Organic LETTERS

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Accessing Benzimidazoles via a Ring Distortion Strategy: An Oxone Mediated Tandem Reaction of 2-Aminobenzylamines

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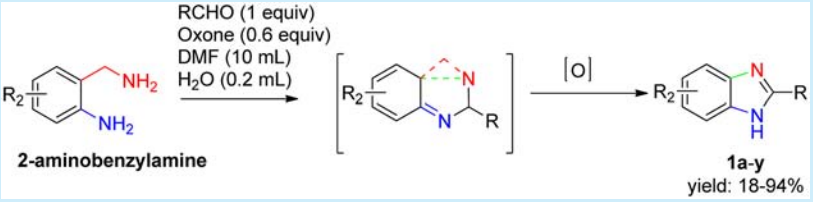
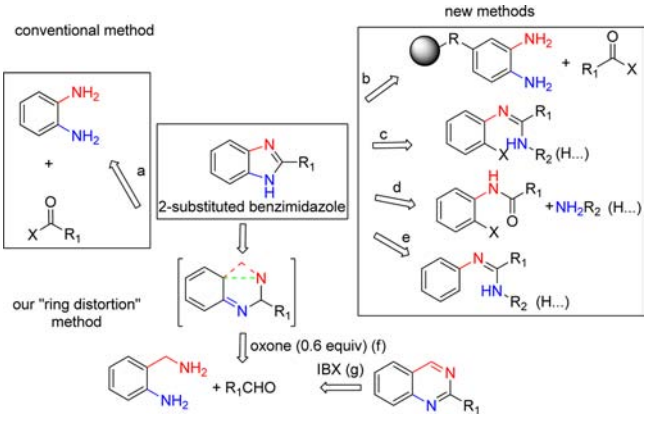
Supporting Information



ABSTRACT: An exceptional oxone mediated tandem transformation of 2-aminobenzylamines to 2-substituted benzimidazoles is reported. It occurs at room temperature with aromatic, heteroaromatic, and aliphatic aldehydes. In this reaction initial condensation of 2-aminobenzylamine with appropriate aldehydes afforded a tetrahydroquinazoline intermediate which underwent oxone-mediated ring distortion to afford the desired compounds in moderate to excellent yields.

Benzimidazole, a pharmaceutically relevant moiety, is present in a plethora of biologically active natural products and active pharmaceutical ingredients.[1] They are successfully implemented as antimicrobial compounds, anthelmintic and antipsychotic drugs, and antiulcer and anticancer agents.[2−8] Owing to their intriguing biological properties, attention has been focused toward the synthesis of these molecules. In general the available syntheses are divided into two groups. The classical strategy, involving the construction of the basic scaffold via condensation followed by oxidative cyclization of benzene-1,2-diamine with appropriate carbaldehydes or its derivatives (Scheme 1, pathway a), required strong acidic conditions and high temperatures.[9] A few noteworthy modern strategies encompass oxidative cyclization of carbaldehydes and its derivatives with solids support benzene-1,2-diamine (Scheme 1, pathway b), cross-coupling based C−N bond formation of aromatic halides followed by transition metal catalyzed aromatic C−H activation (Scheme 1, pathway c), iodobenzene catalyzed C−H amination of N-substituted amidines (Scheme 1, pathway d), and cascade arylamination/condensation of *o*-haloaryl amides (Scheme 1, pathway e).[10−13] Recently, Jui et al. reported an efficient synthesis of *N*-arylbenzimidazoles by harnessing cascade palladium catalysis.[14] Unfortunately, many of these methodologies are plagued with limitations, such as harsh reaction conditions and low yields (due to the formation of several byproducts). Consequently strategies under mild reaction conditions with stable reactants and amenable reagents are desirable for the prudent synthesis of benzimidazoles. In one of our recent projects we devised a one-pot synthesis of aromatic quinazolines by condensation of *o*-aminobenzylamine with various aldehydes followed by *in situ* oxidative dehydrogenation of the tetrahydroquinazoline intermediate with IBX (2-iodoxybenzoic acid) (Scheme 1, pathway g).[15] During this study, a variety of oxidants

