), as described for **10a**. There was isolated **11c** as a red oil (13.4 g, 95%), which was used immediately in the next step.

Ketalization of **11c** (13.3 g, 0.046 mole) with ethylene glycol (15.0 g, 0.25 mole) and 4-toluenesulfonic acid monohydrate (3.0 g, 0.02 mole) in benzene (200 ml) for 7.5 hours was performed as described for **12a**. There was obtained **12c** as an amber oil, (15.1 g, 99%). This unstable product was used immediately for the next reaction.

1-(4-Fluorophenyl)-4-(1-methyl-2-imidazolyl)-1-butanone (**15c**).

Lithiation-substitution was carried out as described for the synthesis of **13a**. From 1-methylimidazole (4.1 g, 4.0 ml, 0.05 mole), butyllithium in hexane (2.4 *M*, 20 ml, 0.05 mole) in dry tetrahydrofuran (100 ml), and subsequent reaction with **12c** (15.3 g, 0.046 mole) in anhydrous tetrahydrofuran (25 ml), there was obtained **13c** (13.0 g, 98%) as an amber oil.

Anal. Calcd. for $C_{16}H_{19}FN_2O_2 \cdot 0.25H_2O$: C, 65.18; H, 6.67; N, 9.50. Found: C, 65.39; H, 6.65; N, 9.08.

Immediate hydrolysis of **13c** (11.5 g, 0.040 mole) in 2 *N* hydrochloric acid (120 ml) and methanol (100 ml), as reported for **13a**, yielded an oil (quantitative), which crystallized from ether-petroleum ether (1:1), mp 54-55°.

Anal. Calcd. for $C_{14}H_{15}FN_2O \cdot 0.5H_2O$: C, 65.86; H, 6.32; N, 10.98. Found: C, 66.05; H, 6.40; N, 11.06.

2-(4-Chlorophenyl)-2-[3-(1-trityl-2-imidazolyl)propyl]-1,3-dioxolane (**14a**).

To a stirred solution of 1-tritylimidazole (**2**, 4.6 g, 0.015 mole) in anhydrous tetrahydrofuran (200 ml) was added, dropwise, a solution of butyllithium in hexane (7.5 ml, 2.0 *M*, 0.015 mole) over 5 minutes at -10 to -20° (dry nitrogen). After stirring this mixture (20 minutes) at this temperature, a solution of **12a** (5.2 g, 0.015 mole) in anhydrous tetrahydrofuran (50 ml) was added, dropwise (25 minutes). The mixture was stirred at -10 to 0° (3 hours), allowed to stand at 10° (4 hours) and then poured into a saturated aqueous sodium bicarbonate solution (30 ml). After the usual workup (methylene chloride), there was obtained a product which was recrystallized with petroleum ether-ethyl acetate to afford pure **14a** (3.4 g) as colorless needles, mp 172°. The mother liquor was evaporated, *in vacuo*, and the residue by chromatographed (silica gel, 180 g, eluted with petroleum ether-acetone, 3:2) to provide additional **14a** (2.0 g), the combined yield being 5.4 g (69%); tlc, R_f = 0.62 (petroleum ether-acetone, 3:2).

Anal. Calcd. for $C_{34}H_{31}ClN_2O_2$: C, 76.32; H, 5.84; N, 5.24. Found: C, 76.14; H, 5.91; N, 5.24.

1-(4-Chlorophenyl)-4-(2-imidazolyl)-1-butanone (**16a**).

A solution of **14a** (3.6 g, 0.007 mole) in methanol (100 ml) containing 80% acetic acid (3 ml) and concentrated hydrochloric acid (5 ml) was refluxed for 2 hours. Solvents were evaporated, *in vacuo*. The residue was diluted with water (100 ml) and concentrated hydrochloric acid (5 ml). Extraction with dichloromethane (2 x 100 ml) provided triphenylmethanol (1.46 g, 83%) as a colorless solid, mp 162-163°, identical to an authentic sample obtained from Aldrich Chemical Co. (mp 160-163°).

The *p*H of aqueous layer was adjusted to 8 by means of a saturated sodium bicarbonate solution. This mixture was extracted with dichloromethane (3 x 200 ml) and, after the usual workup, yielded colorless needles (1.52 g), which were recrystallized from ethyl acetate to furnish pure **16a** (1.45 g, 87%), mp 142°; tlc, R_f = 0.61 (dichloromethane-methanol, 9:1).

Anal. Calcd. for $C_{13}H_{13}ClN_2O$: C, 62.80; H, 5.27; N, 11.27. Found: C, 62.45; H, 5.32; N, 11.11.

1-(4-Chlorophenyl)-4-(1-trityl-2-imidazolyl)-1-butanone (**17a**).

To a cold solution (0-5°) of **16a** (86 mg, 0.36 mmole) and triethylamine (0.055 ml) in dichloromethane (10 ml) was added trityl chloride (101 mg, 0.36 mmole). After stirring at room temperature for 7 hours, the starting material had disappeared (tlc). The mixture was diluted with dichloromethane (40 ml) and washed with water (2 x 10 ml), and worked up as usual, to furnish a product which was chromatographed (silica, 20 g). Elution with dichloromethane-methanol (20:1, 120 ml) afforded pure **17a** (157 mg, 92%), mp 203.5-204.5°; tlc, R_f = 0.46 (dichloromethane-methanol, 20:1).

Anal. Calcd. for $C_{32}H_{27}ClN_2O \cdot 0.5H_2O$: C, 76.86; H, 5.64; N, 5.60. Found: C, 76.91; H, 5.42; N, 5.56.

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