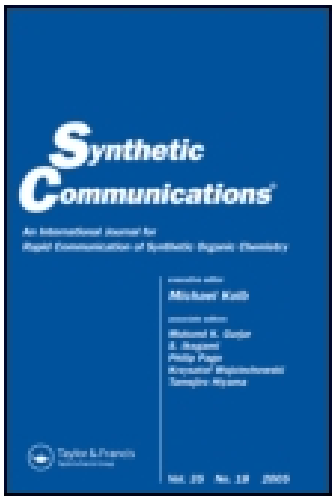

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AMMONIUM SULPHATE-MAGNESIUM SELECTIVE REDUCTION OF *N*-2-NITROPHENYLIMIDATES: SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLES

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ABSTRACT

Various *N*-2-nitrophenylimidates were selectively reduced by $(NH_4)_2SO_4$-Mg to the non-isolated *N*-2-aminophenylimidates which cyclise to the corresponding 2-substituted benzimidazoles.

INTRODUCTION

Benzimidazoles derivatives are an important class of heterocyclic compounds which have biological activities[1–3] and interesting pharmacological

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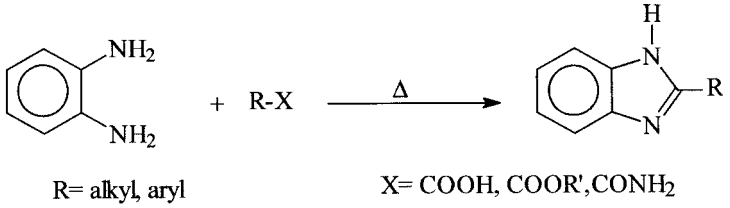
properties.[4,5] In general, 2-substituted benzimidazoles depicted in Scheme 1 were prepared by the condensation of *o*-phenylenediamine with carbonyl-containing compounds, such as carboxylic acids, esters or amides.[6-8]



Scheme 1.

As a part of our continuing studies on *N*-substituted imidates,[9–12] we report in the present investigation the synthesis of some 2-substituted benzimidazoles, in a single step and under very mild conditions, by using *N*-2-nitrophenylimidates as starting materials.

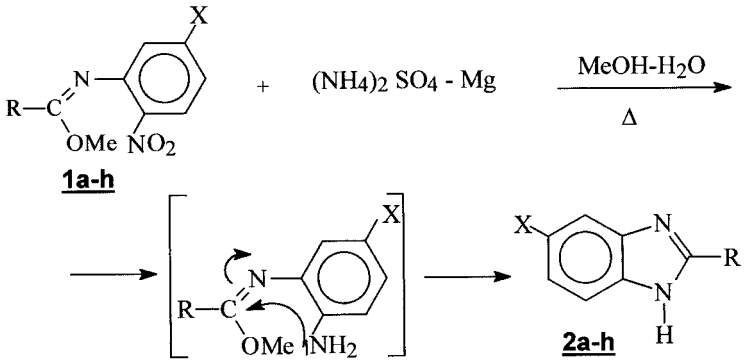
RESULTS AND DISCUSSION

Treatment of *N*-2-nitrophenylimidates **1a–h** with the reducing system $(NH_4)_2SO_4$-Mg described by Prajapati and Al.,[13] using methanol and water as solvent and heating at 60°C during 0.5 h gives respectively benzimidazoles **2a–h** in good yield (table). The formation of compounds **2** proceeds

Table. Reduction of *N*-2-nitrophenylimidates by $(NH_4)_2SO_4$-Mg and Formation of Benzimidazoles **2**

Product	R	X	Yield (%)	M.P. (°C)	Reported (M.P.)[14]
2a	CH_3	H	92	168–170	169–171
2b	C_2H_5	H	88	177–179	178–180
2c	Ph	H	85	265–267	266–269
2d	H	H	76	106–108	108–110
2e	CH_3	CH_3	86	198–200	280–301
2f	C_2H_5	CH_3	82	216–218	218–220
2g	Ph	CH_3	85	231–233	232–234
2h	H	CH_3	78	121–122	119–121

presumably by selective reduction of the functional group -NO_2 and formation of the non-isolated intermediary *N*-2-aminophenylimidates which undergo cyclization (Scheme 2).



Scheme 2.

The structures of compounds **2a–h** have been unambiguously characterized on the basis of their IR, NMR (^{1}H, ^{13}C) and mass spectra.

The IR spectra show the characteristic bands of NH, C=N and C=C aromatic, the ^{1}H and ^{13}C NMR spectra display the characteristic signals of protons and carbons of all the substituents (aromatics, R and X), their spectral data are presented in the experimental part. It is noteworthy that the EI-MS spectra of the compounds **2** record the existence of the molecular ion peaks as the base peaks indicating that the heterocycle skeletons are stable under the EI-MS conditions.

In conclusion, these results demonstrated a versatile and selective reducing system for *N*-2-nitrophenylimidates; the *N*-2-aminophenylimidates were not isolated and the reaction afforded directly the corresponding 2-substituted benzimidazoles **2** in good yield.

EXPERIMENTAL

The uncorrected melting points were determined by a Büchi 510 apparatus. IR spectra were recorded on a Perkin-Elmer 681 and band positions were reported in wave numbers (cm^{-1}) (KBr pellet). NMR spectra of compounds **2** (^{1}H at 300 MHz ($CDCl_3$) and ^{13}C at 75 MHz ($CDCl_3$)) were carried out on a VARIAN unity spectrometer using tetramethylsilane as the

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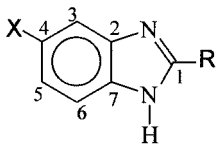
internal standard. Mass spectra were recorded on a HP micromass 5890A instrument.

