Regioselective Alkylation of 4(5)-Nitro-1*H*-imidazoles in Acidic Media: Study of Temperature Effects

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Alkylation of 4(5)-nitro-1*H*-imidazoles in acidic media with reactive alkylating agents such as benzyl chloride and allyl bromide resulted in the predominant formation of the 5-nitro isomers at lower temperatures (75 °C) and the 4-nitro isomers at higher temperatures (140 °C). With less reactive alkylating agents, only the 5-nitro isomers were produced irrespective of temperature. The mechanism was shown to involve quaternization of the initially formed 1-alkyl-5-nitro-1*H*-imidazoles followed by preferential dealkylation to yield the thermodynamically more stable 4-nitro-1*H*-imidazoles.

The regiospecific *N*-alkylation of 4(5)-nitro-1*H*-imidazoles has been a problem of great significance because of the chemotherapeutic and pharmacological utility of 1-alkyl-5-nitro-1*H*- and 1-alkyl-4-nitro-1*H*-imidazoles.[1-6] Despite the information that acidic media favour the 5-nitro orientation and basic media favour the 4-nitro orientation during alkylation of 4(5)-nitro-1*H*-imidazoles with alkyl sulfates and halides,[7] there is a lack of high-yielding, regioselective syntheses of either 4- or 5-nitro-1*H*-imidazoles. Recently our studies have established the conditions for obtaining excellent yields of 1-alkyl-4-nitro-1*H*-imidazoles from 4(5)-nitro-1*H*-imidazoles and alkyl halides in basic media.[8] In continuation of our studies on 4- and 5-nitroimidazoles,[9,10] we have now turned our attention to the alkylation of 4(5)-nitro-1*H*-imidazoles in acidic media.

Alkylations of 4(5)-nitro-1*H*-imidazoles with alkyl toluene-*p*-sulfonates are known to produce the 5-nitro isomers in high selectivity but in poor to moderate yields.[11,12] Alkylations employing 2-alkylsulfonylethyl, prop-2-ynyl and 2-cyanoethyl toluene-*p*-sulfonates have been reported. Esters of polyphosphoric acid have also been used to carry out regioselective alkylations to obtain the 5-nitro isomers exclusively.[13] However, this method has been applied only to methylation and ethylation. It has also been observed that alkylation of 4(5)-nitro-1*H*-imidazoles in carboxylic acid or in polar aprotic solvents such as dimethyl sulfoxide (DMSO) improves the selectivity for the formation of the 5-nitro isomers and also the yields.[14] The specific solvents employed activate the nucleophilic character of 4(5)-nitro-1*H*-imidazole substrates and improve the regioselectivity of the alkylation of the nitrogen adjacent to the nitro group. The yields, however, remain in the range of 15–40%.

An examination of various other reported examples of alkylation of 4(5)-nitro-1*H*-imidazoles in acidic media revealed that a good number of exceptional cases, such as benzylation and alkoxymethylation, needed explanation.[15-18] The predominant formation of 5-nitro isomers is not always observed. In a few instances, the 4-nitro isomers have been the sole products isolated. In the examples cited above, alkyl halides of varying reactivities have been used in the alkylation reactions of 4(5)-nitro-1*H*-imidazoles employing different temperatures. This prompted us to make a systematic study of the temperature effects on the course of the alkylation of 4(5)-nitro-1*H*-imidazoles in acidic media and the results are reported here.

Results and Discussion

The studies on the alkylation of 4(5)-nitro-1*H*-imidazoles were carried out on two representative substrates 4(5)-nitro-1*H*-imidazole **1** and 2-methyl-4(5)-nitro-1*H*-imidazole **2**. The reactive alkylating agents chosen for the study were benzyl chloride and allyl bromide. 2-(Ethylsulfanyl)ethanol in conc. H_2SO_4 was used as an example where the reactive alkylating species is generated *in situ*. Relatively unreactive alkylating agents such as diethyl sulfate, ethyl bromide and propyl bromide were also used for comparative evaluation.

