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Phosphite-Mediated Synthesis of Benzimidazoles: A One-Pot Four-Component Approach from Nitrophenols

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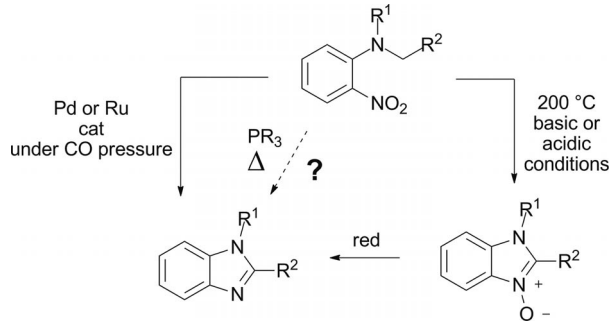
Benzimidazoles may be formed in high yield through the phosphite-triggered reductive cyclization of *o*-nitroaniline derivatives. This reaction was used for the one-pot synthesis of benzimidazoles from *o*-nitrophenols and isocyanides. The mechanism is discussed in relation with nitroso intermediates.

Introduction

In the last 20 years the renewed interest for isocyanide chemistry and isocyanide-based multicomponent reactions (IMCR)[1] is certainly due to their ability to deliver libraries of medicinally privileged structures[2] by using fast and efficient synthetic pathways. Benzimidazoles have been extensively used in medicinal chemistry, displaying antiarrhythmic, antiulcer, anticancer, fungicidal, and antiviral activities.[3] Following our interest in the multicomponent synthesis of heterocycles, we wished to develop fast, multicomponent access towards these scaffolds from simple nitroarene derivatives. Benzimidazoles are usually prepared from *o*-phenylenediamine derivatives,[4] which may be obtained from reduction of nitroaniline intermediates. Two direct paths are reported for the cyclization of *N*,*N*-dialkyl-*o*-nitroanilines (Scheme 1). Their thermal dehydration gives access to benzimidazole oxides that must be reduced in a further step.[5] Metal-catalyzed reductive coupling under CO pressure[6] is more straightforward, but hampered by high prices and safety issues. Thinking about a more convenient cyclodehydration towards benzimidazoles, we surmised that heating the product under reductive conditions with phosphites could lead to benzimidazoles in one step through nitroso intermediates. Nitroarenes, under treatment with phosphites, are known to form nitroso and nitrene derivatives that might insert into various C–H bonds in an intramolecular manner (Cadogan reaction).[7] The Cadogan reaction usually involves C–H aryl bond insertion, but interesting couplings with allyl residues (nitroso–ene reaction)[8] and N–N or N–P bond formation[9] have also been observed. We could not find any benzimidazole synthesis starting from *N*-alkyl-substituted *o*-nitroanilines under Cadogan conditions.[10]



Scheme 1. Benzimidazole formation from nitroanilines.

Results and Discussion

To test these hypotheses on a functionalized starting material, Ugi–Smiles adduct **1a** was prepared from the corresponding benzylamine, isocyanide, and *o*-nitrophenol.[11] Compound **1a** was then heated under neat conditions with triethyl phosphite at 160 °C for 2 h (Scheme 2). We were delighted to observe the formation of benzimidazole **2a** in a 48% isolated yield. After testing different solvents (acetonitrile, toluene, DMF) and temperatures, **1a** was isolated in 69% yield by heating the reaction to reflux in toluene (1 M) by using 12 equiv. of triethyl phosphite. This could be further optimized under microwave conditions: heating in DMF (2 M) at 165 °C for 25 min with $P(OEt)_3$ (8 equiv.) gave **2a** in 80% isolated yield. Both steps, Ugi–Smiles and phosphite reductive cyclization, could be performed in the same pot just replacing MeOH by DMF in the second step with a similar yield (Table 1, Entry 1). This new benzimidazole synthesis was tested on several Ugi–Smiles adducts, as displayed in Table 1, with yields given directly from the starting *o*-nitrophenols.

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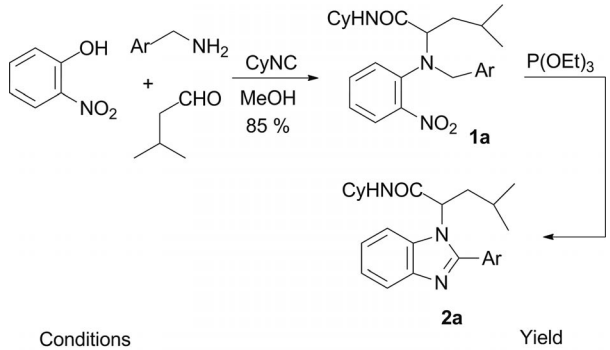
Table 1.One-pot four-component synthesis of benzimidazoles.

