Synthesis of Aryl ω-(1-Methyl-5-imidazolyl and 1*H*-5-Tetrazolyl)alkyl Ketones [1]

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Successful syntheses of 2,4-dichlorophenyl 2-(1-methyl-5-imidazolyl)ethyl and 2,4-dichlorophenyl 3-(1-methyl-5-imidazolyl)propyl ketones are described. In addition, syntheses of 2,4-dichlorophenyl and 4-chlorophenyl 3-(1-methyl-1*H*-5-tetrazolyl)propyl ketones are reported.

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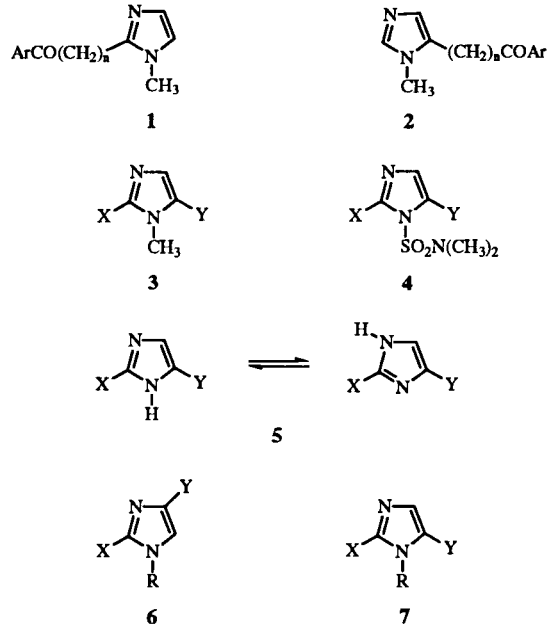
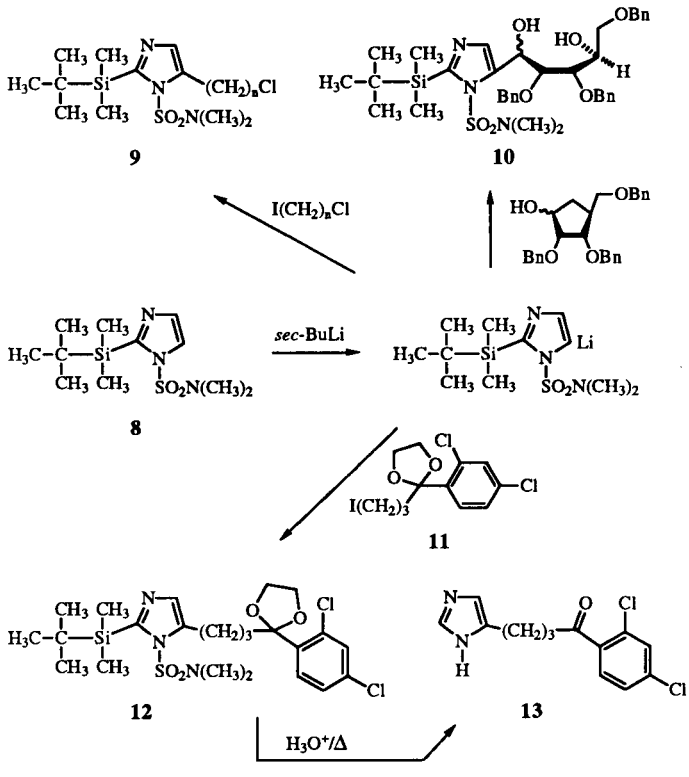
Diverse approaches were utilized in our Laboratory to synthesize a number of aryl ω-(1-methyl-2-imidazolyl)alkyl ketones **1** (n = 1 to 4). Literature methods, such as the acylation of 1,2-dimethylimidazole [2], were used for the preparation of the ketone in which one methylene group separates the 1-imidazolyl group from the aromatic ketone. Lithiation of 1-methylimidazole and 1,2-dimethylimidazole followed by substitution by an ω-iodoalkyl ketal furnished the next higher homologs **1** (n = 3 or 4) [3,4]. A Claisen-Schmidt condensation of a 1-methyl-2-imidazolecarboxaldehyde with an acetophenone, followed by hydrogenation of the alkene gave rise to the ketone in which 2 methylene groups separate the aryl ketone from imidazole [5].

Entirely different approaches were needed to prepare the corresponding aryl ω-(1-methyl-5-imidazolyl)alkyl ketones **2**. An attractive route appeared to be the one which would start with 1-methylimidazole bearing a "protective" group at C-2, such as a trialkylsilyl, sulfide or carboxylic acid, summarized by general structure **3**, Y = H, and X = SiR_3, [6], SR, [7], CO_2H [8]. Such 1,2-disubstituted imidazoles would lithiate at C-5, **3** (Y = Li) and be substituted by aldehydes, ketones, esters, amides and alkyl halides introducing group Y [C(OH)CRR', CHO or CH_2R] at C-5 in **3** [9,10]. Removal of the protective group X would in effect produce an 1,5-disubstituted imidazole.

Attempts to apply such a synthetic scheme to convert 1-methylimidazole *via* a 1-methyl-2-protected imidazole, first to a 1-methyl-2-protected-5-substituted imidazole and then to a 1,5-disubstituted imidazole, are frequently fraught with problems. The first step can alreadybe a problem. Lithiation of 1-methylimidazole (**3**, X = Y = H) followed byreaction with a trialkylsilyl halide already produces a mixture of 2- and 2,5-disilylated products [6]. Also a 2-trialkylsilylimidazole tends to be a relative labile entity and has been shown that upon further lithiations has the silyl group "dance" to position 5 and unexpected products are obtained [11-13]. By contrast, some cognate syntheses starting from an 1-protected imidazole will proceed well to a 1,2-di-protected-5-substituted imidazoles which can be converted to 1-protected-5-substituted imidazole [9]. Some of these transformations were remarkably successful when the ring *N*-substituent is a removable one, like, CH_2OR, CH_2NR_2, $C(C_6H_5)_3$, $SO_2N(CH_3)_2$, instead of a permanent one, like CH_3. However, removal of the *N*-protective groups from *N*-1 and C-2 from such a 1,2,5-trisubstitutedimidazole **4** leads to a 4(5)-*N*-unsubstituted imidazole **5**. It is well documented [10] that methylation of tautomeric **5** leads primarily to an 1-methyl-4-substituted **6** and *not* 5-substituted imidazole **7**. Some recent examples attest to this mode of alkylation [14-16].

