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A mild, one-pot synthesis of disubstituted benzimidazoles from 2-nitroanilines

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Abstract—A one-pot synthesis of disubstituted benzimidazoles from 2-nitroanilines is described. Hydrogenation of N-substituted 2-nitroanilines with palladium on carbon as catalyst in the presence of trimethyl orthoformate and catalytic pyridinium *p*-toluenesulfonate (PPTS) at room temperature provided good to excellent yields of the corresponding disubstituted benzimidazoles.

Benzimidazoles have a ubiquitous presence in pharmaceuticals,[1] such as in entire classes of anthelmintics[2] and proton pump inhibitors.[3] Classically, benzimidazoles are prepared from 1,2-dianilines by acid-promoted dehydrative cyclocondensation with a carbonyl derivative, often at elevated temperatures.[4] The requisite 1,2-dianilines are most often produced by reduction of the corresponding 2-nitroaniline compounds.

This common sequence of events suggested to us and other groups that these transformations could be conveniently combined into one pot. Indeed, others have recently reported methods for preparing benzimidazoles directly from 2-nitroanilines.[5–9] These methods, however, use stoichiometric amounts of toxic metals or require forcing conditions such as strong protic acids and/or elevated temperatures. We now report a simple and mild one-pot method for the synthesis of benzimidazoles from 2-nitroanilines by hydrogenation with a suitable heterogeneous catalyst at room temperature in the presence of trimethyl orthoformate,[10] either as solvent or a co-solvent, and a mild acid co-catalyst (pyridinium *p*-toluenesulfonate or formic acid).

The general process is outlined in the reaction optimization for the conversion of nitroaniline **1a** to benzimidazole **2a** (Table 1). Simply, hydrogenation of **1a** with a suitable heterogeneous catalyst at room temperature in the presence of trimethyl orthoformate, either as solvent or a co-solvent with ethyl acetate, and a mild acid co-catalyst directly afforded **2a**.

A variety of heterogeneous catalysts may be used (Table 1, entries 1–6), with the exception of rhodium on alumina. Further optimization was conducted with palladium on carbon as the catalyst. It was not necessary to use trimethyl orthoformate as the solvent; a 10-fold excess was sufficient to provide good yields, although using less than 10 equiv resulted in a reduction in yield (entries 7 and 8). The optimal catalyst loading was determined to be 5 mol %; further reduction in catalyst loading resulted in prolonged reaction times and diminished yields (entries 9 and 10). Both pyridinium *p*-toluenesulfonate (PPTS) and formic acid were suitable acid co-catalysts (entries 7 and 12). Ultimately, it was determined for this particular substrate that an acid co-catalyst was not necessary at all (entries 11 and 13). This phenomenon was not general when extended to other substrates, however. Therefore, the preferred conditions were hydrogenation at 50 psi with 5 mol % palladium on carbon, using ethyl acetate as solvent, in the presence of 10 equiv of trimethyl orthoformate and 10 mol % PPTS.[11] The ability to employ a number of different catalysts, however, can provide a wider scope of functional group tolerance (vide infra).

The substrate scope of this method is outlined in Table 2. A variety of functionality can be placed on the aniline

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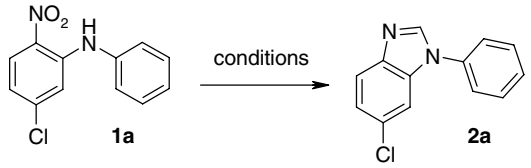
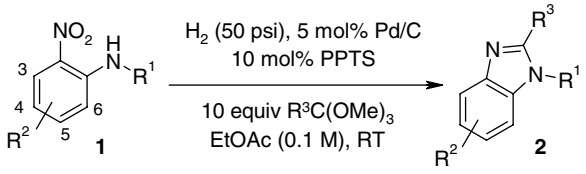
Table 1. Optimization of one-pot hydrogenation/cyclization conditions for substrate **1a**[a]

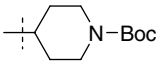
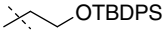


Entry	Catalyst (mol %)	Co-catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1	Pd/C (5)	PPTS (10)	$HC(OMe)_3$	2.5	92
2	Pt/C (5)	PPTS (10)	$HC(OMe)_3$	4	95
3	Sulfided Pt/C (5)	PPTS (10)	$HC(OMe)_3$	5	92
4	$Pd(OH)_2/C$ (5)	PPTS (10)	$HC(OMe)_3$	6	98
5	Rh/Al_2O_3 (5)	PPTS (10)	$HC(OMe)_3$	5	0
6	Pd/C (10)[c]	PPTS (20)	$HC(OMe)_3$	17	85[d]
7	Pd/C (5)	PPTS (10)	EtOAc + 10 equiv $HC(OMe)_3$	7	100
8	Pd/C (5)	PPTS (10)	EtOAc + 1.5 equiv $HC(OMe)_3$	3	74[d]
9	Pd/C (1)	PPTS (10)	EtOAc + 1.5 equiv $HC(OMe)_3$	24	<10
10	Pd/C (2.5)	PPTS (10)	EtOAc + 10 equiv $HC(OMe)_3$	6	74[d]
11	Pd/C (5)	PPTS (1)	EtOAc + 10 equiv $HC(OMe)_3$	8	100
12	Pd/C (5)	HCO_2H (10)	EtOAc + 10 equiv $HC(OMe)_3$	5	100
13	Pd/C (5)	None	EtOAc + 10 equiv $HC(OMe)_3$	3	90[d]

[a] All reactions were conducted in a Fischer–Porter hydrogenation apparatus at 50 psi of H_2 unless otherwise indicated.
[b] Yields refer to yields of pure (by LC/MS) product following aqueous work-up. Column chromatography was not required unless otherwise indicated.
[c] Reaction was conducted under a balloon (~1 atm) of H_2.
[d] Isolated yield following column chromatography.

