Syntheses of condensed imidazoles by lead tetraacetate oxidation of amidines

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2-Phenylbenzimidazoles, 2-benzylbenzimidazoles, 2-phenyl-1*H*-naphtho[1,2-*d*]imidazole, and 2-benzyl-1*H*-naphtho[1,2-*d*]-imidazole have been synthesized in excellent yields (77–98%) by lead tetraacetate oxidation of suitable *N*-arylbenzamidines, *N*-arylphenylacetamidines, *N*-α-naphthylbenzamidine, and *N*-α-naphthylphenylacetamidine respectively. The mechanism of nitrene insertion and intramolecular competitive nitrene insertion leading to these heterocycles has also been discussed.

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On a synthétisé, avec d'excellents rendements (77–98%), les composés suivants: phényl-2 benzimidazoles, benzyl-2 benzimidazoles, phényl-2 1*H*-naphtho[1,2-*d*] imidazole et benzyl-2 1*H*-naphtho[1,2-*d*] imidazole par l'oxydation, au moyen du tétraacétate de plomb, des composés suivants convenablement choisis: *N*-arylbenzamidines, *N*-arylphénylacétamidines, *N*-α napthylbenzamidine et *N*-α naphthylphénylacétamidine respectivement. On discute également des mécanismes d'insertion du nitrène et d'insertion intramoléculaire compétitive du nitrène conduisant à ces hétérocycles.

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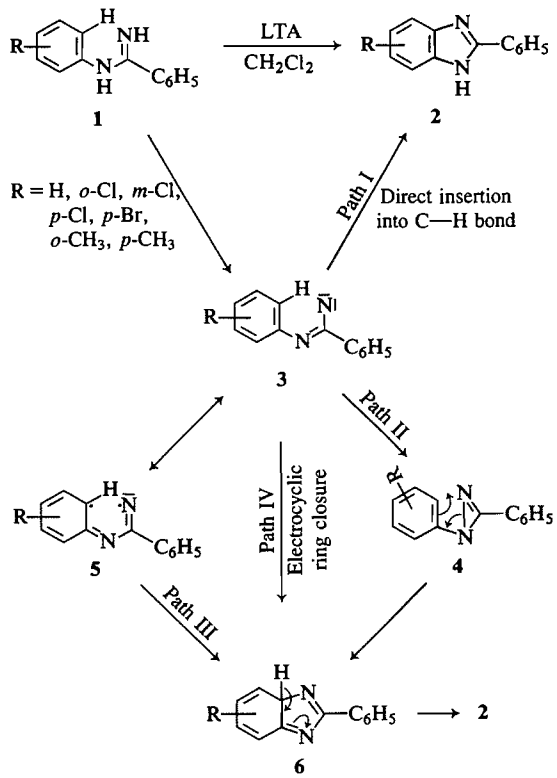
Because of the increasing importance of benzimidazoles, a simpler approach to the synthesis of these heterocyclics was thought to be of great value. The procedure for the synthesis of benzimidazoles usually involves the condensation of *o*-phenylenediamine or *o*-nitroaniline with a carboxylic acid derivative. In each case, the cyclization involves coupling at the *o*-phenylene nitrogens.

Since *N*-arylamidines are easily available (1–3), it appeared that substituted amidines could be potential precursors for the synthesis of benzimidazoles, if they could be induced to cyclize by some oxidative means. The formation of benzimidazoles from *N*-arylamidines was first reported by Partridge and Turner and required the prior conversion of *N*-arylamidines to *N*-hydroxy amidines (4). Later on it was found that *N*-arylamidine hydrochlorides could be transformed into benzimidazoles with one mole of sodium hypochlorite and base (5, 6). Often the yields of *N*-chloro derivatives are unsatisfactory, which in turn is reflected in lower yields of benzimidazoles.

We report here the syntheses of various 2-phenyl and 2-benzyl condensed imidazoles, in excellent yields (77–98%), by lead tetraacetate (LTA) oxidation of suitable amidines (Schemes 1–3). The object of the present investigation has also been to explore intramolecular competitive nitrene insertions and the nitrene insertion mechanism leading to these heterocycles.