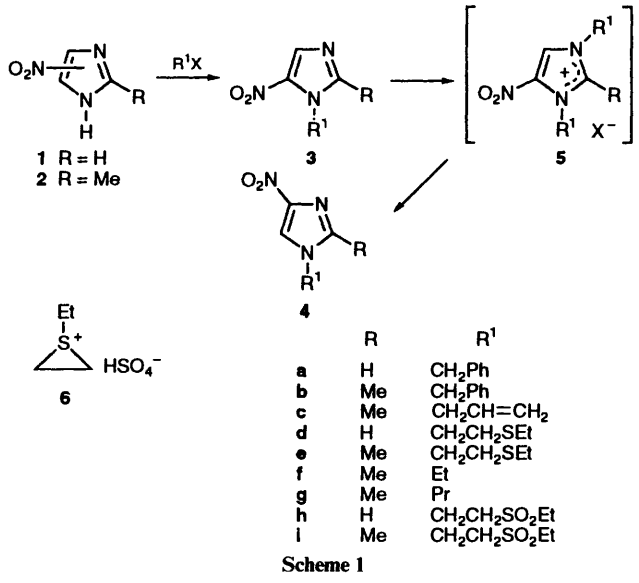
Factors favouring S_E2' alkylation have been employed using excess of AcOH–DMF as the reaction medium and maintaining a low pH throughout. The alkylation reactions were studied in the temperature range 70–145 °C and the isolated products in each case were analysed by ^1H NMR and HPLC to determine the 5-NO_2–4-NO_2 isomer distribution. Typically, the experiments were carried out with the mol ratio of 4(5)-nitro-1*H*-imidazole : alkylating agent as 1 : 1.2. In the case of 2-(ethylsulfanyl)ethanol, the reactive alkylating species was generated by employing a mol equiv. of conc. H_2SO_4. In this case acetic acid was used alone as the solvent. The alkylation reactions in the temperature range 70–110 °C were carried out for 10 h and those above 110 °C were carried out for 5 h.

The isomer distribution in the benzylation, allylation and 2-(ethylsulfanyl)ethylations of the 4(5)-nitro-1*H*-imidazoles **1** and **2** showed remarkable temperature dependence. In all three cases, lower temperatures (70–80 °C) favoured 5-nitro isomer formation. Increasing the temperature produced increased amounts of 4-nitro isomers, although the extent varied from case to case. In the temperature range 130–145 °C, the 4-nitro isomers were the exclusive products isolated.

Benzylation of **1** and **2** at 80 °C produced the 5-nitro isomers **3a**, **3b** and the 4-nitro isomers **4a**, **4b** in an approximately 90 : 10 ratio (Scheme 1, Table 1). Below 80 °C, the reactions were very sluggish; increasing the temperature resulted in the formation of increased amounts of the 4-nitro isomers and at 140 °C they were the exclusive products. The total yield of the benzylated products increased steadily from about 8% at 80 °C to 65% at 140 °C.

Allylation of 2-methyl-4(5)-nitro-1*H*-imidazole **2** at 80 °C produced the 5-nitro and 4-nitro isomeric products **3c** and **4c** in the ratio 70 : 30 (Scheme 1, Table 2). Even at 70 °C, 22% of the 4-nitro isomer **4c** was formed and no product formation was observed below 70 °C. As in the case of benzylation, the total yield of the allylated products **3c** + **4c** increased steadily and reached a maximum of 53% at 140 °C.

For alkylations with 2-(ethylsulfanyl)ethanol in the presence of conc. H_2SO_4 and AcOH, similar regioselectivity was observed. Ethylsulfanylethylation of **1** at 70 °C produced the 5-nitro isomer **3d** and the 4-nitro isomer **4d** in a 95 : 5 ratio, and of



Scheme 1

Table 1 Benzylation of 4(5)nitro-1*H*-imidazoles **1** and **2**

Entry	*T*/°C	Product mixture	Yield (%)	Product composition (5-NO_2:4-NO_2) ^{1}H NMR [a] ($CDCl_3$)	HPLC
1	80	**3a** + **4a**	8	90:10	—
2	100	**3a** + **4a**	27	55:45	57:42
3	120	**3a** + **4a**	39	21:79	—
4	130	**3a** + **4a**	61	7:93	8:92
5	140	**3a** + **4a**	67	1:98	1.0:98.5
6	80	**3b** + **4b**	9	92:8	91:9
7	100	**3b** + **4b**	25	59:41	—
8	110	**3b** + **4b**	31	48:52	—
9	120	**3b** + **4b**	58	16:84	15:85
10	140	**3b** + **4b**	66	1:98	0.5:99.2