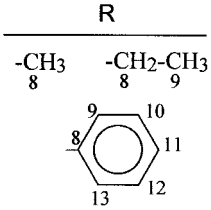
Synthesis of *N*-2-Nitrophenylimidates 1a–h: The *N*-2-nitrophenylimidates **1** were obtained according to the literature[16,17] by the following procedure: A solution of 2-nitroaniline (1.38 g, 10 mmol) in triethylorthoacetate (30 mL) was refluxed until TLC (ethyl acetate : hexane : 1 : 1) indicated that the starting material was converted. Excess of orthoacetate was removed *in vacuo*, and the resultant nearly pure **1a** obtained on more than 80% was used without further purification.

Synthesis of 2-Substituted Benzimidazoles 2a–h: General procedure: A solution of the *N*-2-nitrophenylimidate **1a** (5.12 g, 20 mmol) was added to a mixture of magnesium (2.19 g, 120 mmol) and ammonium sulphate (26.40 g, 200 mmol dissolved in 6 ml of water) in methanol (50 mL). The reaction mixture was stirred at 60°C for about 30 min and then quenched by addition of water and ether. The product was extracted with ether (3×50 mL), washed with water and dried over Na_2SO_4. After evaporation of the solvent the residual oily material was chromatographed on a silica gel 60 (Fluka) (ether : ethylacetate : 70 : 30) to yield 2-substituted benzimidazoles **2a** as a solid recrystallized from ethanol.

Spectroscopic data (IR: ν (cm^{-1}), ^{1}H-NMR: δ (ppm), J (Hz), ^{13}C-NMR: δ (ppm), MS: (*m*/*z* (%)) of benzimidazoles **2a–h** are given here:



2a-h



2a: IR: 3360 (NH), 1630 (C=N), 1580 (C=C); ^{1}H-NMR 3.0 (s, 3H), 7.4–7.8 (m, 4H), 9.6 (s, 1H, NH); ^{13}C-NMR 149.5 (C1), 136.8 (C2), 131.6 (C7), 18.9 (C8), 114.5–126.4 (other C. arom.); MS: 132 (M^+, 100), 131 (79), 104 (12), 133 (12), 77 (8).

2b: IR: 3350 (NH), 1635 (C=N), 1560 (C=C); ^{1}H-NMR: 1.1 (t, 3H, J = 7.5), 3.1 (q, 2H, J = 7.5), 7.3–7.9 (m, 4H), 9.0 (s, 1H, NH); ^{13}C-NMR: 149.3 (C1), 137.4 (C2), 130.2 (C7), 20.0 (C9), 54.5 (C8), 115.5–124.5 (other C. arom.); MS: 146 (M^+, 100), 145 (95), 147 (10), 77 (6), 56 (10).

2c: IR: 3370 (NH), 1640 (C=N), 1560 (C=C); ^{1}H-NMR: 7.2–8.1 (m, 9H), 9.5 (s, 1H, NH); ^{13}C-NMR: 149.7 (C1), 136.8 (C2), 131.6 (C7), 118.8–128.2 (other C. arom.); MS: 194 (M^+, 100), 193 (92), 166 (9), 77 (8), 104 (12).

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2d: IR: 3350 (NH), 1640 (C=N), 1550 (C=C); ^{1}H-NMR: 6.4 (s, 1H), 7.3–7.7 (m, 4H), 8.5 (s, 1H, NH); ^{13}C-NMR: 150.6 (C1), 136.8 (C2), 131.6 (C7), 119.2–127.0 (other C. arom.); MS: 118 (M^+, 100), 117 (85), 77 (12), 104 (6).

2e: IR: 3365 (NH), 1635 (C=N), 1560 (C=C); ^{1}H-NMR: 2.4 (s, 3H), 3.0 (s, 3H), 7.3–7.9 (m, 3H), 10.2 (s, 1H, NH); ^{13}C-NMR: 150.1 (C1), 137.7 (C2), 129.6 (C7), 20.2 (C8), 13.8 (C14), 112.5–121.7 (other C. arom.); MS: 146 (M^+, 92), 145 (100), 77 (18), 104 (15), 51 (16).

2f: IR: 3360 (NH), 1630 (C=N), 1550 (C=C); ^{1}H-NMR 1.1 (t, 3H, J = 7.2), 3.2 (q, 2H, J = 7.2), 2.5 (s, 3H), 7.2–8.0 (m, 3H), 9.2 (s, 1H, NH); ^{13}C-NMR: 149.8 (C1), 136.8 (2), 128.8 (C7), 19.6 (C8), 57.0 (C9), 14.5 (C14), 120.0–128.5 (other C. arom.); MS: 160 (M^+, 100), 159 (90), 104 (12), 77 (15).

2g: IR: 3340 (NH), 1640 (C=N), 1560 (C=C); ^{1}H-NMR: 2.4 (s, 3H), 7.1–8.0 (m, 8H), 8.5 (s, 1H, NH); ^{13}C-NMR: 150.5 (C1), 135.8 (C2), 130.2 (C7), 13.0 (C14), 118.8–128.2 (other C. arom.); MS: 208 (M^+, 100), 207 (77), 209 (18), 104 (22), 77 (20).

2h: IR: 3355 (NH), 1640 (C=N), 1550 (C=C); ^{1}H-NMR: 2.4 (s, 3H, 6.5 (s, 1H), 7.2–7.7 (m, 3H), 9.0 (s, 1H, NH); ^{13}C-NMR: 150.4 (C1), 136.6 (C2), 130.2 (C7), 13.5 (C14), 122.5–126.0 (other C. arom.); MS: 132 (M^+, 100), 131 (83), 77 (18), 133 (12), 77 (8).

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