1-(*N,N*-Dimethylsulfamoyl)imidazole (**4**, X = Y = H) has been shown to be a useful and reliable starting material which can be converted by lithiation-substitutions, first to a 1,2-disubstituted imidazole **4** (Y = H). A further lithiation-substitution can lead to a 1,2,5-trisubstituted imidazole. Now, if the 2-substituent in such a tri-substituted imidazole is removable, deprotection yields a 1,5-disubstituted imidazole **4** (X = H) [17]. 1-(*N,N*-Dimethylsulfamoyl)-2-[(*tert*-butyldimethyl)silyl]imidazole (**8**), is a proven and useful intermediate. The bulky *N*- and *C*-2 substituents did not seem to impede the introduction of a large group at *C*-5. For example, after lithiation of **8** at *C*-5,

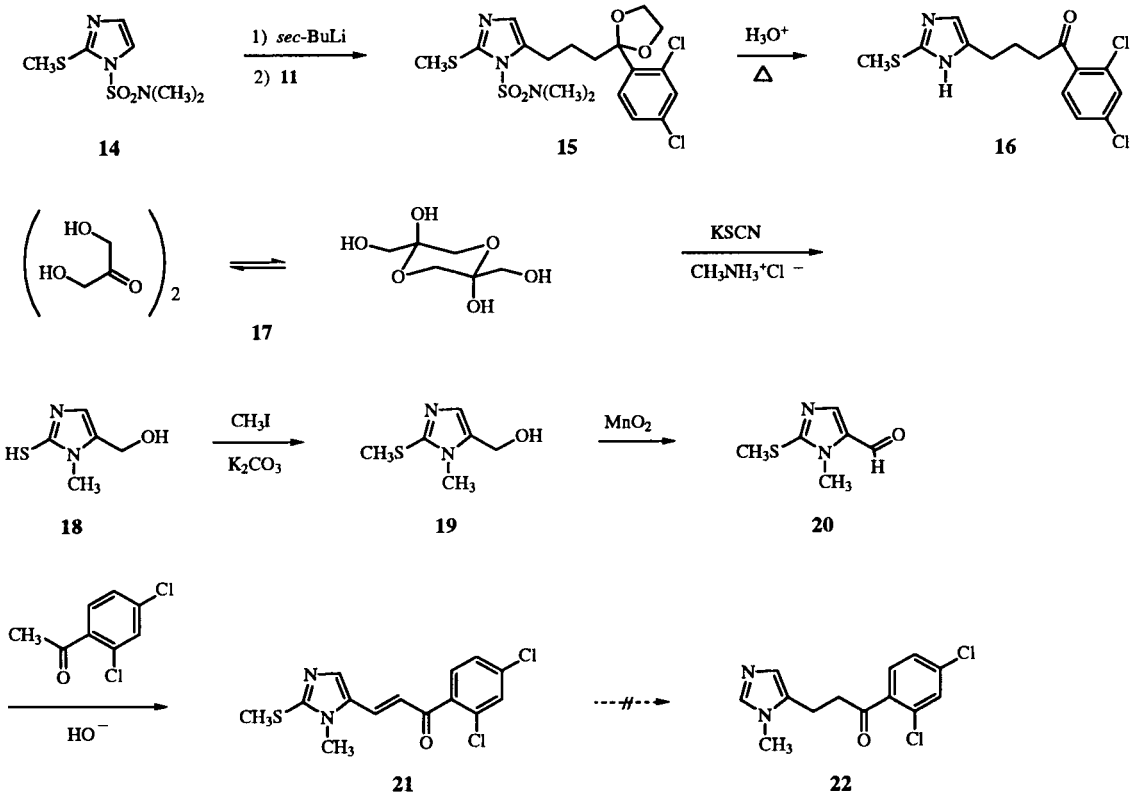




have found that **8** also reacted with the iodo ketal **11** to furnish **12**, which after complete hydrolysis yielded **13**, albeit in only 13% overall yield from **8**. However, when 1-methylimidazole was lithiated, and then substituted by **11**, followed by acid hydrolysis, none of the required ketone **2** (n =3) was obtained.

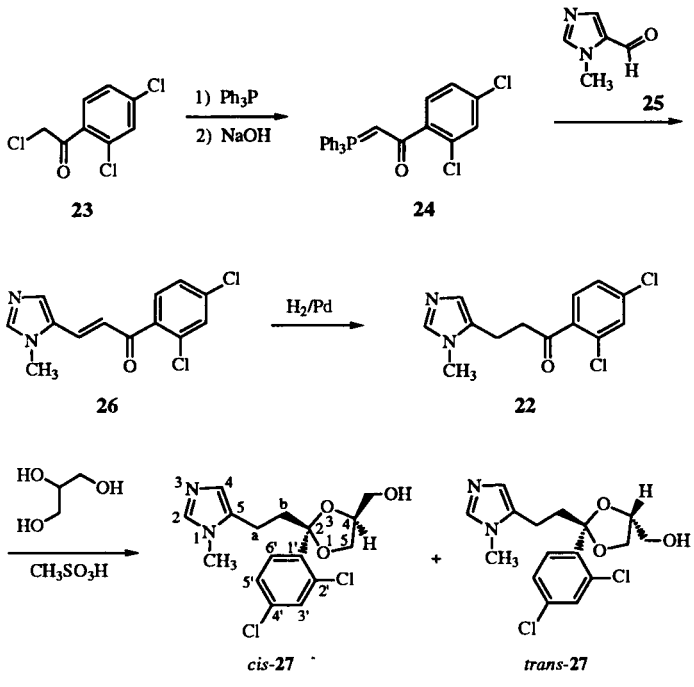
In a related sequence, and using a sulfide as the *C*-2 protective group, 1-(*N*,*N*-dimethylsulfamoyl)-2-(methylthio)]imidazole (**14**) was reacted with *sec*-butyllithium and then with iodo ketal **11** to yield **15** (30%). Hydrolysis of **15** provided **16** in 78% yield. Attempts to utilize 1-methyl-2-(methylthio)imidazole (**3**, X = SMe, Y = H) [7] in a similar reaction sequence led to different results. Already in the reaction with butyllithium there was obtained starting 1-methyl-2-(methylthio)imidazole and an unidentified new compound. Therefore this sequence was abandoned.

