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Rapid one-pot preparation of 2-substituted benzimidazoles from 2-nitroanilines using microwave conditions

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Abstract—A high yielding one-pot procedure for the generation of 2-substituted benzimidazoles directly from 2-nitroanilines by in situ reduction and cyclization using a microwave procedure is described.
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1. Introduction

The benzimidazole scaffold is a useful structural motif for displaying chemical functionality in biologically active molecules. Optimization of benzimidazole-based structures has resulted in marketed medicines such as Omeprazole[1] and Pimobendan[2] and lead compounds in a wide range of therapeutic areas (e.g., casein kinase 2,[3] factor Xa,[4] hepatitis C virus[5]). From a combinatorial chemistry perspective, the benzimidazole scaffold allows the stepwise incorporation of diverse functionality with control of regiochemistry, making it a suitable target for library synthesis. Library synthesis has been reported using solid[6] and solution[7,8] phase approaches as well as parallel polymer-assisted synthesis.[9,10]

Synthetic approaches to 2-substituted benzimidazoles from *o*-halonitroaromatics or from 2-nitroanilines have been described; however, these procedures require a multistep process resulting in compromised yields and purity. The conversion of 2-nitroanilines to benzimidazoles is a two-step process. In the first step, the nitro group is reduced using one of many possible reagents (e.g., zinc,[11] iron,[12] tin(II) chloride,[13] hydrogen,[10] or Raney nickel[14]). The second step is the ring closure performed with either a carboxylic acid or an aldehyde. The condensation/cyclization with the carboxylic acid is frequently done thermally,[15] while the closure with an aldehyde is an oxidative process.[16]

Early preparations of 2-substituted benzimidazoles from phenylenediamines and carboxylic acids or carboxylic acid derivatives were carried out under vigorous dehydrating conditions.[17] Performing the reaction under milder conditions by the addition of Lewis acids,[15] inorganic clays,[18,19] mineral acids,[12] or PyBOP,[11] has improved both the yield and purity of this reaction. Long reaction times for this condensation[4] have been mitigated by the use of microwave heating,[20,21] both with and without polyphosphoric acid.[22] Many of these procedures require chromatographic purification of the intermediate phenylenediamine, decreasing both the usefulness and throughput of these approaches. Herein, we report a one-pot, high-yield synthesis of 2-substituted benzimidazoles directly from 2-nitroanilines.

2. Results and discussion

The reduction of nitro aromatics is readily achieved by treatment with tin(II) chloride.[13] Although this reaction can be carried out effectively in a variety of solvents, such as DMF or alcohols, the rate of reaction is greatly enhanced in the presence of mineral acids.[12] During the course of our studies, we optimized a simple, microwave-based procedure for the formation of benzimidazoles by cyclization of phenylenediamines with carboxylic acids, greatly reducing the reaction time required and enhancing the yield of the process.[23] We hypothesized

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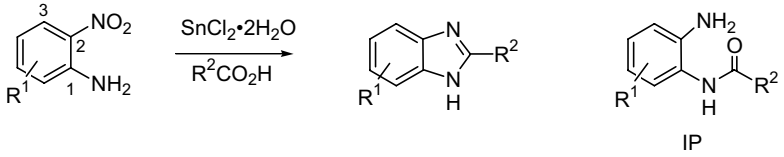
that the formation of the 2-substituted benzimidazoles could be achieved directly from the 2-nitroanilines by substituting the carboxylic acid from the second step for the mineral acid during the tin(II) chloride reduction. Thus treatment of *o*-nitroaniline with tin(II) chloride using formic acid as solvent under microwave conditions resulted in clean conversion to 2-*H* benzimidazole (Scheme 1). The reactions were carried out in a CEM[24] focused microwave heating to 130 °C for 5 min.

With the initial success of this reaction, we set out to determine the scope and variability of the procedure. Using a variety of substituted nitroanilines and three different acids, we used a standard set of conditions to test this new method. For all combinations of nitroaniline and acid, the desired benzimidazole was observed as the major product with complete conversion in 16 of 24 reactions. The *N*-acylphenylenediamine was observed as the side product where complete conversion was not obtained. A large variety of functionality was tolerated on the nitroaniline, including phenol, carboxylic acid, halogen, and nitrile (see Table 1). Interestingly, the carboxylic acid substituent on the nitroaniline did not participate in the reaction resulting in clean formation of benzimidazoles **5**, **13**, and **21** with none of the dimeric derivative being observed.[25] For all reactions, the conversion to the heterocycle as well as the residual quantity of the starting nitroaniline and the *N*-acylphenylenediamine (IP in Table 1) were first determined by LC–MS using chemiluminescent nitrogen detection (CLND). The benzimidazole was then obtained by extraction and chromatography. None of the corresponding unsubstituted phenylenediamines were seen by LC–MS in any of the reactions.

