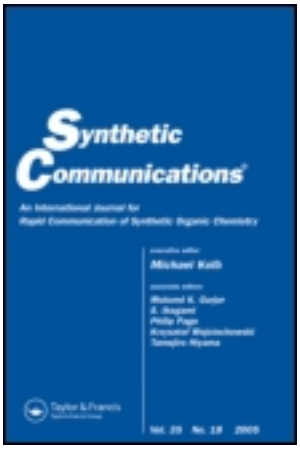

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N-Hydroxyphthalimide/Cobalt Acetate, a New Catalytic Oxidative System for the Synthesis of Benzimidazoles

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Abstract: Benzimidazoles are readily prepared from 1,2-phenylenediamine and an aldehyde using air and catalytic N-hydroxyphthalimide/$Co(OAc)_2$ as the oxidant. Both electron-donating and electron-withdrawing groups are tolerated.

Keywords: Aerobic oxidation, aldehyde, benzimidazoles, N-hydroxyphthalimide

INTRODUCTION

The benzimidazole heterocycle is an important structural element present in a variety of pharmacologically active molecules including the essential vitamin B-12. 2-Arylbenzimidazoles play an important role as pharmacophores in molecules exhibiting antiviral,[1] antibacterial,[2] anti-inflammatory,[2–4] antitumor,[5] anti-hypertensive,[6] and cardiotonic[7] activities.

Classical preparation of 2-arylbenzimidazoles (**5**) involves acylation of 1,2-phenylenediamine (**1**) to provide amide **2** followed by a dehydrative cyclization under thermal conditions,[8] acidic conditions (e.g., HOAc,[9] p-TosOH,[10] HCl,[11] zeolite[12]), or neutral conditions using reagents such as P_2O_5.[13] Another route that has gained popularity is a single-step procedure involving the condensation of **1** with an aldehyde

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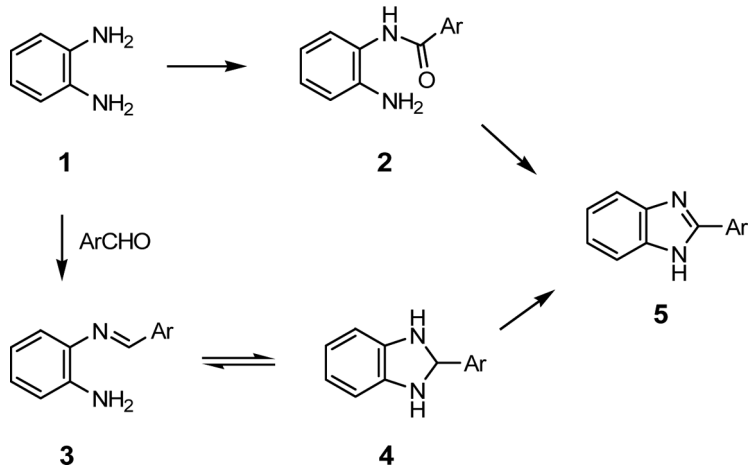
to afford Schiff base **3**, which then proceeds through the intermediacy of benzimidazoline **4**, which, in the presence of an oxidizing agent, affords the desired benzimidazole **5**. A wide variety of oxidants such as $Pb(OAc)_4$,[14] $FeCl_3$,[15] sulfamic acid,[16] $Yb(OTf)_3$,[17] $Sc(OTf)_3$,[18] oxone,[19] H_2O_2/HCl,[20] and $KHSO_4$[21] have been employed to effect the dehydrogenation step. Although many of these methods are practical, some have liabilities such as dangerous or toxic reagents, stoichiometry of the reactants, or the formation of N-benzylbenzimidazole side products resulting from further reaction of the aldehyde with **4** prior to oxidation.



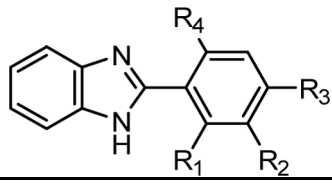
The organic catalyst N-hydroxyphthalimide (NHPI) has sporadically been used in aerobic oxidations of hydrocarbons,[22] proceeding via a phthalimide N-oxyl radical. Reactions are performed under an oxygen atmosphere in benzonitrile at elevated temperatures. The scope of the oxidation was broadened to include alcohols by enhancing the catalytic activity of NHPI with small quantities of $Co(acac)_n$ ($n = 2$ or 3)[23,24]; however, the process still required elevated temperature (100 °C). It was later found that using $Co(OAc)_2$ as the cocatalyst allowed reactions to be performed at ambient temperature.[25] This methodology has also been applied to the oxidative aromatization of Hantzsch dihydropyridines to pyridines with similar results. In the presence of only NHPI, aromatization occurs in refluxing acetonitrile over several hours[26]; however, in the presence of both NHPI and $Co(OAc)_2$, the reaction proceeds at ambient temperature.[27] These encouraging results prompted the investigation as to whether this catalytic system could be used in the oxidative dehydrogenation of **4** to **5**.