Methods to prepare 1,5-disubstituted imidazoles from aliphatic precursors were screened. The Marckwald type of synthesis [20-25] lends itself well to the construction of an 1-alkylimidazole bearing a one-carbon substituent at *C*-5. The starting material is dihydroxyacetone (**17**), in equilibrium with its dimer [26-28] which reacts with potassium thiocyanate and methylamine hydrochloride to furnish 1-methyl-2-mercapto-5-hydroxymethylimidazole (**18**) [29]. Methylation proceeds as expected to yield the thioether **19**



reaction with ω-chloroalkyl iodides generated **9** [18] and with 2,3,5-tri-*O*-benzyl-D-ribose provided **10** [19]. We [33] which was oxidized by manganese dioxide to the aldehyde **20**, as also described in a recent paper [25]. Claisen-

Schmidt condensation with 2,4-dichloroacetophenone proceeded well to afford the α,β-unsaturated ketone **21**. Attempts to reduce the alkene catalytically failed and is attributed to the presence of the sulfide group. Attempts top remove the sulfide group first by Raney-nickel desulfurization of **21** yielded a mixture which contained a very small quantity of the target ketone **22**, admixed with mono- and di-dechlorinated ketones. In essence, experiments to convert **21** to **22** were abandoned.



Desulfurization of **18** either by nitric acid oxidation [23] or Raney-nickel desulfurization using the method of Corelli *et al.* [34] provided 1-methyl-5-hydroxymethylimidazole which was oxidized by manganese oxide to the known aldehyde **25** [35]. Claisen-Schmidt condensation of **25** with 2,4-dichloroacetophenone gave a hopeless mixture and this approach was abandoned in favor of a Wittig reaction. The reaction of triphenylphosphine with 2,4-dichlorophenacyl chloride (**23**) led to a phosphonium salt which was neutralized to provide the Wittig ylide **24**. Condensation of **24** with **25** furnished the α,β-unsaturated ketone **26** which was smoothly reduced to **22**. Condensation of **22** with glycerol, catalyzed by methanesulfonic acid [36], gave a mixture of cis and trans ketals **27**. A large amount of *cis*-**27** could be crystallized from the mixture. However, *trans*-**27** was obtained pure only after the mixture of *cis* and *trans* **27** was converted to a mixture of *cis* and *trans benzoates*, which were separated by column chromatography on silica gel. Hydrolysis of the *trans*-benzoate provided pure *trans*-**27**. The structure of the isomers was determined using standard ^{1}H, ^{13}C, nOe, HMBC and HMQC nmr experiments and followed the approaches described by us in previous papers [4,36,48].

To synthesize the next homologous ketones **32** and **33**, in which three methylene group separate the 5-imidazolyl group from the aromatic ketone, the van Leusen synthesis of imidazoles was used. In essence, this approach utilized dipolar cycloaddition of the active methylene anion of 4-toluenesulfonylmethyl isocyanide to an *N*-substituted imine [37-44]. The availability of the nitrile ketals **28** and **29** [4] made this route an attractive one. Reduction of the nitrile with diisobutylaluminum hydride yielded, upon a

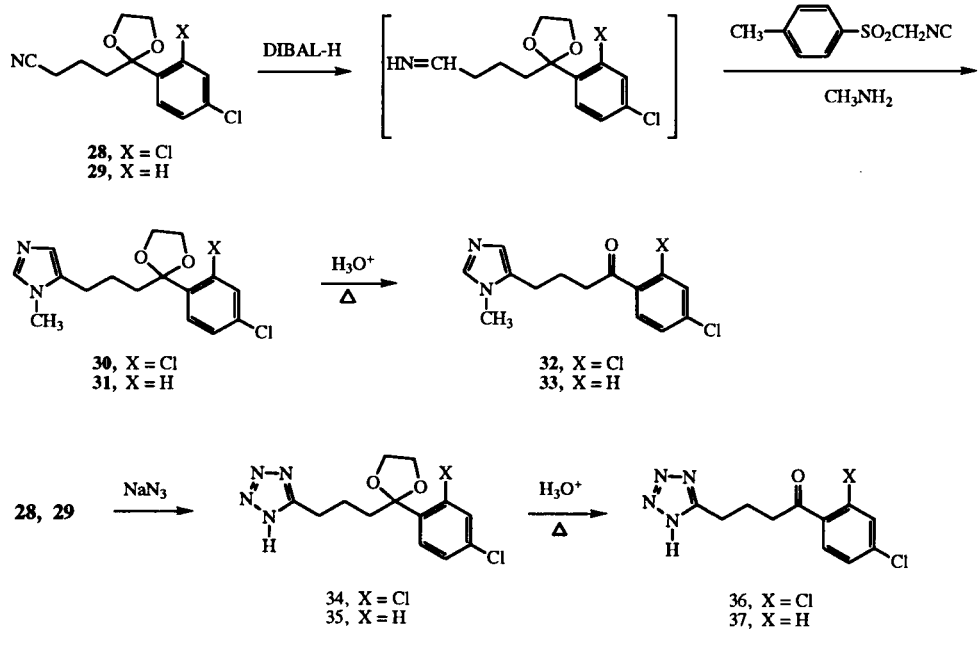


Table 1

Selected Carbon-13 Chemical Shifts of Azolyl-[$(CH_2)_a$-$(CH_2)_b$-$(CH_2)_c$]-Ketals *or* Ketones and Related Compounds [a,b,c]

	Azolyl				Alkyl Spacers			1,3-Dioxolanes				
Compound	C-2	C-4	C-5	*N*-Me	$(CH_2)_a$	$(CH_2)_b$	$(CH_2)_c$	C-2	C-4	C-5	CH_2-OR at C-4	C=O
15	147.0	126.9	134.5	-	36.9	22.0	38.3	109.7	64.6	64.6	-	-
16	140.6	119.1	137.2	-	26.0	23.6	41.9	-	-	-	-	202.0
22	136.9	125.2	129.8	30.5	17.5	-	40.4	-	-	-	-	199.2
29	-	-	-	-	19.8	17.0	38.8	109.3	64.5	64.5	-	-
32 [d]	-	-	-	31.0	22.9, 22.3		41.5	-	-	-	-	201.1
33	137.6	126.4	131.0	31.1	23.1, 22.3		37.2	-	-	-	-	198.2
35	-	-	156.3	-	23.1, 21.3		36.2	109.2	64.5	64.5	-	-
36 [e]	-	-	155.7	-	22.5, 21.6		38.9	109.0	64.3	64.3	-	-
37 [e]	-	-	155.5	-	22.0, 21.3		41.0	-	-	-	-	201.0
38 [e]	-	-	155.6	-	22.1, 21.4		37.0	-	-	-	-	198.3
cis-**27** [f]	137.3	125.4	131.5	31.2	17.8	-	35.9	109.5	76.5	66.4	62.4	-
trans-**27** [f]	137.0	125.0	131.2	31.0	17.6	-	36.4	109.3	78.1	67.4	62.2	-
cis-**27** Benzoate [d]	-	-	-	31.4	17.6	-	35.5	109.8	73.5	66.2	64.3	166.1
trans-**27** Benzoate [d]	-	-	-	31.4	17.7	-	36.5	109.9	75.4	66.3	62.8	165.9