Scheme 1. A Summary of Available Methods and Our Synthesis of 2-Substituted Benzimidazole



viz. SeO_2, $KMnO_4$, NBS, and oxone were applied. The majority of them afforded the desired dihydroisoquinoline and aromatic isoquinolines. Interestingly, reaction monitoring of the oxone mediated transformation through LCMS (liquid chromatography mass spectroscopy) revealed a different product which was isolated and upon complete characterization was identified to be the 2-substituted benzimidazole **1a** (Scheme 1, pathway f). Herein we report this unprecedented synthesis of 2-substituted benzimidazoles under oxone in dimethylformamide (DMF) and water at room temperature (rt). Mechanistically the reaction proceeds via a tetrahydroquinazoline intermediate that underwent ring distortion in the presence of oxone to generate the

Received: April 26, 2016
Published: June 22, 2016

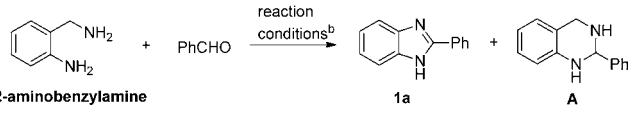
DOI: 10.1021/acs.orglett.6b01217
Org. Lett. 2016, 18, 3090−3093

benzimidazoles (**1a**–**y**). The generic utility of this procedure was demonstrated in the synthesis of a variety of 2-substituted benzimidazoles in moderate to excellent yield. A mechanistic pathway is proposed along with control experiments that supported the putative mechanism.

To begin with, 2-aminobenzylamine (1 equiv) and benzaldehyde (1 equiv) were reacted in the presence of oxone (1 equiv) at room temperature (rt), in DMF (10 mL) and water (0.2 mL) to afford the desired benzimidazole in 3 h in a moderate yield of 62% (Table 1, entry 1) along with the formation of tetrahydroquinazoline **A** as the minor product. Exploring the reaction in various polar solvents such as dimethyl sulfoxide (DMSO) (Table 1, entry 2), 1, 4-dioxane (Table 1, entry 3), isopropanol (Table 1, entry 4), and acetonitrile (Table 1, entry 5) did not improve the yield further (58–28%). To improve the efficiency of this transformation we investigated the reaction in the presence of catalytic oxone. Executing the reaction with 0.1 equiv of oxone (Table 1, entry 6) resulted in the formation of 64% of **A** after 72 h, with no generation of the desired benzimidazole. The gradual increase of oxone by 0.1 equiv improved the yield only after 0.3 equiv, and the best outcome was obtained with 0.6 equiv, which furnished **1a** in 72% isolated yield in 8 h. Any further increase of the ratio of oxone did not improve the yield of **1a**. Hence the optimized conditions for this transformation consisted of reacting 2-aminobenzylamine (1 equiv) with benzaldehyde (1 equiv) in the presence of oxone (0.6 equiv) with DMF (10 mL) and water (0.2 mL) at rt.

Having optimized the reaction protocol, we focused our attention on exploring the scope of our strategy with a variety of substituted *o*-aminobenzylamines and aromatic, heteroaromatic, and aliphatic aldehydes. The results are depicted in Scheme 2. The reaction with quinoline-2-aldehyde afforded the corresponding product **1l** in excellent yield (82%), but 4-bromothiophene-2-carbaldehyde furnished **1m** in moderate yield (58%). Perhaps the presence of bromo-functionality in the thiophene interfered during the reaction that resulted in low yields. In general the monosubstituted aromatic aldehydes with electron-donating functionalities such as 3-anisaldehyde and 2- and 4-tolylaldehyde afforded the desired products **1b**, **c**, and **j** in good yields (74 → 84%). Interestingly electron-donating