[a] Determined by integration of the NC*H*$_2$Ph resonance: **3a** δ_H 5.55 (s); **4a** 5.20 (s); **3b** δ_H 5.55 (s); **4b** 5.10 (s).

Table 2 Allylation of 2-methyl-4(5)-nitro-1*H*-imidazole **2**

Entry	*T*/°C	Yield (%) (**3c** + **4c**)	Product composition (5-NO_2:4-NO_2) ^{1}H NMR [a] ($CDCl_3$)	HPLC
1	70	6	78:22	—
2	80	10	70:30	72:27
3	90	16	47:53	—
4	100	30	15:85	14:85
5	130	38	5:95	—
6	140	53	2:98	1:99

[a] Determined by integration of ring-H resonance: **3c** δ_H 7.95 (s, 4-H); **4c** δ_H 7.70 (s, 5-H).

2 at 80 °C produced the corresponding isomers **3e** and **4e** in a 97:3 ratio (Scheme 1, Table 3). Increased amounts of 4-nitro isomers were produced at higher temperatures and at 140 °C they were the exclusive products. In contrast to the case with benzylated and allylated products, fairly good yields (45%) of ethylsulfanylethylated products were obtained even at 80 °C. However, a proportional increase in yield was not observed at higher temperatures. Competing dealkylation was taking place

Table 3 Ethylsulfanylethylation of 4(5)nitro-1*H*-imidazoles **1** and **2**

Entry	*T*/°C	Product mixture	Yield (%)	Product composition (5-NO_2:4-NO_2) ^{1}H NMR [a]	HPLC [b]
1	70	**3d** + **4d**	30	95:5	94:5
2	80	**3d** + **4d**	45	89:11	92:8
3	100	**3d** + **4d**	63	65:35	68:32
4	130	**3d** + **4d**	65	15:85	18:81
5	140	**3d** + **4d**	60	5:95	2:97
6	80	**3e** + **4e**	45	97:3	98:2
7	90	**3e** + **4e**	52	87:13	88:12
8	100	**3e** + **4e**	61	78:22	—
9	110	**3e** + **4e**	66	67:33	71:29
10	120	**3e** + **4e**	63	29:71	—
11	140	**3e** + **4e**	60	2:98	1:99
12	150	**3e** + **4e**	52	2:98	—

[a] δ_H($CDCl_3$) Determined by integration of the NCH_2 resonance: **3d** δ_H 4.55 (t); **4d** δ_H 4.25 (t). δ_H([$^2H_6$]DMSO), determined by integration of the ring-H resonance: **3e** δ_H 8.05 (s, 4-H); **4e** δ_H 8.35 (s, 5-H). [b] The sulfide mixtures **3d**, **4d** and **3e**, **4e** in each case were oxidized to the corresponding sulfones and then analysed.

as evidenced by the drop in yield beyond 140 °C and recovery of an increased amount of the substrates **1** and **2**.

The temperature effect was not observed when ethyl bromide, diethyl sulfate and propyl bromide were used for the alkylations of **1** and **2**. The 5-nitro isomers **3f** and **3g** were formed at all temperatures in the range 80–140 °C with great selectivity. About 3% of 4-nitro isomers **4f** and **4g** were formed at 80 °C and this amount remained fairly constant in the entire temperature range. The yields of alkylation products were however low (10–20%) in these cases.

The chemical shift values of the N–CH_2 resonances in the ^{1}H NMR spectra, the solvent induced shifts for 4,5-H and the intensities of $M^+ - NO_2$ fragments in the mass spectra were used in the structure assignment of compounds **3a–3g** and **4a–4g**.[9,19]

Compounds **3b**, **3c**, **3e**, **4a**, **4b** and **4e** are known and the observed physical properties are in accordance with those reported. The nitroimidazoles **3d**, **3e** and **4d**, **4e** with sulfide side chains on N-1 were oxidized to the corresponding sulfones **3h**, **3i** and **4h**, **4i**, which have the expected physical and spectral properties.