Table 2. Substrate scope of one-pot reduction–cyclization of 2-nitroanilines



Entry	Nitroaniline	R^1	R^2	R^3	Time (h)	Product	Yield[a] (%)
1	**1a**	Ph	5-Cl	H	3	**2a**	100[b]
2	**1b**	H	5-Cl	H	23	**2b**	0[c]
3	**1c**	H	4-OMe	H	12	**2c**	0[d]
4	**1d**	H	5-OMe	H	5	**2d**	0[c]
5	**1e**	Me	5-Cl	H	6	**2e**	88
6[e]	**1f**	*i*-Pr	H	H	6	**2f**	73
7[f]	**1g**	Bn	H	H	6	**2g**	82
8	**1h**	*p*-$MeOC_6H_4$	H	H	3	**2h**	95
9[e]	**1i**		H	H	6	**2i**	94
10	**1j**		H	H	16	**2j**	80
11[f]	**1k**	Ph	6-Br	H	16	**2k**	75
12[e]	**1l**	*i*-Pr	5-OMOM	H	22	**2l**	60
13	**1m**	Ph	5-Cl	Me	72	**2m**	0[d]

[a] Yield refers to isolated yield of analytically pure (by LC/MS) product following column chromatography, unless otherwise stated.
[b] Product was analytically pure by LC/MS without column chromatography.
[c] Starting material was recovered unchanged.
[d] Starting material was reduced to the dianiline (by LC/MS), but the cyclized product was not observed.
[e] Reaction was performed using the orthoformate as solvent.
[f] Sulfided Pt/C used as catalyst.

nitrogen, such as alkyl, branched alkyl, aryl, and benzyl (entries 1 and 5–10). Both electron-donating and electron-withdrawing substituents are tolerated on the aryl ring (entries 1, 5, and 11–12). A preliminary experiment using trimethyl orthoacetate to obtain a 2-methyl benzimidazole (entry 13) was unsuccessful. In some cases (entries 7 and 11), sulfided platinum on carbon was successfully employed as the catalyst to prevent debenzylation or dehalogenation, respectively, of the substrate.

Interestingly, the only class of substrates for which the method failed was when the aniline nitrogen was unsub-

stituted (entries 2–4). In some cases, only starting 2-nitroaniline was observed. In other cases, we have determined by mass spectroscopy and ^{1}H NMR that the nitro group was rapidly reduced to provide the 1,2-dianiline, but no cyclized products were observed. One hypothesis for this latter result is that the cyclization event is not kinetically favorable for unsubstituted dianilines at room temperature. For example, hydrogenating **1c** to the dianiline in neat trimethyl orthoformate (6 h reaction time), removing the reaction mixture from the hydrogenator, filtering to remove the catalyst, and then heating the filtered solution to 100 °C for 3 h affected complete conversion (by LC/MS) to benzimidazole **2c**. Further experiments are planned to understand the nature of this differential reactivity.

In summary, we have developed a simple and mild one-pot method for the conversion of 2-nitroanilines to benzimidazoles. This method is notable for its mild conditions, requiring only an acid co-catalyst, and may be readily performed at room temperature to prepare a variety of functionalized benzimidazoles.

References and notes

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11. Typical experimental procedure: Benzimidazole **2a** (6-chloro-1-phenyl-1*H*-benzimidazole). To a stirred solution of nitroaniline **1a** (497 mg, 2.00 mmol) and pyridinium *p*-toluenesulfonate (50 mg, 0.20 mmol) in ethyl acetate (20 mL) and trimethyl orthoformate (2.2 mL, 20 mmol) was added palladium on carbon (10 wt %, 106 mg, 0.10 mmol Pd). The reaction mixture was hydrogenated in a Fischer–Porter apparatus under 50 psi of H_2 for 6 h. At the end of the reaction, H_2 was removed and the apparatus was purged with nitrogen. The reaction mixture was filtered to remove the catalyst, and the filter cake was washed with dichloromethane (25 mL). The combined filtrates were concentrated, then redissolved in dichloromethane (25 mL) and washed with 0.1 N aqueous HCl (1×25 mL), saturated aqueous $NaHCO_3$ (1×25 mL), and brine (1×25 mL). The organic fraction was dried over Na_2SO_4, filtered, and concentrated to afford 457 mg (100%) of benzimidazole **2a** as a light gray solid. The product was judged to be >95% pure by HPLC analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.78 (d, 1H, $J = 8.7$ Hz), 7.63–7.57 (m, 2H), 7.52–7.47 (m, 4H), 7.31 (dd, 1H, $J = 2.0$, 8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.0, 142.7, 135.8, 134.4, 130.2, 129.6, 128.4, 124.1, 123.5, 121.5, 110.6. HRMS (ESI): calcd for $C_{13}H_{10}ClN_2$ $[M+H]^+$ 229.0533, found 229.0540. All products in Table 2 gave satisfactory analytical data (^{1}H NMR, HRMS, and LC/MS).