[a] Spectra determined in deuteriochloroform and shifts are reported in ppm (δ) downfield from tetramethylsilane. Assignments are primarily by analogy with chemical shifts reported for very similar compounds in refs 4,36. Relatively close chemical shifts may be interchangeable. [b] Azolyl is either 1-methyl-5-imidazolyl or 1*H*-5-tetrazolyl. [c] Benzenoid chemical shifts are not listed in general. [d] No attempts were made to identify the chemical shifts of imidazole from aromatic ring carbons. [e] Spectrum taken in deuteriodimethyl sulfoxide. [f] In *cis*-**27**, (Ar is 2,4-dichlorophenyl), the chemical shifts of the aromatic ring carbons are assigned unequivocally, as follows: 137.1 (C-1'), 132.7, C-2'), 131.2 (C-3'), 134.6 (C-4'), 126.9 (C-5'), 129.6 (C-5'); In *trans*-**27**, (Ar is 2,4-dichlorophenyl), the chemical shifts of the aromatic ring carbons are assigned unequivocally, as follows: 138.0 (C-1'), 132.3 (C-2'), 130.8 (C-3'), 134.3 (C-4'), 126.6 (C-5'), 129.1 (C-5').

Table 2

Selected Proton Chemical Shifts of Azolyl-[$(CH_2)_a$-$(CH_2)_b$-$(CH_2)_c$]-Ketals *or* Ketones and Related Compounds [a,b]

	Azolyl			Alkyl Spacers			1,3-Dioxolane		
Compound	H-2	H-4	N-Me	$(CH_2)_a$	$(CH_2)_b$	$(CH_2)_c$	H-4	H-5	CH_2-OR at C-4
13	7.58	6.79	-	2.70	2.06	2.97	-	-	-
15	-	6.72	-	2.73	1.71	2.19	3.78, 4.05		-
16	-	6.79	-	2.69	2.03	2.97	-	-	-
22	7.35	6.74	3.57	2.93	-	3.29	-	-	-
29	-	-	-	2.38	1.74	2.00	3.76, 4.02		-
32	7.38	6.78	3.57	2.64	2.04	3.02	-	-	-
33	7.39	6.80	3.58	2.65	2.07	3.04	-	-	-
35	-	-	-	3.15	1.95	2.20	3.80	4.09	-
36 [c]	-	-	-	2.88	1.70	1.91	3.69, 3.99		-
37 [c]	-	-	-	2.98	2.06	3.07	-	-	-
38 [c]	-	-	-	2.97	2.06	3.15	-	-	-
cis-**27**	7.36	6.75	3.52	2.63	-	2.43	4.12	3.86, 3.93	3.68
trans-**27**	7.31	6.67	3.51	2.59	-	2.37	4.38	3.60, 4.25	3.46, 3.58
cis-**27** Benzoate	7.82	6.89	3.43	2.65	-	2.43	4.12	3.89, 4.05	4.45, 4.66
trans-**27** Benzoate	7.75	6.87	3.55	2.63	-	2.40	4.58	3.77, 4.22	4.33, 4.48

[a] Spectra determined in deuteriochloroform and shifts are reported in ppm (δ) downfield from tetramethylsilane. [b] Azolyl is either 5-imidazolyl or 1*H*-5-tetrazolyl, and the ketal is a 1,3-dioxolane. [d] Spectrum taken in deuteriodimethyl sulfoxide.

mildly acidic aqueous workup, amorphous substances which defied both purification and characterization. It was eminently clear that these products were devoid of an aldehyde group (lack of nmr signals around δ 7.5-8.0 in the ^1H, and around δ 180 in the ^{13}C nmr spectra). It is conceivable that these imines polymerized to either a long chain or cyclic aminal [42]. These masked imines decomposed upon column chromatography and yielded new substances (^1H nmr). One of these substances is presumed to be a polymer of the expected aldimine, which had to be in the form of an aminal. Apparently, this new substance underwent amine exchange with methylamine, since upon reaction with methylamine in methanol containing 4-toluenesulfonylmethyl isocyanide formed the expected 1-methylimidazolyl ketals **30** and **31**. Therefore, these amorphous substances were capable of trans-imination with methylamine and condense with 4-toluenesulfonylmethyl isocyamide to form imidazoles **30** and **31**. Acid

hydrolysis of these ketals furnished the expected imidazolyl ketones **32** and **33** in about 30% yield, each from **28** and **29**.

The availability of these ketal nitriles **28** and **29** provided a chance to synthesize tetrazole ketones **36** and **37**. Reaction of **28** and **29** with sodium azide in DMF [44,45] led to the ketal tetrazoles **34** and **35** which underwent acid-catalyzed hydrolysis to form **36** and **37**.

EXPERIMENTAL

Research chemicals and solvents were purchased from the Aldrich Chemical Co., Milwaukee, WI, except for a 33% solution of methylamine in ethanol (8.03 *M*), which was purchased from Fluka Chemical Corp., Ronkonkoma, NY. Petroleum ether refers to that fraction boiling between 30-60°. All reagents or solvents were used, as supplied. Thin layer chromatograms (tlc) was run on silica gel (impregnated with a 254 nm fluorescent indicator) on glass, layer thickness 250μm, particle size <60μm, pore size 60Å (Aldrich). Spots were visualized by iodine vapor and short wave uv light. Column chromatography was carried out on Aldrich silica gel (grade 60, 200-400 mesh). Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Evaporation or distillation of solvents, *in vacuo*, implies their removal by means of a rotary evaporator at the water pump (20-30 torr) at the lowest possible temperature. The majority of the reactions were followed by tlc and judged complete when the starting material ceased to appear as a visible spot on tlc plates. When tlc data were inconclusive in judging the progress of a reaction, small samples were retrieved periodically, worked up minimally to obtain a ^{1}H nmr spectrum. In working up mixtures containing acetals, the reaction is always poured into a saturated aqueous sodium bicarbonate solution so as to maintain a *p*H of 8, or higher. Unless the product was acidic, the "usual" work-up procedure consisted of extracting the organic product into dichloromethane or ethyl acetate. The extract was washed with saturated aqueous sodium bicarbonate solution, then with brine, dried (sodium sulfate) and the solvent(s) removed, *in vacuo*. The product was either crystallized or purified by column chromatography. Analytical samples were dried (50-70° at 1 torr) by the laboratory (Midwest Microlab, Indianapolis, IN) prior to microanalysis.