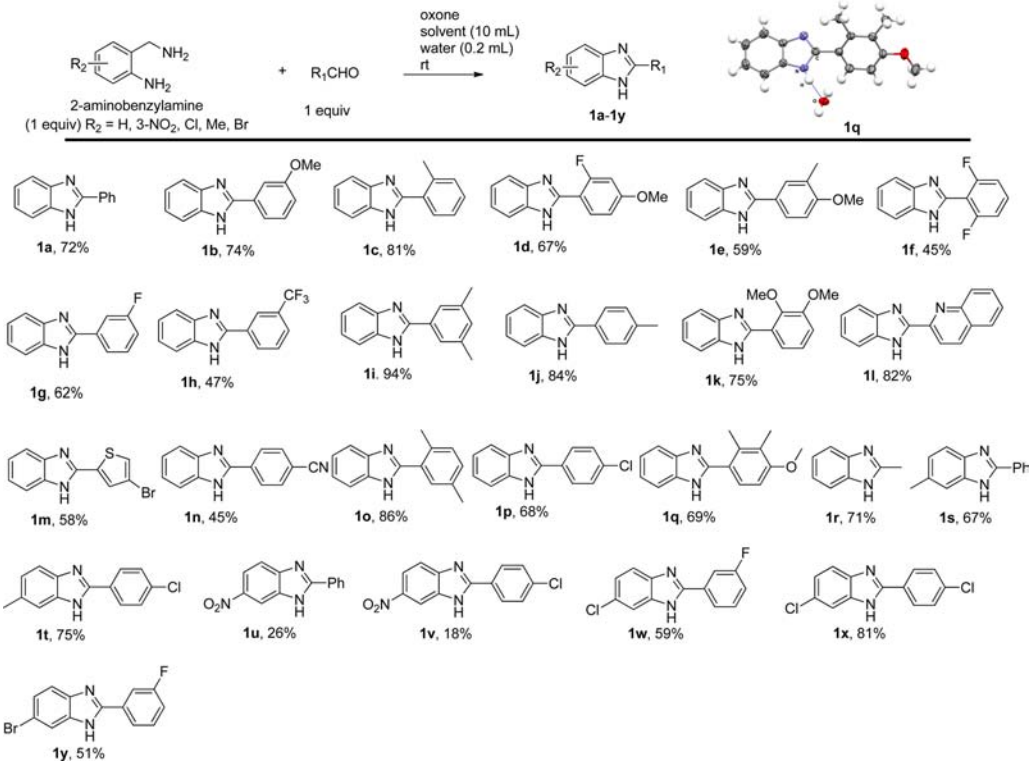
Table 1. Reaction Optimization of the Synthesis of Benzimidazoles from 2-Aminobenzylamine and Benzaldehyde



				yield[a] (%)	
no.	solvents	Oxone (equiv)	time (h)	**1a**	**A**
1	DMF	1	6	62	12
2	DMSO	″	7	58	10
3	dioxane	″	5.5	42	12
4	IPA	″	6	28	08
5	ACN	″	8	34	12
6	DMF	0.1	72	ND	64
7	″	0.2	70	ND	51
8	″	0.3	46	14	42
9	″	0.4	14	28	21
10	″	0.5	12	44	ND
11	″	0.6	8	72	ND

[a]Isolated yield. [b]Solvent (10 mL), oxone, water (0.2 mL), room temperature. DMSO: dimethyl sulfoxide; IPA: isopropyl alcohol; ACN: acetonitrile; DMF: dimethylformamide; ND: not detected.

Scheme 2. Scope of the Tandem Reaction of 2-Aminobenzylamine with a Variety of Aldehydes[a]



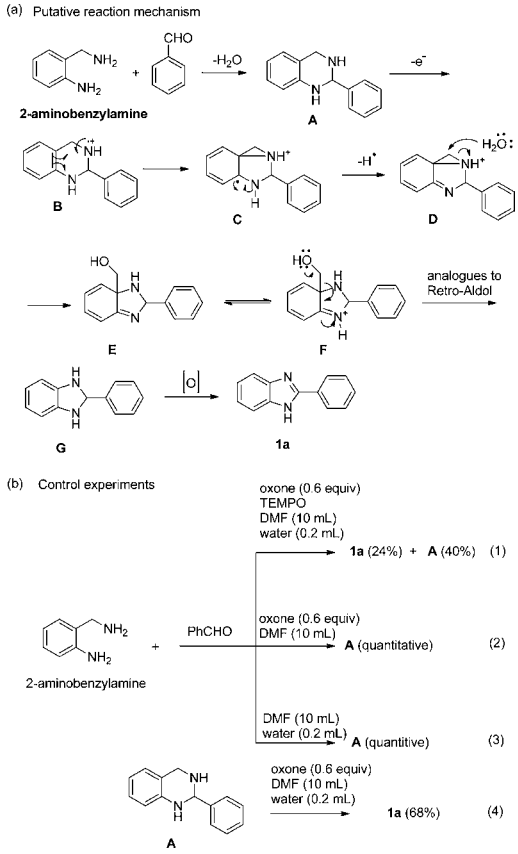
[a]The isolated yield is furnished.

