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Phenyl-Trimethyl-Ammonium Tribromide: Facile Catalyst for the One Pot Synthesis of Substituted Benzoxazoles

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ABSTRACT

Phenyl-trimethyl-ammonium tribromide, a stable, crystalline organic ammonium tribromide has been used as an alternative electrophilic bromine source for the efficient oxidative cyclisation of substituted benzaldehydes and 2-aminophenoles to the corresponding benzoxazoles under mild conditions.

Key words: 2-Aminophenol, Substituted benzaldehydes, PTAB, oxidative cyclisation.

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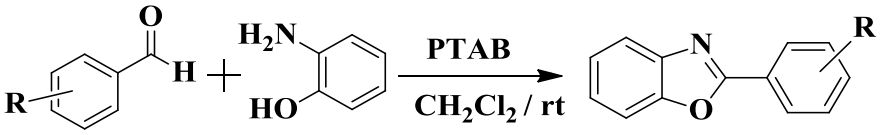
INTRODUCTION

Benzoxazoles are an important class of molecules and are a common heterocyclic scaffold in biologically active and medicinally significant compounds. Benzoxazoles are found in a variety of natural products [1] and are important targets in drug discovery [2]. Also, much attention has been paid to benzoxazoles because they have a number of optical applications such as photoluminescents [3], whitening agents [4] and in dye lasers [5]. They are also used as intermediates for several therapeutic materials [6, 7]. Pyrazines are found in the luminescent chromophores or certain marine organisms [8] in cephalostatins isolated from Cephalodiscus gilehrist, which are powerful anticancer agents [9], in the fungal metabolite aspergillic acid [10] and in food in the form of potent flavor compounds [11]. They have been also used as ligands in asymmetric synthesis [12]. The extensive applications of these heterocycles have prompted wide studies for their synthesis. A number of methods have been reported for the preparation of these heterocycles including the condensation of carboxylic acids [13], orthoesters [14], acid chlorides [15], nitriles [16], amides [17], aldehydes [18] and esters [19] with o-Aminophenol. However, most of these procedures have some drawbacks such as long reaction times, low yields of products, the use of expensive, toxic or non-reusable catalysts, high temperatures, harsh reaction conditions and use of toxic solvents and/or co-occurrence of several side reactions. In some cases more than one step is required for the synthesis of these heterocycles. Therefore, it is necessary to find a better catalyst for the synthesis of benzoxazoles in terms of operational simplicity, non-toxicity, reusability and environmental and economical acceptability. In continuation of our works on the synthesis of heterocyclic compounds [20]. Herein we report a new and efficient route for the one-pot synthesis of substituted benzoxazoles from substituted benzaldehydes and 2-aminophenoles. When substituted benzaldehyde and 2-aminophenole is dissolved in a suitable solvent and treated with equimolar amount of a PTAB, rapid and efficient oxidative cyclisation takes place as shown in Scheme-1. , Easy handling, cheapness, efficiency, non-toxicity make this catalyst eco-friendly, synthetically acceptable and economically viable.



Scheme-1

Experimental

Reagents and Equipment

All chemicals and reagents were of analytical grade and Melting points were recorded on Superfit melting point apparatus and are uncorrected.

Infrared spectra were measured on a Shimadzu IR-470 Spectrophotometer. NMR (^{1}H & ^{13}C) spectra were recorded on a Bruker 400 MHz spectrometer using $CDCl_3$ as the solvent with

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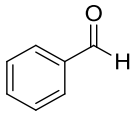
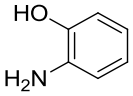
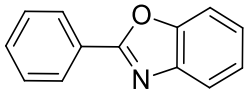
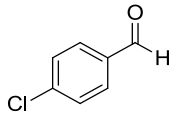
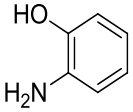
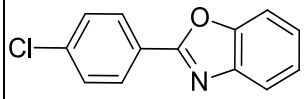
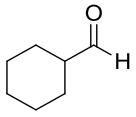
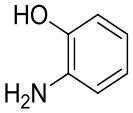
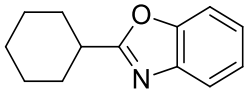
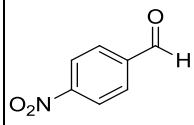
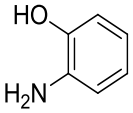
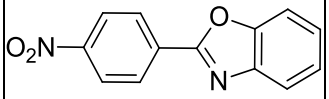
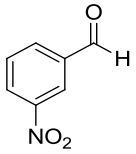
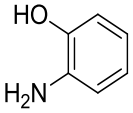
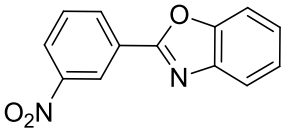
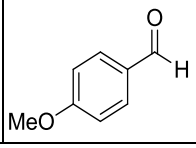
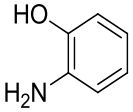
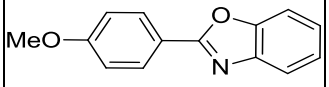
TMS as an internal standard. All reactions were monitored by Thin Layer chromatography (TLC) carried out on glass plates coated with silica gel along with I_2 as development reagents. All evaporations were carried out under reduced pressure on Superfit rotary evaporator below 50°C.

Experimental procedure for the synthesis of 2-(p-tolyl)benzo[d]oxazole:

A mixture of 4-methylbenzaldehyde (2mmol), 2-aminophenol (2mmol) and PTAB (4mmol) in CH_2Cl_2 (20 ml) was refluxed for the time as mentioned in Table-1. The progress of the reaction was monitored by TLC. After completion of reaction, it was treated with $NaHCO_3$ (2 x 10 ml) and extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum pump, and residue was purified by column chromatography using the ethyl acetate/pet.ether (1:9) as eluent, to obtain highly pure product.