In the case of LTA oxidation of *N*-*o*-tolylbenzamidine, where there is a possibility of nitrene insertion into both the C—H bond of methyl and the C—H bond of phenyl, insertion takes place exclusively into the C—H bond of phenyl. This is perhaps due to the aromatic stabilization of the benzimidazole ring formed by insertion into the phenyl C—H bond, which is not the case with dihydroquinazoline formed by insertion into the methyl C—H bond (Scheme 2). Similarly, in the case of oxidation of *N*-*m*-chlorophenylbenza-



SCHEME 1

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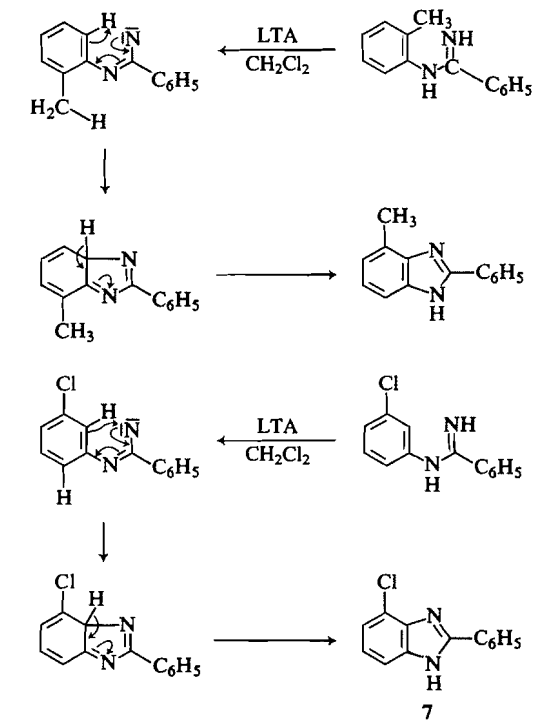
midine there exists a possibility of nitrene insertion into the C—H bond either *ortho* or *para* to chlorine. The product formed in this case is 4(7)-chloro-2-phenylbenzimidazole (**7**) confirmed by its superimposable ir spectrum and undepressed mixture melting point with the product obtained by oxidation of *N*-*o*-chlorophenylbenzamidine. This observation indicates that the nitrene insertion has taken place into the C—H bond *ortho* to chlorine (Scheme 2).

In the case of LTA oxidations of *N*-arylphenylacetamidines in refluxing dichloromethane, the yield of the 2-benzylbenzimidazoles was always between 20–30%. The tlc of the reaction mixture, even on addition of excess of LTA (2 equiv.), always showed the presence of unreacted amidine. A number of futile attempts were made to improve the yields of 2-benzylbenzimidazoles, e.g., by carrying out the oxidation (*i*) in refluxing benzene; (*ii*) in acetic acid. In the case of oxidation with LTA/acetic acid, 2-benzylbenzimidazole was not formed at all. It was concluded that the acetic acid was perhaps protonating amidine and inhibiting the attack of nitrogen on lead of LTA. With this in mind pyridine was used as a scavenger for acetic acid and oxidations of *N*-arylphenylacetamidines with LTA/CH_2Cl_2/pyridine gave excellent yields (85–98%) of 2-benzylbenzimidazoles.[2]

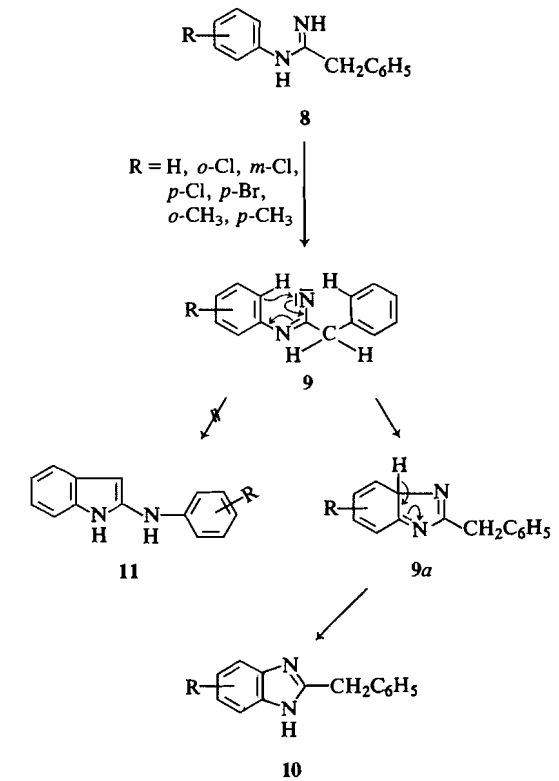
In the case of LTA oxidations of *N*-arylphenylacetamidines (**8**), there exists a possibility of nitrene insertion into a C—H bond of either of the two phenyl groups. But the intermediate azomethine nitrene (**9**), in this case, appears to be highly selective in undergoing cyclization leading to 2-benzylbenzimidazoles (Scheme 3).