Under neutral or mildly acidic conditions, the predominant 4-nitro tautomeric forms of 4(5)-nitroimidazoles **1** and **2** are alkylated on N-3 (adjacent to the NO_2 group) resulting in preferential formation of 1-alkyl-5-nitro-1*H*-imidazoles.[20] Protonation of the more basic 5-nitro tautomers further enhances regioselectivity in distinctly acidic media. This must be operating only at lower temperatures. At higher temperatures, quaternization of the initially formed 5-nitro products takes place on N-1 producing the quaternary salts **5**. Preferential dealkylation on N-3 also becomes a competing factor at higher temperatures leading to the formation of increased amounts of 4-nitro isomers (Scheme 1).

The quaternization–dealkylation process in *N*-substituted imidazoles is known to be very facile when allyl and benzyl groups are involved.[21] The dealkylation of 1,3-dialkylimidazolium salts during pyrolysis is sluggish with simple alkyl groups such as Et and Pr. These factors together with the thermodynamic stability of the 4-nitro isomers explain the observed temperature effects discussed above. The 2-(ethylsulfanyl)ethanol–H_2SO_4 system must be operating *via* the highly reactive sulfonium ion intermediate **6**[22] and the corresponding alkylation–dealkylation must also be very facile. The postulation that the 4-nitroimidazoles **4a–e** are

Table 4 Physical and spectral properties of compounds **3a**, **3d**, **3h**, **4c**, **4d** and **4h**[a,b]

Entry	Yield (%)	M.p. (°C)	δ_H(ppm)[c]	δ_C(ppm)	MS (*m/z*, rel. intensity)	Elemental analysis (%) Found (Required) C	H	N
3a	9	91–92	($CDCl_3$) 5.60 (s, 2 H), 7.35–7.50 (m, 5 H), 7.65 (d, 1 H, *J* 1.5, 2-H), 8.00 (d, 1 H, *J* 1.5, 4-H) 4-H: $\Delta\delta$([$^2H_6$]DMSO–$CDCl_3$) 0.05	—	157 ($M^+ - NO_2$, 100), 91 (90), 203 (M^+, 20)	58.9 (59.11)	4.4 (4.43)	20.6 (20.69)
4c	45	62–64	($CDCl_3$) 2.40 (s, 3 H), 4.55 (m, 2 H), 5.25–5.45 (m, 2 H), 5.70–6.30 (m, 1 H), 7.70 [s, 1 H, 5-H: $\Delta\delta$-([$^2H_6$]DMSO–$CDCl_3$) 0.50]	([$^2H_6$]DMSO) 11.7 (q), 48.3 (t), 117.8 (t), 119.8 (d), 130.3 (d), 144.2 (s), 145.0 (s)	41 (100), 167 (M^+, 60) 121 ($M^+ - NO_2$, 3)	50.45 (50.30)	5.4 (5.39)	25.2 (25.15)
3d	30	Oil	($CDCl_3$) 1.25 (t, 3 H), 2.50 (q, 2 H), 2.95 (t, 2 H), 4.55 (t, 2 H), 7.70 (d, 1 H), 8.05 (d, 1 H) 4-H: $\Delta\delta$([$^2H_6$]-DMSO–$CDCl_3$) 0.05	—	155 ($M^+ - NO_2$, 100), 201 (M^+, 45)	41.85 (41.80)	5.5 (5.47)	20.95 (20.90)
4d	60	Oil	($CDCl_3$) 1.20 (t, 3 H), 2.15 (q, 2 H), 2.95 (t, 2 H), 4.25 (t, 2 H), 7.55 (d, 1 H), 7.95 [d, 1 H, 5-H: $\Delta\delta$([$^2H_6$]DMSO–$CDCl_3$) 0.55]	—	89 (100), 75 (90), 201 (M^+, 40), 155 ($M^+ - NO_2$, 3)	41.85 (41.80)	5.5 (5.47)	20.9 (20.90)
3h	79	100–102	([$^2H_6$]DMSO–CF_3CO_2H) 1.30 (t, 3 H), 3.15 (q, 2 H), 3.75 (t, 2 H), 4.90 (t, 2 H), 8.25 (s, 1 H), 8.40 (s, 1 H)	([$^2H_6$]DMSO) 5.9 (q), 41.0 (t), 47.0 (t), 50.3 (t), 133.4 (d), 138.3 (s), 143.5 (d)	187 ($M^+ - NO_2$, 100), 233 (M^+, 20) (Found: M^+, 233.0473. $C_7H_{11}N_3O_4S$ requires *M*, 233.0470)	—	—	—
4h	84	98–100	([$^2H_6$]DMSO) 1.25 (t, 3 H), 3.15 (q, 2 H), 3.80 (t, 2 H), 4.60 (t, 2 H), 7.95 (d, 1 H), 8.50 (d, 1 H)	([$^2H_6$]DMSO) 6.1 (q), 41.3 (t), 47.2 (t), 50.6 (t), 121.8 (d), 137.8 (d), 147.1 (s)	140 (100), 233 (M^+, 30), 187 ($M^+ - NO_2$, 1) (Found: M^+, 233.0473. $C_7H_{11}N_3O_4S$ requires *M*, 233.0470)	—	—	—

