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One-Pot Synthesis of Benzimidazoles from o-Nitroanilines under Microwaves via a Reductive Cyclization

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Abstract: An efficient microwave irradiation synthesis of 2-substituted benzimidazoles in one step via the $Na_2S_2O_4$ reduction of o-nitroanilines in the presence of aldehydes is described. The method is simple and a good option to obtain the title compounds in a very short time.

Keywords: benzimidazoles, microwaves, $Na_2S_2O_4$, reductive cyclization

INTRODUCTION

Benzimidazole is a versatile core contained in several substances possessing a broad spectrum of pharmacological activity such as anticancer, antimicrobial, pesticide, and antithelmintic properties.[1] This class of molecules has also found commercial applications in several therapeutic areas such as anti-ulcerative, antiviral, and antihistaminic agents.[2] Hence, the development of new synthetic methods for benzimidazoles, which are currently not easily attainable by existing methods, is considered important by organic chemists.

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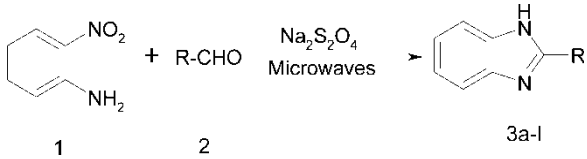
The most popular synthetic approaches generally involve the condensation of an arylenediamine with a carbonyl equivalent[3] or with organic acids, employing hydrochloric acid,[4] polyphosphoric acid,[5] boric acid,[6] or para-toluene sulphonic acid (*p*-TSA)[7] as catalyst. However, all these reactions often require longer reaction times and tedious workup. Several improved procedures for the preparation of benzimidazoles have been reported either by fusion of 2-aminobenzamide and organic acid[8] or by reaction of o-phenylenediamine and organic acid using $FeCl_3/O_2$[9] in a catalytic Fe^{+2}/Fe^{+3} redox cycling approach. Recently, benzimidazoles have also been prepared from o-nitroanilines using sodium dithionite in the presence of aldehydes,[10] by the condensation of orthoesters with o-phenylenediamine in a dry medium under monomode microwave irradiation,[11] and from phenylenediamines and organic acids in the presence of polyphosphoric acid (PPA) under microwaves.[12] In addition, the development of novel but more complex solid-phase routes to benzimidazoles has been advanced.[13]

Microwave irradiation of organic reactions has rapidly gained in popularity because it accelerates a variety of synthetic transformations.[14] The application of microwaves with certain catalysts or reagents provides unique chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity, and ease of manipulation. Hence, microwave irradiation is becoming an increasing popular technology.[11–15]

Here we report the direct synthesis of benzimidazoles from o-nitroanilines using sodium dithionite under microwaves. Sodium dithionite ($Na_2S_2O_4$) is a very inexpensive and efficient reducing reagent that acts as a single-electron-transfer donor and has been reported to reduce aryl nitro groups to aryl amines by a six-electron mechanism.[16] This observation, coupled with mild reaction conditions of the method and a demonstrated tolerance for other functional groups such as halogens, aldehydes, ketones, and olefins, rendered $Na_2S_2O_4$ a prime candidate for reductive cyclization of o-nitroaniline.

The o-nitroaniline (1 mmol) and the aldehyde (1 mmol) were taken in dimethyl formamide (DMF) (4 ml). To this solution, an aqueous solution (1M) of $Na_2S_2O_4$ (3 mmol) was added. This reaction mixture was then irradiated in a household microwave oven (Type: LG, Little Chef) for 60 s at a power of 160 W. After the reaction was complete (as observed from thin-layer chromatography, TLC), the reaction mixture was allowed to cool at room temperature and was then treated with 5 N NH_4OH. The solid product that was formed was filtered and washed with water (2×15 ml) and dried under suction. The product was purified using ethanol. To extend the scope of the reaction, we tried the reaction of o-nitroaniline with substituted aldehydes. The reactions went on smoothly, affording complete conversion of the reactants in a short time. The results are summarized in Scheme 1 and Table 1.



Scheme 1.

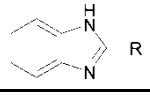
EXPERIMENTAL

All products are known compounds and are well characterized by ^{1}H NMR and IR spectroscopy.

2-Phenylbenzimidazole (3a): A Typical Procedure

A mixture of o-nitroaniline (1 mmol) and benzaldehyde (1 mmol) was taken in DMF (4.0 ml) in a 25-ml round-bottom flask. To this solution, an aqueous solution (1M) of $Na_2S_2O_4$ (3 mmol) was added. A funnel was kept on the mouth of the flask, and this flask was kept in a 100-ml beaker. The entire assembly was then placed in the microwave oven and the mixture then irradiated with microwaves four times at a power of 160 W with pulse 15 s each and a 20-s cooling period between each pulse. After allowing the

Table 1. Microwave-assisted 2-substituted benzimidazoles using sodium dithionite



Entry	R	Yield (%)[a]
3a	C_6H_5	81
3b	4-ClC_6H_4	78
3c	2-ClC_6H_4	68
3d	2-BrC_6H_4	65
3e	4-FC_6H_4	80
3f	2-OHC_6H_4	75
3g	3,4-$(CH_3O)_2C_6H_4$	75
3h	4-$OCH_3C_6H_4$	82
3i	4-N,N-$(CH_3)_2C_6H_4$	92
3j	2-Furyl	65
3k	4-$CH_3C_6H_4$	84
3l	4-BrC_6H_4	79

[a]Isolated and unoptimized yields.

reaction mixture to cool at room temperature, it was treated with 5 N NH_4OH dropwise to get the product. The product was filtered and washed with water (2×15 ml) and dried under reduced pressure. The crude product was purified from ethanol and gave 81% yield, mp 292–293°C.

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