In the case of LTA oxidation of *N*-*o*-tolylphenylacetamidine the product obtained was also that of nitrene insertion into the phenyl C—H bond. The oxidation of *N*-*m*-chlorophenylphenylacetamidine gave the same product as obtained by oxidation of *N*-*o*-chlorophenylphenylacetamidine, indicating again that the nitrene insertion has taken place into the phenyl C—H bond which is *ortho* to chlorine.

This oxidation method was extended to the synthesis of 2-phenyl-1*H*-naphtho[1,2-*d*]imidazole[3] and 2-benzyl-1*H*-naphtho[1,2-*d*]imidazole by the oxidation of *N*-α-naphthylbenzamidine and N-α-naphthylphenylacetamidine with LTA/CH_2-



SCHEME 2



SCHEME 3

[2]Yield of 2-benzylbenzimidazole by the method of Haruki *et al.* (14) is only 36%.

[3]The yield of 2-phenyl-*1H*-naphtho[1,2-*d*]imidazole by the method of Haruki *et al.* (14) is only 24%.

Cl_2/pyridine. It may be mentioned here that LTA oxidation of *N*-α-naphthylbenzamidine in refluxing dichloromethane gave only about 30% of the product and the yield improved tremendously by carrying out the oxidation in the presence of pyridine.

In the case of oxidation of *N*-arylbenzamidines (**1**), the probable intermediate azomethine nitrene (**3**) may lead to 2-phenylbenzimidazoles (**2**) by any of the four paths shown in Scheme 1. The probable intermediate **3** may lead to 2-phenylbenzimidazoles (**2**) by direct insertion of nitrene into the C—H bond (Path I); it may lead to imidazole ring formation by ring expansion of the diazirine intermediate **4** (Path II); the resonance stabilization of the azomethine nitrene **3** may lead to 2-phenylbenzimidazoles via intermediates **5** and **6** (Path III); or the intermediate **3** may, via the electrocyclic ring closure to intermediate **6**, lead to **2** (Path IV).

The biradical mechanism involved in Path III may be ruled out because it has been shown by Lwowski and others that acylnitrenes, to which **3** bears a more than superficial resemblance, insert into C—H as singlets (7–11)

Direct insertion (Path I) may be ruled out of the other alternatives, and the electrocyclic ring closure mechanism (Path IV) favoured, on the basis of the following observations.

(*i*) As already pointed out in the case of LTA oxidations of *N*-arylphenylacetamidines (**8**), there exists a possibility of nitrene insertion into a C—H bond of either of two phenyl groups. Direct nitrene insertion would lead to 2-benzylbenzimidazoles (**10**) or 2-anilinoindoles (**11**), both of which possess aromatic stabilization. But the intermediate **9** appears to be highly selective in undergoing cyclization leading to 2-benzylbenzimidazoles rather than 2-anilinoindoles (Scheme 3). This discrimination between two possible ring closures may be attributed to electron delocalization[4] in an intermediate azomethine nitrene (**9**), indicating the preference for reaction Path IV for the formation of these benzimidazoles via **9***a*.

(*ii*) In the case of oxidation of *N*-*m*-chlorophenylbenzamidine and *N*-*m*-chlorophenylphenylacetamidine, insertion of nitrene takes place *ortho* to chlorine, though insertion at the *para* position should be favoured for steric reasons. This can also be explained by a delocalization mechanism, i.e., Path IV is favoured and insertion at the *ortho* position takes place because of the pull of electrons towards chlorine due to its inductive effect.

(*iii*) In the case of oxidation of *N*-*o*-tolylbenzamidine the exclusive formation of 4(7)-methyl-2-phenylbenzimidazole can also be explained by this electrocyclic ring closure mechanism (Path IV).

Further work on such reactions in the presence of various 1,3-dipolarophiles, in order to trap the nitrene intermediate and to look into its spin multiplicities, is in progress.

Experimental

All the mp's are uncorrected. The ir spectra were recorded on a Perkin–Elmer Model 297 ir spectrometer. The nmr traces were recorded on a Varian EM-390 90 MHz nmr spectrometer.