Although all of the acids used (formic, acetic, and trifluoroacetic) resulted in acceptable yields, the use of trifluoroacetic acid resulted in lower overall yields, particularly for 4-carboxy-2-nitroaniline. For all of the reactions which resulted in incomplete conversion, further microwave irradiation at 130 °C (5–10 min) was sufficient to effect full conversion. Reaction of phenylenediamine with acetic acid under the same conditions, either in the presence or absence of tin(II) chloride resulted in complete conversion to 2-methylbenzimidazole, suggesting that once the reduction of the nitro group is complete, acylation and cyclization occur rapidly.



Scheme 1. $SnCl_2 \cdot 2H_2O$ (3 equiv), RCO_2H (0.35 M), 130 °C, 5 min.

Table 1. Conversion and isolated yield for the formation of substituted benzimidazoles

Entry #	R^1	R^2	Conversion[a]	%IP	%SM	Isolated yield[b]
1	H	H	100			99
2	4,5-Dimethyl	H	92.3	6.2	1.5	87
3	5-OH	H	98.0		2.0	95
4	5-OCH_3	H	100			99
5	5-CO_2H	H	83.2	16.8		60
6	5-CN	H	90.7		9.3	86
7	5-CF_3	H	100			98
8	4,6-Dichloro	H	100			99
9	H	CH_3	100			100
10	4,5-Dimethyl	CH_3	100			100
11	5-OH	CH_3	93.7	6.3		86
12	5-OCH_3	CH_3	100			98
13	5-CO_2H	CH_3	100			86
14	5-CN	CH_3	100			100
15	5-CF_3	CH_3	100			96
16	4,6-Dichloro	CH_3	100			99
17	H	CF_3	100			100
18	4,5-Dimethyl	CF_3	100			100
19	5-OH	CF_3	100			89
20	5-OCH_3	CF_3	78.7	21.3		72
21	5-CO_2H	CF_3	58.3	40.5	1.2	45
22	5-CN	CF_3	100			100
23	5-CF_3	CF_3	64.7	35.3		45
24	4,6-Dichloro	CF_3	100			96

[a] Determined by HPLC/MS/CLND.
[b] Isolated via column chromatography. Determined by CLND. All compounds gave satisfactory HPLC, MS, and ^1H NMR data.[26]

In summary, we have described a simple, rapid, one-pot procedure for the generation of 2-substituted benzimidazoles directly from 2-nitroanilines using a microwave procedure. An advantage of this approach is that the intermediate phenylenediamines or *N*-acyl derivatives are not isolated. Additionally, although it is possible that *N*,*N*-diacylphenylenediamines may form post-reduction of the nitro functionality due to the presence of excess acid, none of the corresponding 2,4-disubstituted-3,1,5-benzoxadiazepines, derived by cyclization of the diacyl compounds were formed, thus leading to simple isolation of the desired benzimidazole. Work aimed at investigating further the scope of the reaction is currently being pursued and will be reported when complete.

3. General procedure

In a CEM microwave vial with a stir-bar (optional), the nitroaniline (0.36 mmol), carboxylic acid (1.03 mL, 0.35 M), and $SnCl_2{\cdot}2H_2O$ (3.0 equiv) were combined and heated at 130 °C (125 W, 1.0 min ramp time) for 5 min. After cooling, the reaction mixture was diluted with water (4 mL) and neutralized with 50% aq NaOH ($pH = 7.0 \pm 0.5$). It was extracted with ethyl acetate (3×4 mL) and the combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was analyzed by HPLC/MS/CLND and purified by passing through a plug of silica gel (500 mg prepacked columns) using 30 mL of ethyl acetate. Compounds with purity below 95% were further purified using the ISCO CombiFlash 16sqx with a gradient of either 5–100% EtOAc–hexanes or 0–20% DCM–MeOH (**5**, **13**, and **21**).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.130.

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23. Unpublished Results.
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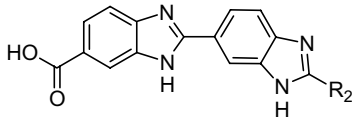
25. For reactions of 5-carboxy-2-nitroaniline, none of the dimeric derivative, potentially formed from participation of the carboxylic acid substituent, was detected:



26. NMR data for all the benzimidazoles can be found in Supplementary data.