[a] Compounds **3a**, **4a**, **3b**, **4b**, **3c** and **4c** were prepared by Method A and **3d**, **4d**, **3e** and **4e** by Method B. Compounds **3h**, **4h**, **3i** and **4i** were prepared by oxidation of **3d**, **4d**, **3e** and **4e**, respectively. Compounds **3a–e** were purified further from isomer mixtures. [b] Known compounds [yield (%), m.p. (°C)]: **4a** [53, 74 (lit.,[18] 76)], **3b** [8, 110–112 (lit.,[18] 112)], **4b** [56, 104–106 (lit.,[23] 104–105)], **3c** [6, 88–90 (lit.,[18] 90)], **3e** [45, oil (lit.,[12] oil)], **4e** [60, 57–59 (lit.,[18] 60)], **3i** [77, 126–27 (lit.,[19] 125–27)] and **4i** [85, 134–36 (lit.,[24] 130–34)]. [c] *J* Values are given in Hz.

formed *via* the quaternary salts generated from the initially formed 5-nitro isomers **3a–e** was experimentally verified. Thus heating pure 1-benzyl, 1-allyl- and 1-ethyl-sulfanylethyl-5-nitro-1*H*-imidazoles **3a–e** with benzyl chloride, allyl bromide and 2-(ethylsulfanyl)ethanol–H_2SO_4 respectively at 140 °C, effected the isomerizations and the corresponding 4-nitro-1*H*-imidazoles were isolated. Heating the 5-nitro-1*H*-imidazoles alone did not result in any isomerization. The literature results of alkylation of 4(5)-nitro-1*H*-imidazoles with alkoxymethyl chloride, acyloxymethyl chloride *etc.*, can now be interpreted similarly.

Thus, a correlation between 5-nitro–4-nitro isomer mixture composition and reaction temperature has been established for the alkylation of 4(5)-nitro-1*H*-imidazoles involving reactive alkylating agents in acidic media.

Experimental

^1H and ^{13}C NMR spectra were recorded on JEOL FX 60Q and JEOL FX 90Q FT NMR instruments. HPLC analyses were carried out on a Waters HPLC instrument using an M481 UV Detector. Low and high resolution mass spectra were recorded on JEOL JMS-DX 300 double focusing and JEOL JMS-DX 303 GC–MS instruments using the direct inlet mode.