The following *N*-arylbenzamidines and *N*-arylphenylacetamidines, with yields (%), mp (°C), (lit. mp (°C)), and (reference) were prepared by the reported methods (2, 3). *N*-phenylbenzamidine, 75, 113–114 (116) (12); *N*-phenylphenylacetamidine, 70, 134–135 (133–135) (13); *N*-*o*-tolylbenzamidine, 98, 102–103; *N*-*o*-tolylphenylacetamidine, 71, 107–108; *N*-*p*-tolylbenzamidine, 76, 99–100, (100.5–101) (12); *N*-*p*-tolylphenylacetamidine, 84, 117–118 (119) (12); *N*-*o*-chlorophenylbenzamidine, 85, 109–110; *N*-*o*-chlorophenylphenylacetamidine, 42, 109–110 (111–112) (12); *N*-*m*-chlorophenylbenzamidine, 34, 106–107; *N*-*m*-chlorophenylphenylacetamidine, 82, 87–88; *N*-*p*-chlorophenylbenzamidine, 99, 116–119; *N*-*p*-chlorophenylphenylacetamidine, 68, 114–115; *N*-*p*-bromophenylbenzamidine, 65, 115–116; *N*-*p*-bromophenylphenylacetamidine, 57, 119–120; N-α-naphthylbenzamidine, 54, 139–140 (140–142) (14); *N*-α-naphthylphenylacetamidine, 39, 123–124.

LTA oxidation of N-*phenylbenzamidine*

To a stirred solution of *N*-phenylbenzamidine (1.96 g, 0.01 mol) in dichloromethane (25 mL) was added LTA (4.88 g, 0.011 mol) in small portions over 15 min. After the complete addition of LTA, the reaction mixture was refluxed for 1½ hours. After careful removal of the solvent, the reaction mixture was treated with hot benzene and filtered. The filtrate was then washed with water and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the 2-phenylbenzimidazole (1.73 g; 89%), obtained on addition of a mixture (1:1) of benzene and hexane to the residue, was recrystallized from a mixture (9:1) of benzene and ethanol; mp. 288–289°C (lit. (14) mp 289–290°C); ir (Nujol) ν_{max}: 3400 (weak broad band, ν_{N-H}), 2960, 2920, 2860 (ν_{C-H}), 1590, 1540, 1495 (v. weak), 1465, 1445 ($\nu_{C=C}$ and $\nu_{C=N}$). (These ir bands are common in all the 2-arylbenzimidazoles reported in this paper). *Anal.* calcd. for $C_{13}H_{10}N_2$: C 80.41, H 5.16, N 14.43%; found: C 80.77, H 5.09, N 13.94%. Mol. Wt. calcd.: 194; found (ms): 194.

Other 2-phenylbenzimidazoles (Table 1, 2–6) were obtained similarly by LTA oxidation of the corresponding *N*-arylbenzamidines.

LTA oxidation of N-*phenylphenylacetamidine*

To a stirred solution of *N*-phenylphenylacetamidine (2.10 g; 0.01 mol) in dichloromethane (25 mL) and pyridine (8 mL) was added LTA (4.88 g; 0.011 mol) in small portions in about 15 min. After the complete addition of LTA, the reaction mixture was heated in an oil bath (80–90°C) for 1½ hours. The solvent was then removed under reduced pressure and the residue so obtained was extracted with hot benzene. The benzene extracts were washed with water and dried over anhydrous sodium sulphate. The solvent was then removed under reduced pressure and the 2-benzylbenzimidazole (1.89 g; 90%), obtained on addition of a mixture (1:1) of benzene and hexane, was

[4]This kind of electron delocalization is absent for the formation of 2-anilinoindoles (**11**).

TABLE 1. Condensed 2-phenylbenzimidazoles

No.	Name of the compound[a,b]	Melting point °C (lit. mp) (ref)	Yield (%)	Nuclear magnetic resonance spectrum (δ)[c]
1.	2-Phenylbenzimidazole	288–289 (289–290) (14)	89	3.20 (b, 1H, —N—H) and 7.60 (m, 9H, aromatic)
2.	4(7)Methyl-2-phenylbenzimidazole	246–247 (247–248)	77	2.45 (s, 3H, —CH_3), 3.22 (b, 1H, —N—H), and 7.60 (m, 8H, aromatic)
3.	5(6)Methyl-2-phenylbenzimidazole	241–242 (241–243) (15)	77	2.42 (s, 3H, —CH_3), 3.10 (b, 1H, —N—H), and 7.55 (m, 8H, aromatic)
4.	5(6)Chloro-2-phenylbenzimidazole	209–210 (210–212) (15)	83	3.65 (b, 1H, —N—H) and 7.65 (m, 8H, aromatic)
5.	4(7)Chloro-2-phenylbenzimidazole	226–227	78	2.90 (b, 1H, —N—H) and 7.60 (m, 8H, aromatic)
6.	5(6)Bromo-2-phenylbenzimidazole	201–202	77	3.45 (b, 1H, —N—H) and 7.65 (m, 8H, aromatic)
7.	2-Phenyl-1*H*-naphtho[1,2-*d*]imidazole	213–214 (215–216) (14)	83	3.50 (b, 1H, —N—H) and 7.90 (m, 12H, aromatic)

[a]Satisfactory elemental analysis was found for all these compounds.
[b]All these compounds were recrystallized from a mixture (9:1) of benzene and ethanol.
[c]The nmr spectra were taken in $CDCl_3$ with the minimum amount of added DMSO d_6.