Table 1: Formation of substituted benzoxazoles from substituted benzaldehydes and 2-aminophenoles using PTAB in CH_2Cl_2

Entry	Comp. A	Comp. B	Product	Yield%	Time (h)	Mp °c (Mp Lit.)
1				82	1.30	101 (102)[21]
2				79	1.12	146 (147)[21]
3				58	1.20	40 (39)[22]
4				77	2	266 (266-68)[21]
5				78	2	242
6				80	1.40	102 (101-03)[21]

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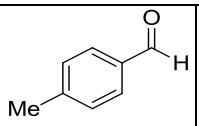
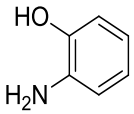
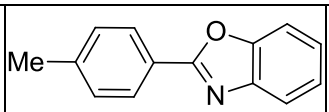
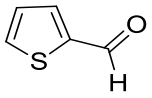
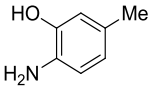
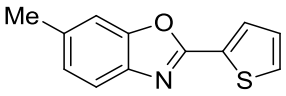
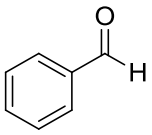
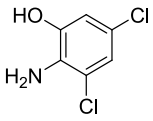
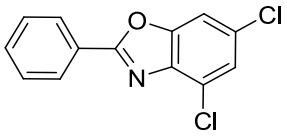
7				82	1.30	113 (113-114)[21]
8				80	1.80	75-77 (74-76)[23]
9				79	2.84	144

Selected Spectroscopic Data of Isolated Products:

2-phenylbenzo[d]oxazole (Entry 1).IR (KBr, cm-1): 3051, 1640, 1600, 1540, 1490, 1380, 1259,690, 735. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96–7.55 (m, 5H), 7.22 (d, 2H, ArH), 7.45 (d, 2H, ArH). ^{13}C NMR (100 MHz $CDCl_3$): 108.5, 118.8, 121.7, 123.1, 125.2, 126.1, 127.4, 127.3, 139.5, 148.8, 162.7.

2-(4-methoxyphenyl)benzo[d]oxazole (Entry 2). IR (KBr, cm-1): 3012, 2930, 2840, 1639, 1605, 1515, 1435, 1391, 1295, 1258, 1166, 1022, 828, 777, 743. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3H,), 6.94 (d, 2H), 7.36 (m, 4H), 7.95 (d, 2H). ^{13}C NMR (100 MHz $CDCl_3$): δ 52.7, 108.5, 118.8, 121.7, 123.1, 124.8, 125.0, 129.80, 142.7, 152.6, 162.9 164.0.

2-(4-chlorophenyl)benzo[d]oxazole (Entry 3). IR (KBr, cm-1): 3032, 1641, 1609, 1515, 1433, 1304, 1295, 1258, 828, 777, 743. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 4H), 7.55 (d, 2H, 9.0 Hz), 7.75 (d, 2H, 9.0 Hz) . ^{13}C NMR (100 MHz $CDCl_3$): δ 108.5, 118.8, 121.7, 123.1, 124.1, 129.29, 130.0, 132.1, 139.5, 148.8, 162.7.

2-cyclohexylbenzo[d]oxazole (Entry 5). IR (KBr, cm-1): 3100, 2995, 1671, 1609, 1515, 1433, 1304, 1260, 735 690. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (m, 2H), 7.36 (d, 1H, 9.1 Hz), 7.56 (d, 1H, 9.0 Hz), 2.19-1.35 (m, 11H). ^{13}C NMR (100 MHz $CDCl_3$): δ 23.4, 26.3, 31.1, 34.4, 108.5, 118.8, 121.7, 123.1, 139.5, 148.8, 162.7.

RESULT AND DISCUSSION

However, some of these methods suffer from one or more of the following drawbacks such as strong acidic conditions, long reaction times, low yields of the products, tedious work-up; need to use excess amounts of reagent and the use of toxic reagents, catalysts and solvents. Therefore, there is a strong demand for a highly efficient and environmentally benign method for the synthesis of these heterocycles. In recent years, studies of low-waste routes and

reusable reaction media for enhanced selectivity and energy minimization have occupied the interests of synthetic organic chemists.

Phenyltrimethylammonium tribromide (PTAB) mediated oxidative cyclisation of 4-methylbenzaldehyde and 2-aminophenole to 2-p-tolylbenzo[d]oxazole was investigated. In a typical experiment to a mixture of 4-methylbenzaldehyde (1mmol) and 2-aminophenole (1mmol) in CH_2Cl_2 (10ml),) was added and the reaction mixture was stirred for 2 hours at room temperature. The reaction proceeds for the formation of oxidative cyclisation in satisfactory yield. Of the solvents tested for this reaction ($CHCl_3$, CH_2Cl_2, MeOH and MeCN), CH_2Cl_2 was found to be the most efficient for maximum yield of the oxidation product.

Using above optimized reaction conditions, a wide range of benzaldehydes and 2-aminophenole were subjected to the oxidative cyclisation using PTAB. In all the cases good to excellent yields of the products were obtained. All the reactions were complete within 1-2h.

CONCLUSION

A one-pot synthesis of 2-aryl benzoxazoles, in excellent yields has been developed under ambient conditions using PTAB as reaction medium and promoter. There is no need to add any catalyst, which is generally required in the methodologies reported so far. The ambient reaction conditions, absence of a catalyst makes this an environment friendly methodology amenable for scale up.

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