General Procedure for Alkylations.—Method A: Alkylation with alkyl halides. A stirred mixture of 4(5)-nitro-1*H*-imidazole (50 mmol), the alkyl halide (60 mmol), glacial AcOH (15 cm^3) and dimethylformamide (DMF) (15 cm^3) was heated to the desired temperature (70–110 °C) for 10 h. The alkylation experiments above 110 °C were carried out for 5 h. The solvents were evaporated under reduced pressure and then the residue was triturated with $CHCl_3$. The precipitated starting material, if any, was filtered off. The filtrate was extracted with aq.NH_3 (2 × 15 cm^3) at 15 °C. The organic layer was washed with ice-cold water (20 cm^3) and dried over Na_2SO_4. The extract was evaporated under reduced pressure and then the residue weighed and analysed by ^1H NMR and HPLC.

Method B: Alkylation with 2-(ethylsulfanyl)ethanol. A mixture of 4(5)-nitro-1*H*-imidazole (50 mmol), 2-(ethylsulfanyl)-ethanol (6.4 g, 60 mmol) and glacial AcOH (15 cm^3) was cooled in an ice bath to 15 °C. To the well stirred mixture was added conc. H_2SO_4 (5.9 g, 60 mmol) and during the addition the temperature maintained below 25 °C. The stirred reaction mixture was then heated to the desired temperature (80–100 °C)

for 10 h. The experiments above 100 °C were carried out only for 5 h. The reaction mixture was cooled to 15 °C and basified with aq. NH_3 (40 cm^3). The oily product was stirred with $CHCl_3$ (50 cm^3) and filtered. The organic layer of the filtrate was separated, washed with aq. NH_3 (20 cm^3) followed by water (20 cm^3) and then dried over Na_2SO_4. The organic extract was evaporated under reduced pressure and then the residue weighed and analysed by ^1H NMR and HPLC.

The yields and physical and spectral properties of the compounds prepared are presented in Table 4.

Reaction of Benzyl Chloride and 1-*Benzyl*-2-*methyl*-5-*nitro*-1H-*imidazole* **3b**.—A mixture of imidazole **3b** (2.2 g, 10 mmol), benzyl chloride (1.5 g, 12 mmol), glacial AcOH (5 cm^3) and DMF (5 cm^3) was heated at 140 °C for 5 h. The solvents were evaporated under reduced pressure and then the residue was neutralized with aq. NH_3 (5 cm^3) and extracted with $CHCl_3$ (30 cm^3). The $CHCl_3$ layer was washed with water and extracted with HCl (10 mol dm^{-3}; 2 × 15 ml). The aq. layer was neutralized with aq. NH_3 (27 cm^3) and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to yield a pale brown solid (2.0 g) which was crystallized from EtOAc–hexane to give 4-nitro-1*H*-imidazole **4b** (1.7 g, 77%), m.p. 110–112 °C. The product was identical with **4b** prepared earlier by benzylation of **2** at 140 °C.

Reaction of 2-(*Ethylsulfanyl*)*ethanol and* 1-*Ethylsulfanyl*-*ethyl*-2-*methyl*-5-*nitro*-1H-*imidazole* **3e**.—A mixture of **3e** (2.15 g, 10 mmol), 2-(ethyl sulfanyl)ethanol (1.27 g, 12 mmol), conc. H_2SO_4 (1.2 g, 12 mmol) and glacial AcOH (5 cm^3) was heated at 140 °C for 5 h. The reaction mixture was worked-up following Method B for alkylation to yield a brown product (1.6 g) which was crystallized from hexane to give 4-nitro-1*H*-imidazole **4e** (1.4 g, 65%), m.p. 57–58 °C. The product was identical with **4e** prepared earlier by ethylsulfanylethylation of **2** at 140 °C.