The ^{1}H and ^{13}C nmr spectra and NOE nmr experiments were run on a Varian XL-300 spectrometer in deuteriochloroform at 300 and 75.4 MHZ, respectively. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane. Signals are designated as singlets (s), doublets (d), triplets (t), multiplets (m), if broad, by br. Nmr assignments for benzenoid atoms are abbreviated to Ar, those imidazole by Im. Heteronuclear Multiple-Quantum Correlation (HMQC) and Heteronuclear Multiple-Bond Connectivities (HMBC) nmr spectra were obtained from a GE Omega 500 MHz instrument, using standard programs.

1-(2,4-Dichlorophenyl)-3-[4(5)-imidazolyl]-1-butanone (**13**).

Under a blanket of nitrogen, at -78°, there was added dropwise a 2.5 *M* solution of butyllithium solution in hexanes (1.32 ml, 3.3 mmoles) to a stirred solution of 1-(*N,N*-dimethylsulfamyl)-imidazole [47] (525 mg, 3.0 mmoles) in dry tetrahydrofuran (8 ml). After 20 minutes, *tert*-butyldimethylsilyl chloride (1 *M* solution in tetrahydrofuran, 3.3 ml, 3.3 mmoles) was added. Stirring was continued at -78° for 20 minutes and then at room temperature for 1 hour. The mixture was cooled to -78° and treated dropwise with butyllithium in hexanes (2.5 *M*, 1.44 ml, 3.6 mmoles). After 30 minutes, 2-(2,4-dichlorophenyl)-2-(3-iodopropyl)-1,3-dioxane [48] was added and the mixture was allowed to warm to and remain at room temperature (12 hours). Usual workup, and using ethyl acetate as extraction solvent, provided crude **12** as a brown gum (1.04 g), which was immediately hydrolyzed. A solution of this crude product in methanol (15 ml) containing 2 *N* hydrochloric acid (15 ml) was refluxed (3 hours). Most solvents were removed, *in vacuo*. The residue was extracted with ethyl acetate to remove impurities. The aqueous solution was neutralized by sodium bicarbonate, and extracted with dichloromethane. Usual workup provided **13** as a yellowish gum (98 mg, 13%), after column chromatography (eluted with dichloromethane-methanol, 10:1).

Anal. Calcd. for $C_{13}H_{12}Cl_2N_2O$: C, 55.14; H, 4.27; N, 9.89. Found: C, 55.12; H, 4.32; N, 9.65.

2-(Methylthio)-1-(*N,N*-dimethylsulfamyl)imidazole (**14**).

At -78° (nitrogen), a solution of a 2.5 *M* solution of butyllithium in hexanes (25.2 ml, 63 mmoles) was added dropwise (10 minutes) to a stirred solution of the 1-(*N.N*-dimethylsulfamyl)imidazole [47] (10.5 g, 60 mmoles) in dry tetrahydrofuran (100 ml). Lithiation was allowed to proceed at this temperature (30 minutes), and then methyl disulfide (5.67 ml, 63 mmoles) was added slowly. After 1 hour at -78°, the mixture was allowed to warm to room temperature (5 hours). The usual workup (ethyl acetate) provided a brown solid (13.6 g). Chromatography (dichloromethane) furnished a slightly yellow solid (10.9 g, 82%), which was recrystallized from ethyl acetate-petroleum ether (1:5) to form colorless prisms (9.5 g), mp 66-67°; ^{1}H nmr: δ 2.61 (s, SMe), 2.92 (s, NMe), 6.98 (d, J = 1.5 Hz, Im H-4), 7.26 (d, J = 1.5 Hz, Im H-5). The assignment of Im H-4 and H-5 was based on a subsequent lithiation experiment with butyllithium at -78°, when after quenching with deuterium oxide produced a product devoid of a signal at δ 7.26, indicative that H-5 underwent proton-deuterium exchange; ^{13}C nmr: δ 15.1 (SMe), 38.6 (NMe), 120.9 (Im C-4), 128.5 (Im C-5), 145.7 (Im C-2).

Anal. Calcd. for $C_6H_{11}N_3O_2S_2$: C, 32.56; H, 5.01; N, 18.99. Found: C, 32.56; H, 4.91; N, 18.76.

2-(2,4-Dichlorophenyl)-2-[3-(1-*N,N*-Dimethylsulfamyl)-2-(methylthio)-5-imidazolyl)propyl]-1,3-dioxolane (**16**).

To a stirred solution of **14** (2.21 g, 10.0 mmoles) in anhydrous tetrahydrofuran (30 ml) and 1,2-dimethoxyethane (30 ml) at -78° (nitrogen) there was added, dropwise (5 minutes), *sec*-butyllithium in cyclohexane (1.3 *M*, 8.46 ml, 11.0 mmoles). After stirring at -78° for 1 hour, there was added a solution of **11** [48] (4.06 g, 10.5 mmoles) in a 1:1 mixture of of tetrahydrofuran and 1,2-dimethoxyethane (10 ml). After 12 hours at room temperature and 2 hours at reflux, the mixture was quenched with a saturated bicarbonate solution (40 ml). The major solvents were removed and then extracted with ethyl acetate. Usual workup of the organic layer produced a brown gum (5.12 g). Chromatography and elution with ethyl acetate-petroleum ether (1:10) furnished first unreacted **11** (848 mg) and then, with ethyl acetate-petroleum ether (1:5) an unidentified mixture (726 mg). Further elution with ethyl acetate-petroleum ether (1:1) gave pure **15** (1.04 g, 22%) as a gum, and a mixture of **15** and **14** (*ca.* 1.5:1, 568 mg), as well as some pure **14** (1.08 g).

The hydrolysis of **15** (240 mg, 0.5 mmole) was conducted in boiling methanol (8 ml) containing 2 *N* hydrochloric acid (6 ml) for 4 hours. Solvents were removed, *in vacuo*. The mixture was

neutralized by sodium bicarbonate solution and extracted with ethyl acetate. After usual workup, a brown gum (193 mg) was chromatographed and **16** was eluted with ethyl acetate-methanol (10:1) as a gum (129 mg, 78%).

Anal. Calcd. for $C_{14}H_{14}N_2OSCl_2$: C, 51.07; H, 4.29; N, 8.51. Found: C, 50.97; H, 4.33; N, 8.21.

1-Methyl-2-methylthio-5-hydroxymethylimidazole (**19**).