RESULTS AND DISCUSSION

Because all previously reported oxidations using NHPI were conducted under an oxygen atmosphere, we wanted to ascertain whether it is imperative to use an oxygen atmosphere or if air would suffice. Gratifyingly, the reaction of **1** with 4-methoxybenzaldehyde catalyzed by 10 mol% NHPI and a minute amount of $Co(OAc)_2$ in acetonitrile in air furnished the benzimidazole in 83% yield. Because it had been reported that benzimidazoles can be formed using only air as the oxidant, albeit at elevated temperatures,[28] a parallel reaction was performed without the NHPI/$Co(OAc)_2$ catalyst, and no benzimidazole was produced.

The scope of the reaction was investigated using a variety of benzaldehydes possessing electron-donating or electron-withdrawing groups at the *ortho*, *meta* or *para* positions, and the results are listed in Table 1. Reactions using benzaldehydes containing electron-donating groups were generally complete within 6 h; however, they were usually allowed to stir

Table 1. Substituted 2-arylbenzimidazoles



Entry	R_1	R_2	R_3	R_4	Yield (%)	Mp (°C)	Lit. Mp (°C) [ref]
1	H	H	OMe	H	83	224–227	226[29]
2	OMe	H	H	H	60	165–168	171.7–173.9[30]
3	H	OMe	OMe	H	83	216–219	227–228[16]
4	SMe	H	H	H	61	222–224	—
5	Me	H	H	H	79	220–222	221[31]
6	H	Cl	H	H	61	229–231	235–239[12]
7	Cl	H	Cl	H	68	224–226	227–228.5[32]
8	Cl	H	H	Cl	63	> 290	—
9	H	CF_3	H	H	85	208–210	—
10	H	H	CF_3	H	81	267	—
11	H	H	COOMe	H	85	228–231	220–222[33]
12	H	H	SO_2Me	H	70	282	> 300[6]
13	H	NO_2	H	H	76	203–206	203–205[16]
14	CN	H	H	H	59	248–250	—

overnight. Reactions with benzaldehydes containing electron-withdrawing groups generally required 18 h for completion, although two analogs, *p*-CF_3 and *p*-SO_2Me (entries 10 and 12), took 72 h and the *o*-CN analog (entry 14) was particularly sluggish, taking 6 days for complete conversion. Performing the reaction under an oxygen atmosphere increases the rate of oxidation somewhat. For example, parallel reactions were carried out on the *m*-CF_3 analog (entry 9), one in air and one under oxygen. After 9 h, conversion of the corresponding benzimidazoline **4** to benzimidazole **5** reached 57%, whereas under oxygen 79% conversion was observed. In either case, complete conversion was achieved after 18 h.

In conclusion, it has been demonstrated that air and NHPI/Co $(OAc)_2$ is a viable catalytic oxidative system for the conversion of benzimidazolines to benzimidazoles in the reaction of 1,2-phenylenediamine with benzaldehydes.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Uni-melt or Büchi B-545 melting-point apparatus and are uncorrected. All ^1H NMR spectra were recorded on a Bruker 400 Ultrashield instrument, and chemical shifts are relative to internal Me_4Si.

General Procedure for the Preparation of Benzimidazoles

A solution of 216 mg (2 mmol) of **1** and 2 mmol of the appropriate aldehyde in 6 mL of MeCN was stirred at room temperature for 15 min, and then 32 mg (0.2 mmol) of NHPI and 2 mg of $Co(OAc)_2$ were added. The mixture became dark brown and was stirred at room temperature for 18 h. Water was added, and the mixture was extracted with EtOAc. The organic phase was washed with brine and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished the crude product, which was purified either by trituration with methylene chloride or by silica-gel chromatography using 10% EtOAc/methylene chloride as eluent.

Spectral Data for Compounds in Table 1

Entry 1: ^1H NMR (DMSO-d_6): δ 12.74 (s, 1H), 8.12 (d, $J = 8.97$ Hz, 2H), 7.56 (s, broad, 2H), 7.17 (m, 2H), 7.11 (d, $J = 8.97$ Hz, 2H), 3.84 (s, 3H).