Entry	R^1	R^2	R^3	R^4	**2**[a] (Yield)
1	Cy	4-ClC_6H_4	*i*Bu	H	**2a** (80%)
2	Cy	4-$MeOC_6H_4$	*i*Bu	H	**2b** (72%)
3	Cy	4-MeC_6H_4	Et	MeO	**2c** (83%)
4	4-$ClC_6H_4CH_2$	4-ClC_6H_4	Et	MeO	**2d** (61%)
5	4-$MeOC_6H_4CH_2$	Ph	$CH_3(CH_2)_5$	MeO	**2e** (64%)
6	3,4-$(MeO)_2C_6H_3CH_2$	4-$MeOC_6H_4$	*i*Bu	MeO	**2f** (72%)
7	4-$MeOC_6H_4CH_2$	4-MeC_6H_4	*i*Bu	Me	**2g** (74%)
8	Cy	2-ClC_6H_4	Et	MeO	**2h** (73%)
9	*t*Bu	2-$MeOC_6H_4$	Et	MeO	**2i** (60%)
10	*t*Bu	2-furyl	*i*Bu	Me	**2j** (23%)
11	Cy	$Me(CH_2)_2$	Et	Cl	–
12	Cy	CH_2=CH	*i*Bu	H	–

[a] Using $P(OEt)_3$ (8 equiv.) in 2 M DMF in the second step.



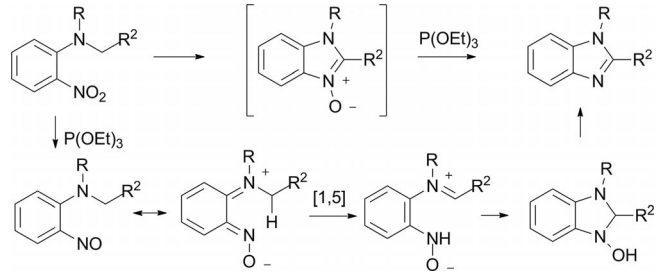
Conditions	Yield
$P(OEt)_3$, neat (1 M) 160 °C 2 h	48 %
$P(OEt)_3$ (10 equiv.), toluene (1 M), 120 °C, 14 h	69 %
$P(OEt)_3$ (10 equiv.), CH_3CN (1 M), 80 °C, 12 h	20 %
$P(OEt)_3$ (10 equiv.), DMF (1 M), 100 °C, 24 h	60 %
$P(OEt)_3$ (8 equiv.), toluene (1 M), MW, 165 °C, 25 min	73 %
$P(OEt)_3$ (8 equiv.), DMF (2 M), 165 °C, 25 min	80 %

Scheme 2. Benzimidazole formation from Ugi–Smiles adduct **1a**.

The reaction is only efficient with benzylic amino derivatives, as shown by the lack of reactivity of allyl and butyl adducts (Table 1, Entries 11 & 12). The lower yield obtained with furfurylamine is due to the formation of important side products in the second step.

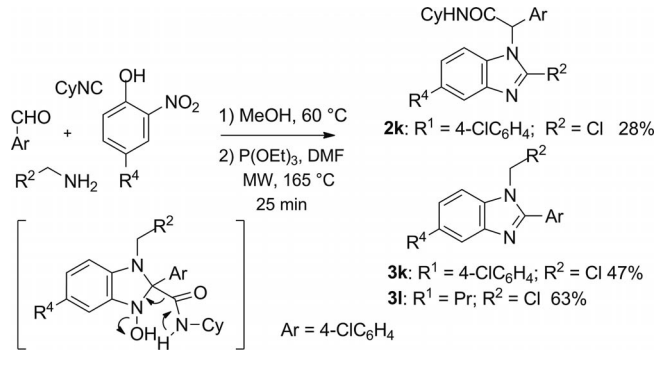
Two mechanistic hypotheses may be advanced for this phosphite-induced reaction. A thermal dehydration to benzimidazole oxides followed by reduction by the phosphite as pictured in Scheme 1 or a prior reduction to nitroso derivatives followed by a 1,5-sigmatropic process, cyclization, and dehydration (Scheme 3).[12]

To give some clues about the mechanism, a solution of Ugi intermediate **1a** in acetic acid was heated at reflux for several days (conditions reported for benzimidazole oxide formation)[5b] as well as heated under microwave conditions at 160 °C for 1 h. The recovery of unreacted **1a** seems to indicate that the nitroso path is more likely followed.