A suspension of 18 [23] (1.0 g, 6.9 mmole), potassium carbonate (0.57 g, 4.1 mmoles) iodomethane (0.64 ml, 10.4 mmoles) in dry methanol (8 ml) was stirred at room temperature for 1 hour. A precipitate was separated by filtration, the solid washed with methanol (5 ml) and the filtrate concentrated, *in vacuo*. The residue was chromatographed on silica gel (15 g) and the product eluted by chloroform-methanol (97:3). The colorless solid (0.81 g, 74%) was recrystallized from petroleum ether, mp 85-86°; tlc, R_f = 0.49 (chloroform-methanol, 9:1); ^1H nmr: δ 2.53 (s, SMe), 3.60 (s, NMe), 4.53 (s, CH_2OH), 6.75 (s, Im H-4); ^{13}C nmr: δ 15.9 (SMe), 30.7 (NMe), 54.1 (CH_2OH), 127.4 (Im C-4), 133.3 (Im C-5), 144.1 (Im C-2).

Anal. Calcd. for $C_6H_{10}N_2OS$: C, 45.55; H, 6.37; N, 17.70. Found: C, 45.51; H, 6.36; N, 17.77.

1-Methyl-2-methylthio-5-imidazolecarboxaldehyde (**20**).

Method A.

A suspension of **19** (0.5 g, 3.16 mmoles) and activated manganese(IV) oxide (1.92 g, 22.15 mmoles) in chloroform (15 ml) was refluxed for 18 hours. The reaction mixture was cooled to room temperature and filtered through Celite. The combined filtrate and washings were evaporated *in vacuo* to furnish colorless **20** (0.46 g, 95%), mp 63-65°, which can recrystallized from ethyl acetate-petroleum ether; tlc, R_f = 0.47 (chloroform-methanol, 97:3); ^1H nmr: δ 2.72 (s, SMe), 3.83 (s, NMe), 7.73 (s, Im H-4), 9.59 (s, CHO); ^{13}C nmr: δ 14.4 (SMe), 32.5 (NMe), 133.2 (Im C-5), 143.6 (Im C-4), 153.8 (Im C-2), 177.8 (CHO).

Anal. Calcd. for $C_6H_8N_2OS$: C, 46.14; H, 5.16; N, 17.93. Found: C, 46.16; H, 5.18; N, 17.90.

Method B.

To a stirred suspension of pyridinium dichromate (16.6 g, 44 mmoles) in dichloromethane (50 ml) at room temperature was added **19** (2.0 g, 1.26 mmoles). After 3 hours, the black reaction mixture was filtered through Celite, washed with ethyl acetate, and the filtrate evaporated *in vacuo*. Column chromatography on silica gel (10 g) and elution with chloroform: methanol (97:3) furnished pure **20** (0.86 g, 44%), identical to the product made by Method A.

1-(2,4-Dichlorophenyl)-3-(1-methyl-2-methylthio-5-imidazolyl)-2-propen-1-one (**21**).

To a solution of the 2,4-dichloroacetophenone (10.42 g, 0.055 mole) and **20** (8.6 g, 0.055 mole) in absolute ethanol (200 ml) at room temperature was added a catalytic quantity of sodium hydroxide (3-4 pellets) and the mixture was stirred for 1 hour under nitrogen. The product was collected by filtration, washed with ethanol and then, with water. The solid was recrystallized from acetone-petroleum ether and dried at 65° (20 hours) to provide **21** as yellow crystals (3.76 g, 76%), mp 145-146°; tlc, R_f = 0.70 (chloroform-methanol, 97:3); ^1H nmr: δ 2.68 (s, SMe), 3.62 (s, NMe), 6.95, 7.40 (two d, *trans*-alkene, J = 15.9 Hz), 7.33 (dd, Ar H-5, J = 2.1, 8.4 Hz), 7.44 (d, Ar H-6, J = 8.4 Hz), 7.46 (d, Ar H-3, J = 2.1 Hz), 7.58 (s, Im H-4); ^{13}C nmr: δ 15.1 (SMe), 31.4 (NMe), 121.4, 127.3, 130.2, 130.3, 130.5, 130.7, 132.2, 134.4, 137.0, 137.6, 149.8 (alkene, Ar and Im), 191.1 (C=O).

Anal. Calcd. for $C_{14}H_{12}Cl_2N_2OS$: C, 51.39; H, 3.70; N, 8.56. Found: C, 51.23; H, 3.66; N, 8.70.

1-Methyl-5-hydroxymethylimidazole.

Method A.

To a solution of **18** (10.2 g, 0.0708 mole) in ethanol (400 ml) at room temperature was added a slurry of Ra-Ni (50 g) with the aid of additional ethanol (100 ml). After stirring at room temperature for 0.5 hour, the mixture was filtered through Celite, evaporated to dryness, *in vacuo*, to furnish 1-methyl-5-hydroxymethylimidazole (4.70 g, 59%) of a colorless solid, mp 112-114°, lit [23] mp 112.5-114°.

Using the method of Dener *et al.*, [23], it was possible to convert **18** to 1-methyl-5-hydroxymethylimidazole in 43% yield.

(2,4-Dichlorophenacyl)triphenylphosphorane (**24**).

2,2',4'-Trichloroacetophenone (60.0 g, 0.26 mole) was added in portions to a solution of triphenylphosphine (65.0 g, 0.24 mole) in dry toluene (220 ml). The mixture was refluxed for 2.5 hours, cooled and diluted with ethyl acetate (60 ml). After 12 hours, (2,4-dichloroaphenacyl)ltriphenylphosphonium chloride was filtered, washed with ethyl acetate and recrystallized from dichloromethane. After drying at 65° (4 hours), the *salt* weighed 112 g (93%), mp 208-210°; ^1H nmr: δ 6.57 (d, CH_2P, $^2J_{P,H}$ = 12.1 Hz), 7.55-8.85 (m, Ar); ^{13}C nmr: δ 41.1 (d, CH_2P, $^1J_{P,C}$ = 233.9 Hz), 191.8 (d, C=O, $^2J_{P,C}$ = 20.5 Hz).

A stirred suspension of the *salt* in toluene (700 ml) and water (700 ml) was treated with aqueous sodium hydroxide solution until *p*H of 9 was reached. After stirring 30 minutes at room temperature, the toluene layer was separated, washed with water (3 x 300 ml), dried and concentrated, *in vacuo* to give a yellow oil (108 g). After triturating with chloroform and petroleum ether, the solvents were decanted and the colorless product was dried, *in vacuo*, to provide **24** (91.79 g, 88%), mp 139-141°. The product was recrystallized from chloroform-petroleum ether; tlc, R_f = 0.51 (chloroform-methanol, 93:7); ^1H nmr: δ 4.10 (d, 1H, CH=P, $^2J_{P,H}$ = 24.8 Hz), 7.16-7.76 (m, 18H, Ar); ^{13}C nmr: δ 55.64 (d, CH=P, $^1J_{P,C}$ = 422.6 Hz), 184.0 (d, C=O, $^2J_{P,C}$ = 14.3 Hz).