References

1 C. Cosar and L. Julou, *Ann. Inst. Pasteur, Paris*, 1959, **96**, 238.
2 C. E. Nord, *J. Antimicrob. Chemother.*, 1982, **10**, Suppl. A, 35.
3 P. Galanaud, *Pharmacologie Clinique. Bases de la Therapeutique*, eds. J. P. Giroud, G. Mathe and G. Meyniel, Expansion Scientifique, Paris, 1978, pp. 1781–1795 (*Chem. Abstr.*, 1979, **90**, B 811015).
4 R. Klink, K. G. R. Pachler and R. Gottschlich, *Arzneim. Forsch.*, 1985, **35**, 1220.
5 J. Morgenstern, R. Otto and S. Scheithauner, Ger. (East) DD 260,062 (1988) (*Chem. Abstr.*, 1989, **110**, 231634r).
6 R. Chibber, I. J. Stratford, I. Ahmed, A. B. Robbins, D. Goodgame and B. Lee, *Int. J. Radiat. Oncol., Biol. Phys.*, 1984, **10**, 1213.
7 B. Cavalleri, *Nitroimidazole Chemistry, Synthetic Methods in Nitroimidazoles. Chemistry, Pharmacology and Chemical applications*, eds. A. Breccia, B. Cavalleri and G. E. Adams, NATO Adv. Study Inst. Ser., Ser A, Plenum Press, New York, 1982, vol. 42, pp. 9–34; J. H. Boyer, *Nitroimidazoles*, in *Nitroazoles: The C-nitro derivatives of five-membered N and N,O heterocycles*, ed. F. Henry, VCH, Deerfield Beach, FL, 1986, ch. 2, pp. 79–185; M. R. Grimmett, *Imidazoles and their benzo derivatives*, in *Comprehensive Heterocyclic Chemistry. The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds*, ed. K. T. Potts, Pergamon Press, Oxford, 1984, vol. 5, pp. 345–456.
8 A. K. S. B. Rao, C. G. Rao and B. B. Singh, *Synth. Commun.*, 1991, **21**, 427.
9 A. K. S. B. Rao, C. G. Rao and B. B. Singh, *J. Org. Chem.*, 1990, **55**, 3702; *J. Chem. Res. (s)*, 1991, 350.
10 A. K. S. B. Rao, G. G. Rao and B. B. Singh, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1352; *Synth. Commun.*, 1991, **21**, 443.
11 K. Butler, H. L. Howes, J. E. Lynch and D. K. Pirie, *J. Med. Chem.*, 1967, **10**, 891.
12 M. W. Miller, H. L. Howes, R. V. Kasubick and A. R. English, *J. Med. Chem.*, 1970, **13**, 849.
13 M. Oklobdzija, V. Sunjic and F. Kajfez, *Synthesis*, 1975, 596.
14 F. Kajfez, V. Sunjic, D. Kolbah, T. Fazdiga and M. Oklobdzija, *J. Med. Chem.*, 1968, **11**, 167.
15 J. S. G. Cox, G. Fitzmaurice, A. R. Katritzky and G. J. T. Tiddy, *J. Chem. Soc. B*, 1967, **13**, 1251.
16 F. Kajfez, N. Blazevic and V. Sunjic, *Farm. Glas.*, 1969, **25**, 49 (*Chem. Abstr.*, 1969, **71**, 70534s).
17 Z. Crnic and B. Gluncic, *Croat. Chem. Acta.*, 1981, **54**, 217.
18 C. Cosar, C. Crisan, R. Horclois, R. M. Jacob, J. Robert, S. Tchelitsheff and R. Vaupre, *Arzneim., Forsch.*, 1966, **16**, 23.
19 K. Nagarajan, V. Sudarsanam, P. C. Parthasarathy, V. P. Arya and S. J. Shenoy, *Ind. J. Chem., Sect. B*, 1982, **21**, 1006.
20 A. Grimison, J. H. Ridd and B. V. Smith, *J. Chem. Soc.*, 1960, 1352 and 1357; J. H. Ridd and B. V. Smith, *J. Chem. Soc.*, 1960, 1363.
21 B. K. M. Chan, N. K. Chang and M. R. Grimmett, *Aust. J. Chem.*, 1977, **30**, 2005; D. S. Noyce and G. T. Stowe, *J. Org. Chem.*, 1973, **38**, 3762.
22 G. C. Barrett, in *Comprehensive Organic Chemistry, The Synthesis and Reactions of Organic Compounds*. Ed. D. N. Jones, Pergamon Press, Oxford, 1979, vol. 3, p. 109.
23 J. D. Albright and D. B. Moran, *J. Heterocycl. Chem.*, 1986, **23**, 913.
24 V. Caplar, V. Sunjic and F. Kajfez, *J. Heterocycl. Chem.*, 1974, **11**, 1055.

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