Entry 2: ^1H NMR (DMSO-d_6): δ 12.12 (s, 1H), 8.32 (d, $J = 9.6$ Hz, 1H), 7.65–7.60 (m, 2H), 7.48 (t, 1H), 7.25 (d, $J = 8.08$ Hz, 1H), 7.19 (m, 2H), 7.12 (t, 1H), 4.03 (s, 3H).

Entry 3: ^{1}H NMR (DMSO-d_6): δ 12.76 (s, broad, 1H), 7.78–7.73 (m, 2H), 7.57 (s, broad, 2H), 7.20–7.15 (m, 2H), 7.13 (d, $J = 8.34$ Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H).

Entry 4: ^{1}H NMR (DMSO-d_6): δ 12.69 (s, 1H), 7.74 (d, $J = 6.44$ Hz, 1H), 7.68 (d, $J = 7.71$ Hz, 1H), 7.53–7.44 (m, 3H), 7.31 (t, 1H), 7.26–7.18 (m, 2H), 2.43 (s, 3H).

Entry 5: ^{1}H NMR (DMSO-d_6): δ 12.62 (s, 1H), 7.74 (d, $J = 7.20$ Hz, 1H), 7.68 (d, $J = 7.58$ Hz, 1H), 7.52 (d, $J = 7.45$ Hz, 1H), 7.43–7.34 (m, 3H), 7.25–7.17 (m, 2H), 2.61 (s, 3H).

Entry 6: ^{1}H NMR (DMSO-d_6): δ 13.05 (s, 1H), 8.23 (s, 1H), 8.15 (d, $J = 7.07$ Hz, 1H), 7.69 (d, $J = 7.45$ Hz, 1H), 7.62–7.54 (m, 3H), 7.23 (m, 2H).

Entry 7: ^{1}H NMR (DMSO-d_6): δ 12.78 (s, 1H), 7.94 (d, $J = 8.46$ Hz, 1H), 7.86 (s, 1H), 7.71 (d, $J = 7.58$ Hz, 1H), 7.63 (d, $J = 10.61$ Hz, 1H), 7.58 (d, $J = 7.58$ Hz, 1H), 7.25 (m, 2H).

Entry 8: ^{1}H NMR (DMSO-d): δ 12.85 (s, 1H), 7.72–7.59 (m, 4H), 7.55 (d, $J = 8.34$ Hz, 1H), 7.25 (m, 2H).

Entry 9: ^{1}H NMR (DMSO-d_6): δ 13.18 (s, 1H), 8.53 (s, 1H), 8.49 (d, $J = 7.83$ Hz, 1H), 7.88–7.79 (m, 2H), 7.71 (d, $J = 7.71$ Hz, 1H), 7.58 (d, $J = 7.58$ Hz, 1H), 7.25 (m, 2H).

Entry 10: ^{1}H NMR (DMSO-d_6): δ 13.19 (s, 1H), 8.39 (d, $J = 8.08$ Hz, 2H), 7.94 (d, $J = 8.21$ Hz, 2H), 7.72 (d, $J = 7.71$ Hz, 1H), 7.58 (d, $J = 7.33$ Hz, 1H), 7.25 (m, 2H).

Entry 11: ^{1}H NMR (DMSO-d_6): δ 13.15 (s, 1H), 8.32 (d, $J = 8.34$ Hz, 2H), 8.13 (d, $J = 8.46$ Hz, 2H), 7.71 (d, $J = 7.58$ Hz, 1H), 7.57 (d, $J = 7.74$ Hz, 1H), 7.25 (m, 2H).

Entry 12: ^{1}H NMR (DMSO-d_6): δ 13.22 (s, 1H), 8.42 (d, $J = 8.46$ Hz, 2H), 8.11 (d, $J = 8.46$ Hz, 2H), 7.72 (d, $J = 7.83$ Hz, 1H), 7.58 (d, $J = 7.71$ Hz, 1H), 7.26 (m, 2H), 3.30 (s, 3H).

Entry 13: ^{1}H NMR (DMSO-d_6): δ 13.31 (s, 1H), 9.02 (s, 1H), 8.62 (d, $J = 7.83$ Hz, 1H), 8.34 (d, $J = 6.82$ Hz, 1H), 7.87 (t, 1H), 7.73 (d, broad, $J = 7.58$ Hz, 1H), 7.59 (d, broad, $J = 7.45$ Hz, 1H), 7.26 (m, 2H).

Entry 14: IR (ATR mode): 2226 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 13.11 (s, 1H), 8.09 (d, $J = 8.59$ Hz, 1H), 8.04 (d, $J = 6.82$ Hz, 1H), 7.90 (t, 1H), 7.76–7.68 (m, 2H), 7.60 (d, $J = 7.71$ Hz, 1H), 7.28 (m, 2H).

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