Anal. Calcd. for $C_{26}H_{19}Cl_2OP$: C, 69.50; H, 4.26. Found: C, 69.36; H, 4.24.

1-(2,4-Dichlorophenyl)-3-(1-methyl-5-imidazolyl)-2-propen-1-one (**26**).

A mixture of **24** (65.0 g, 0.145 mole) and aldehyde **25** [23] (8.0 g, 0.072 mole) was refluxed in toluene (400 ml) for 9 days. After removing the solvent *in vacuo*, the residue (78 g) was triturated with dichloromethane and petroleum ether. After 24 hours, a solid (38 g) crystallized which was chromatographed several times on silica gel (600 g). Elution with chloroform-methanol (99:1) produced **26** as a yellow solid (17.62 g, 88%), mp 110-113°; tlc, R_f = 0.41 (chloroform-methanol, 93:7); ^1H nmr: δ 3.75 (s, NMe), 6.99, 7.46 (two d's, CH=CH, J = 15.9 Hz), 7.35 (dd, Ar H-5, J = 2.1, 8.4 Hz), 7.47 (d, Ar H-6, J = 8.4 Hz), 7.48 (d, Ar H-3, J = 2.1 Hz), 7.58 (s, Im H-2 and 4); ^{13}C nmr: δ 32.5 (NMe), 122.9, 127.4, 128.9, 130.2, 130.5, 130.6, 132.3, 134.2, 137.2, 137.4, 141.9 (alkene, Ar and Im), 191.1 (C=O).

Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O$: C, 55.54; H, 3.59; N, 9.96. Found: C, 55.47; H, 3.64; N, 9.69.

1-(2,4-Dichlorophenyl)-3-(1-methyl-5-imidazolyl)-1-propanone (**22**).

A suspension of **26** (3.76 g) in ethanol (200 ml) containing 5% platinum on charcoal (5.5 g) was hydrogenated at 50 psi (3 hours). The mixture was filtered through Celite and solvents were evaporated, *in vacuo*. The product (3.36 g) was chromatographed on silica gel (40 g) and was eluted by chloroform-methanol (99:1) to provide **22** as a colorless solid (2.8 g, 77%), after crystallization from petroleum ether, mp 78-80°; tlc, R_f = 0.33 (chloroform-methanol, 93:7).

Anal. Calcd. for $C_{13}H_{12}Cl_2N_2O$: C, 55.14; H, 4.27; N, 9.89. Found: C, 55.38; H, 4.53; N, 9.58.

cis- and *trans*-{2-(2,4-Dichlorophenyl)-2-[2-(1-methyl-5-imidazolyl)ethyl]-4-hydroxymethyl}-1,3-dioxolane (**27**).

A mixture of **22** (4.19 g, 0.0148 mole), glycerol (4.3 ml, 0.059 mole), methanesulfonic acid (9.59 ml, 0.148 mole) and benzene (50 ml) was refluxed for 7 hours, with azeotropic removal of water. Solvents were removed, *in vacuo*, and the residue was poured into saturated sodium bicarbonate solution (*p*H 8). The mixture was extracted with dichloromethane (3 x 100 ml) and worked up as usual to afford a mixture of crude *cis*- and *trans*-**27** (4:1, 5.23 g), estimated from the areas under the signals of H-4 (of ketal) at 4.10 (*cis*) and 4.40 (*trans*). Partial separation was effected in the following manner: After dissolving the mixture of crude *cis* and *trans* **27** in dichloromethane, addition of petroleum ether caused crystallization of a considerable amount of pure *cis*-**27** (2.62 g, 50%) as a colorless solid, mp 142-143°; tlc, R_f = 0.28 (chloroform-methanol, 93:7).

Anal. Calcd. for *cis*-$C_{16}H_{18}Cl_2N_2O_3$: C, 53.80; H, 5.08; N, 7.84. Found: C, 53.80; H, 4.96; N, 7.80.

Evaporation of the filtrate yielded a yellow oil which consisted of a mixture of *cis* and *trans* **27** (2.18 g). A batch of *cis* and *trans* **27** (5.7 g, 0.0159 mole) was benzoylated in dry dichloromethane (100 ml) containing dry pyridine (12.9 ml, 0.159 mole) by the dropwise addition of benzoyl chloride (3.67 ml, 0.0318 mole). After stirring for 1 hour at 0-5° and for 3 hour at room temperature, the reaction mixture was diluted with water, extracted with chloroform (3 x 60 ml) and worked us as usual. Chromatography on silica gel (140 g) and elution with chloroform-methanol (99:1) provided first, *cis*-benzoate as a gum, (1.97 g), tlc, R_f = 0.53, chloroform-methanol, 93:7), followed by a mixture of *cis* and *trans* benzoates (3.63 g), and finally, *trans*-benzoate as a gum (2.5 g), tlc, R_f = 0.43, chloroform-methanol, 93:7).

Hydrolysis of the *trans*-benzoate (2.5 g, 0.00542 mole) was achieved upon boiling with potassium carbonate (1.49 g, 0.011 mole) in water (12 ml) and methanol (100 ml) for 3 hours. After evaporation of the solvents, *in vacuo*, the residue was extracted with ethyl acetate and worked up as usual. Chromatography of some of the crude reaction mixture (1.46 g) on silica gel (40 g), yielded upon elution with chloroform-methanol (99:1) pure *trans*-**27** (0.93 g, 49%) as an oil; tlc, R_f = 0.25 (chloroform-methanol, 93:7).

Anal. Calcd. for $C_{16}H_{18}Cl_2N_2O_3$: C, 53.80; H, 5.08; N, 7.84. Found: C, 53.52; H, 4.99; N, 7.53.

A similar hydrolysis of the *cis*-benzoate provided the corresponding alcohol in good yield.

2-(4-Chlorophenyl)-2-(3-cyanopropyl)-1,3-dioxolane (**29**).