TABLE 2. Condensed 2-benzylbenzimidazoles

No.	Name of the compound[a]	Melting point °C (lit. mp) (ref)	Yield (%)	Nuclear magnetic resonance spectrum ($CDCl_3$) δ:
1.	2-Benzylbenzimidazole	182–183 (183–184) (14)	90	4.20 (s, 2H, —CH_2—), 5.30 (b, 1H, —N—H), and 7.30 (m, 9H, aromatic)
2.	2-Benzyl-4(7)-methylbenzimidazole	163	98	2.50 (s, 3H, —CH_3), 4.15 (s, 2H, —CH_2—), and 7.35 (m, 9H, aromatic and —N—H)
3.	2-Benzyl-5(6)-methylbenzimidazole	146–147	95	2.40 (s, 3H, —CH_3), 4.10 (s, 2H, —CH_2—), and 7.15 (m, 9H, aromatic and —N—H)
4.	2-Benzyl-4(7)-chlorobenzimidazole	182	88	4.22 (s, 2H, —CH_2—) and 7.25 (m, 9H, aromatic and —N—H)
5.	2-Benzyl-5(6)-chlorobenzimidazole	172–173	96	4.05 (s, 2H, —CH_2—) and 7.15 (m, 9H, aromatic and —N—H)
6.	2-Benzyl-5(6)-bromobenzimidazole	179–180	86	4.18 (s, 2H, —CH_2—) and 7.50 (m, 9H, aromatic and —N—H)
7.	2-Benzyl-1*H*-naphtho[1,2-*d*]imidazole	185–186	81	4.10 (s, 2H, —CH_2—) and 7.65 (m, 13H, aromatic and —N—H)

[a]Satisfactory elemental analysis was found for all these compounds. All these compounds were recrystallized from benzene.

recrystallized from benzene, mp 182–183°C (lit. (14) mp 183–184°C). *Anal.* calcd. for $C_{14}H_{12}N_2$: C 80.77, H 5.77, N 13.46%; found: C 81.36, H 5.60, N 12.84%.

Other 2-benzylbenzimidazoles (Table 2, 2–6), 2-benzyl-*1H*-naphtho[1,2-*d*]imidazole (Table 2, 7), and 2-phenyl-*1H*-naphtho[1,2-*d*]imidazole (Table 1, 7) were prepared similarly by the LTA/CH_2Cl_2/pyridine oxidation of the corresponding *N*-arylphenylacetamidines, *N*-α-naphthylphenylacetamidine, and *N*-α-naphthylbenzamidine respectively.

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1. R. L. SHRINER and F. W. NEUMANN. Chem. Rev. **35**, 351 (1944).
2. P. OXLEY and W. F. SHORT. J. Chem. Soc. **69**, 449 (1949).
3. P. OXLEY, M. W. PARTRIDGE, and W. F. SHORT. J. Chem. Soc. 1110 (1947).
4. M. W. PARTRIDGE and H. A. TURNER. J. Chem. Soc. 2086 (1958).
5. V. J. GRENDA, R. E. JONES, G. GAL, and M. SLETZINGER. J. Org. Chem. **30**, 259 (1965).
6. S. PATAI. The chemistry of amidines and imidates. John Wiley & Sons, New York. 1975. p. 321.
7. W. LWOWSKI and T. W. MATTINGLY. J. Am. Chem. Soc. **87**, 1947 (1965).
8. J. S. MCCONAGHY and W. LWOWSKI. J. Am. Chem. Soc. **89**, 2357 (1967).
9. I. BROWN and O. E. EDWARDS. Can. J. Chem. **45**, 2599 (1967).
10. S. YAMADA, S. TERASHIMA, and K. ACHIWA. Chem. Pharm. Bull. Jpn. **13**, 751 (1965).
11. W. LWOWSKI and S. LINKE. Justus Liebigs Ann. Chem. 8 (1977).
12. P. OXLEY and W. F. SHORT. J. Chem. Soc. 149 (1946).
13. F. C. COOPER and M. W. PARTRIDGE. J. Chem. Soc. 259 (1953).
14. E. HARUKI, T. INAIKI, and E. IMOTO. Bull. Chem. Soc. Jpn. **41**, 1361 (1968).
15. J. I. G. CADOGAN, R. MARSHALL, D. M. SMITH, and M. J. TODD. J. Chem. Soc. 2441 (1970).