DOI: 10.1021/acs.orglett.6b01217
Org. Lett. 2016, 18, 3090–3093

disubstituted or trisubstituted aromatic aldehydes provided slightly better yields of 59 → 94% for the products **1e**, **i**, **k**, **o**, and **q** (Scheme 2) over the monoanalogs. The aldehydes with electron-withdrawing functionalities afforded the benzimidazoles **1d**, **f**, **g**–**h**, and **n** in moderate yields of 45–67%. The only aliphatic analog **1r** was synthesized in 71% yield (Scheme 2). Conversion of various substituted *o*-aminobenzylamines with different aldehydes resulted in the formation of the desired benzimidazoles (**1s**–**1y**) in 18–81% yield. 3-Nitro-2-aminobenzylamines afforded the corresponding benzimidazoles **1u**–**v** in low yields (18 and 26% respectively) which can be rationalized by poor formation of the corresponding tetrahydroquinazoline intermediates. The benzimidazole structure was further confirmed by single crystal X-ray diffraction studies on **1q** (Scheme 2). To demonstrate the scalability of the process, **1a** was synthesized on the 5 g scale at 68% yield (refer to Supporting Information (SI)).

A putative mechanism for the formation of benzimidazole from 2-aminobenzylamines is described in Scheme 3. The

Scheme 3. (a) Tenable Mechanism for the Oxone Catalyzed Tandem Reaction of 2-Aminobenzylamine to Furnish 2-Substituted Benzimidazoles; (b) Control Experiments



first step is the condensation of the 2-aminobenzylamine with benzaldehyde to furnish the tetrahydroquinazoline intermediate **A**. Next, the oxone probably reacts as a one-electron oxidant to abstract an electron from **A** and generate the tetrahydroquinazolino cation radical **B**, which undergoes delocalization to furnish **C**. Loss of a hydrogen radical from **C** afforded the aziridinium intermediate **D**. It could have been attacked by a water molecule that led to the aziridine ring opening to generate **E**. Protonation of **E** generates **F** and might have triggered a retro-aldol type reaction to provide dihydrobenzimidazole intermediate **G**. **G** undergoes further oxidation to afford the desired **1a**.

To garner support for this mechanism, a reaction in the presence of radical scavenger TEMPO furnished **1a** in substantially reduced yield (24% along with 40% of **A**) (Scheme 3b(1)). The reaction when conducted under dry conditions provided **A** in quantitative yield (Scheme 3b(2)). Similarly **A** was obtained exclusively in the absence of any oxidant (Scheme 3b(3)). In a separate experiment, **A** was isolated and subjected to the optimized reaction conditions, to afford **1a** in 68% yield (Scheme 3b(4)).

There is evidence of oxone mediated oxidative bond cleavage and Hofmann rearrangement of carboxamides to carbamates in the literature. Those examples along with oxidation of aniline for the formation of Mauvien inspired us to propose this mechanism.[16]

In summary, we have demonstrated an oxone mediated facile tandem reaction of various substituted 2-aminobenzylamines with different aldehydes to furnish 2-substituted benzimidazoles. To the best of our knowledge, it constitutes the first example of such a ring distortion strategy toward benzimidazole synthesis. The reaction has been proposed to advance via a radical mechanism. Readily accessible and affordable starting materials and catalyst, mild reaction conditions, and a robust experimental procedure that provides the desired compounds in good yields are some of the appealing aspects of the present protocol. Additionally the methodology can be reproduced at a larger scale.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01217.

Experimental details; X-ray data for **1q**; $^{1}H,^{13}C$ NMR and HRMS data for **1a**–**y** and **A** (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Shiv Nadar University for support.

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DOI: 10.1021/acs.orglett.6b01217
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DOI: 10.1021/acs.orglett.6b01217
Org. Lett. 2016, 18, 3090−3093