A mixture of 2-(4-chlorophenyl)-2-(3-iodopropyl)-1,3-dioxolane [3] (10.0 g, 28.4 mmoles), potassium cyanide (2.2 g, 33.8 mmoles) in dimethylformamide (25 ml) was stirred at room temperature (24 hours) and then 50-60° (1 hour). The reaction mixture was diluted with water and then extracted with ethyl acetate. The extract was worked up as usual to afford an amber oil (8.15 g). After chromatography (ethyl acetate-petroleum ether, 2:3), there was obtained a colorless oil (6.72 g, 94%). After standing at low temperature (< 0°), this oil product solidified as a low melting point crystalline solid which melted < 30°.

Anal. Calcd. for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: C, 61.84; H, 5.61; N, 5.60.

1-(2,4-Dichlorophenyl)-4-(1-methyl-5-imidazolyl)-1-butanone (**32**).

To a solution of **28** [48] (3.54 g, 0.0123 mole) in dry tetrahydrofuran (62 ml) at 0 was added a solution of a 1.0 *M* diisobutylaluminum hydride solution in tetrahydrofuran (37.1 ml, 0.0371 mole) slowly (30 minutes). The reaction mixture was stirred another 3 hours at 0° and carefully quenched by adding ice (5-6 pellets) and acetic acid (5-6 drops). After stirring for 20 minutes at room temperature, the mixture was extracted with ethyl acetate (3 x 50 ml), dried (sodium sulfate), filtered and concentrated to give the crude reduction product (3.42 g), which was not further characterized but used directly in the next step.

A mixture of the crude reduction product (3.42 g, 0.012 mole), methylamine solution (74 ml of 33% in absolute ethanol, 0.592 mole), molecular sieves (4Å, 10 g), tosylmethyl isocyanide (4.60 g, 0.024 mole), and dry ethanol (70 ml) were refluxed for 6.5 hours. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in dichloromethane (150 ml) and the solution was washed with saturated sodium bicarbonate solution, brine and was dried (sodium sulfate). Solvents were removed *in vacuo* to provide the crude ketal **30** (4.92 g), tlc, R_f = 0.45 (chloroform-methanol, 93:7). The ketal was hydrolyzed immediately to the ketone.

A solution of **30** (4.03 g) in methanol (60 ml) containing 2 *N* hydrochloric acid (40 ml) was refluxed for 4 hours. After removal of some of the solvents, the residue was made basic (*p*H = 7-8) with sodium bicarbonate and was extracted with dichloromethane (3 x 110 ml). The combined organic extract was washed with brine, dried over sodium sulfate and concentrated, *in vacuo*, to give the crude product (3.31 g), which was chromatographed on silica gel (100 g) with chloroform-methanol (99:1) to give 1.19 g (32% from **28**) of an oil **32**; tlc, R_f = 0.38 (chloroform-methanol, 93:7).

Anal. Calcd. for $C_{14}H_{14}Cl_2N_2O$: C, 56.58; H, 4.75; N, 9.43. Found: C, 56.30; H, 4.73; N, 9.14.

1-(4-Chlorophenyl)-3-(1-methyl-5-imidazolyl)-1-butanone (**33**).

Starting from nitrile **29**, ketone **33** was prepared in an analogous manner, on the same scale, as that described for the preparation of **32**. The ketone was obtained in 37% (from the nitrile) as an off-white solid, mp 62-63°.

Anal. Calcd. for $C_{14}H_{15}ClN_2O \cdot 0.8H_2O$: C, 60.67; H, 6.04; N, 10.11. Found: C, 60.77; H, 5.69; N, 10.00.

2-(2,4-Dichlorophenyl)-2-[3-(5-tetrazolyl)propyl)-1,3-dioxolane (**34**).

A mixture of **28** (0.74 g, 2.58 mmoles), triethylamine hydrochloride (2.13 g, 15.4 mmoles), sodium azide (0.45 g., 12.9 mmoles) in dimethylformamide (15 ml) was heated at 115° (24 hours). After concentrating the solution, *in vacuo*, the residue was acidified with 6 *N* hydrochloric acid. The product was extracted into ethyl acetate (3 x 30 ml) and the crude product

(0.87 g) was chromatographed (silica gel) and eluted with chloroform-methanol (99:1) as an oil (**34**, 0.84 g, 99%); tlc, $R_f = 0.36$ (chloroform-methanol, 93:7).

Anal. Calcd. for $C_{13}H_{14}Cl_2N4O_2 \cdot 0.4H_2O$: C, 46.42; H, 4.43; N, 16.66. Found: C, 46.62; H, 4.26; N, 16.32.

1-(2,4-Dichlorophenyl)-3-(5-tetrazolyl)-1-butanone (**36**).

A solution of **34** (0.61 g, 1.85 moles) in methanol (6 ml) containing 2 *N* hydrochloric acid (6 ml) was refluxed for 7.5 hours. After removal of solvents, *in vacuo*, the residue was extracted with ethyl acetate. The extract was dried (sodium sulfate) and concentrated, *in vacuo*, to provide colorless **36** (0.45 g. 89%), mp 108-110° (from chloroform-ethyl acetate); tlc, $R_f = 0.37$ (chloroform-methanol, 93:7);

Anal. Calcd. for $C_{11}H_{10}Cl_2N_4O$: C, 46.34; H, 3.53; N, 19.65. Found: C, 46.34; H, 3.50; N, 19.63.

2-(4-Chlorophenyl)-2-[3-(5-tetrazolyl)propyl]-1,3-dioxolane (**35**).

A mixture of nitrile **29** (2.0 g, 8.0 mmoles), sodium azide (2.6 g, 40 mmoles) and trimethylamine hydrochloride (5.5 g, 40 mmoles) in dimethylformamide (25 ml) was heated at 110-120° (20 hours). After removal of the solvent, *in vacuo*, the residue was acidified with 6 *N* hydrochloric acid (30 ml). Extraction with ethyl acetate and usual workup provided a crude white solid (3.12 g). After recrystallization with methanol-ethyl acetate, there was obtained **35** (2.17 g, 92%), mp 155-156°.

Anal. Calcd. for $C_{13}H_{15}ClN_4O_2$: C, 52.98; H, 5.13; N, 19.01. Found: C, 52.89; H, 5.06; N, 18.92.

2-(4-Chlorophenyl)-3-(5-tetrazolyl)-1-butanone (**37**).

A solution of **35** (598 mg, 2.0 mmoles) in methanol (10 ml) containing 2 *N* hydrochloric acid (10 ml) was heated at reflux for 6 hours. Solvents were removed, *in vacuo*. The residue was extracted with ethyl acetate and worked up to provide colorless needles of **37** (456 mg, 91%), mp 124-125°.

Anal. Calcd. for $C_{11}H_{11}ClN_4O$: C, 52.70; H, 4.42; N, 22.35. Found: C, 52.73; H, 4.34; N, 22.16.

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