Scheme 3. Possible mechanism.

All examples given in Table 1 involve aliphatic aldehydes. When aromatic aldehydes and benzylic amines react together in the Ugi–Smiles coupling, the presence of two different benzylic positions in the adduct may be associated with selectivity issues. This was confirmed by the formation of a mixture of benzimidazoles **2k** and **3k** when using *p*-



Scheme 4. Fate of aromatic aldehydes.

chlorobenzaldehyde and a benzylic amine as starting partners (Scheme 4). Product **3k** probably results from an intermediate cyclization followed by a final aromatization through isocyanate release. When the amine component cannot be involved in the cyclization process, this pathway is the only one observed, as shown by the exclusive formation of **3l** when starting with butylamine and *p*-chlorobenzaldehyde (Scheme 4).

Conclusions

As a conclusion, we have disclosed a new phosphite-mediated reductive cyclization of *o*-nitroaniline derivatives through the activation of the C–H aminobenzylic position. Combined with a first Ugi–Smiles step, these conditions allowed us to achieve one of the shortest IMCR routes for access to benzimidazole derivatives from simple commercially available starting materials.[13] We are further studying the interest of phosphite-triggered reactions in IMCRs.

Experimental Section

General Procedure for the Synthesis of Benzimidazoles: To a 3 M solution of carbonyl derivative (1 mmol) in methanol was added successively benzylamine (1 mmol), isocyanide (1 mmol, 1.0 equiv.), and *o*-nitrophenol (1 mmol). The reaction mixture was stirred at 60 °C until completion of the Ugi–Smiles coupling and then cooled to room temperature. After removing the excess amount of methanol, the crude Ugi–Smiles adduct was used in the next step. To a 2 M solution of Ugi–Smiles adduct (1 mmol) in DMF was added triethyl phosphite (8 mmol), and the tube was sealed. The mixture was heated under microwave irradiation (165 °C, 200 W) for 25 min. After completion of the reaction, the excess amount of triethyl phosphite was removed in vacuo, and the residue was purified by flash chromatography on silica gel.

2a: The typical procedure was followed employing the isovaleraldehyde (107 μL, 1.0 mmol), *p*-chlorobenzylamine (122 μL, 1.0 mmol), cyclohexylisocyanide (124 μL, 1.0 mmol), *o*-nitrophenol (139 mg, 1.0 mmol), and triethyl phosphite (1.37 mL, 8.0 mmol) to afford compound **2a** (338 mg, 80%) as a white solid by flash chromatography on silica gel. R_f = 0.8 (petroleum ether/diethyl ether, 50:50). M.p. 177–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 7.8 Hz, 1 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.51 (d, J = 8.3 Hz, 2 H), 7.40 (d, J = 7.8 Hz, 1 H), 7.37–7.28 (m, 2 H), 5.84 (br. d, J = 8.3 Hz, 1 H), 5.04 (dd, J = 4.0, 11.1 Hz, 1 H), 3.94–3.83 (m, 1 H), 2.25–2.16 (m, 1 H), 2.12–2.04 (m, 1 H), 1.92–1.82 (m, 2 H), 1.69–1.53 (m, 3 H), 1.40–1.26 (m, 2 H), 1.09–1.00 (m, 2 H), 0.75–0.65 (m, 1 H), 0.89–0.81 (m, 1 H), 0.59 (d, J = 6.3 Hz, 3 H), 0.43 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.1, 154.1, 143.6, 136.6, 133.3, 130.5, 129.4, 128.1, 123.6, 123.4, 120.7, 112.3, 59.2, 48.8, 37.9, 33.0, 32.8, 25.2, 24.8, 24.7, 24.4, 22.9, 20.5 ppm. IR (thin film): $\tilde{\nu}$ = 3310, 2933, 2857, 1644, 1522, 1477, 1453, 1408, 1369, 1272, 1261, 1091, 1017 cm^{-1}. HRMS: calcd. for $C_{25}H_{30}ClN_3O$ 423.2077; found 423.2074.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for all new compounds.

Acknowledgments

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[12] Even though such a sigmatropic process of nitroso derivatives has, to the best of our knowledge, no precedent in the literature, we find it convenient to explain the activation of a poorly acidic CH_2 position.

[13] For benzimidazole formations using Ugi adducts see ref.[4e–4h] The closest report of benzimidazole preparation from nitrophenol (**4g**) involves a four-step sequence compared to the present two-step synthesis.

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