



One-pot tandem approach for the synthesis of benzimidazoles and benzothiazoles from alcohols

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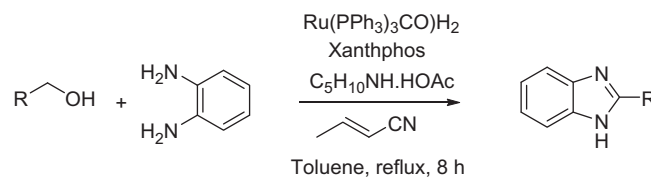
o-Aminothiophenols

ABSTRACT

Propylphosphonic anhydride ([®]T3P) has been demonstrated to be an efficient and mild reagent for the one-pot synthesis of benzimidazoles and benzothiazoles from variety of alcohols. Mild conditions, short reaction time, broad functional group tolerance, low epimerization, easy and quick isolation of the products, excellent chemo selectivity, and excellent yields are main advantages of this procedure. Thus, the present method is utilizing alcohols instead of aldehydes.

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The benzimidazole nucleus is the key building block for a variety of compounds that play crucial role in the activity of a number of biologically important molecules.¹ Benzimidazole and benzothiazole are important pharmacophores in modern drug discovery.² Benzimidazole and benzothiazole derivatives have several therapeutic applications such as antiulcer,³ antihelminthic,³ antihypertensive,⁴ anticoagulant,⁵ antiallergic,⁶ analgesic,⁷ anti-inflammatory,⁸ antimicrobial,⁹ antiviral,¹⁰ antiparasitic,¹¹ and anticancer.¹² It is also reported that the benzimidazole derivatives exhibit significant activity against several viruses such as HIV and influenza.¹² These derivatives have also been used to act as topoisomerase inhibitors.¹³ Several methods have been reported for the synthesis of benzimidazoles and benzothiazoles.^{14–17} More recently, transition metal-catalyzed amination followed by condensation has been reported for the preparation of various benzimidazoles.^{18,19a} However, many of these methods have several limitations such as low yields, a special oxidation process, long reaction time, tedious work-up procedures, co-occurrence of several side reactions, and poor selectivity. The substitution of carboxylic acid or aldehyde component with an alternative functional group has not been widely reported. To the best of our knowledge, there are only very few reports on the synthesis of benzimidazole directly from alcohols.^{19b–e} Recently, Blacker et al.^{19f} reported ruthenium-catalyzed hydrogen-transfer reactions (Scheme 1) for the conversion of alcohols into benzimidazoles under drastic conditions. Also Moorthy et al.^{19g} reported the IBX mediated



Scheme 1. Ruthenium-catalyzed synthesis of benzimidazoles.

synthesis of benzimidazoles from alcohols. However, no report has been found on the synthesis of benzothiazoles directly from alcohols. Also, IBX is not soluble in many organic solvents and explosive in nature.^{19h} Very recently, our group has reported one-pot synthesis of benzimidazoles from gem-dibromomethylarenes.²⁰

In continuation of our work on the development of useful synthetic methodologies,^{21–23} in this study we report the use of [®]T3P as an oxidizing and cyclodehydrating agent for the synthesis of benzimidazole and benzothiazole derivatives under mild conditions. Propylphosphonic anhydride ([®]T3P) functions both as coupling agent and water scavenger,²⁴ offering several advantages such as high yields and purity, low toxicity, broad functional group tolerance, and easy work-up when compared to traditional reagents. Although [®]T3P has been mainly used as an effective and mild condensation reagent in peptide synthesis, new applications have been developed for this reagent,²⁵ which include direct conversion of carboxylic acid into nitriles, dehydrations of amides to nitriles, formation of Weinreb amides, β -lactam synthesis, ester formation, alcohol oxidations,^{25g,h} and preparation of heterocycles.²⁵ⁱ The

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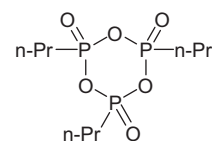
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Table 1
T3P-DMSO mediated synthesis of **1c** under different reaction conditions

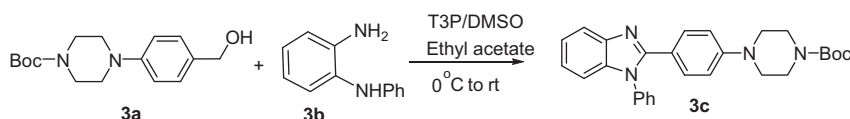
No.	Solvent	T3P (50%) (equiv)	Time (h)	Temperature (°C)	Yield ^a %
1	EtOAc	1.0	8	0–25	10
2	EtOAc	1.5	8	0–25	50
3	EtOAc	2.0	4	0–25	90
4	EtOAc	2.5	4	0–25	88
5	Toluene	2.0	4	0–25	75
6	THF	2.0	6	0–25	20
7	CHCl ₃	2.0	4	0–25	50
8	CH ₃ CN	2.0	4	0–25	60
9	Acetone	2.0	4	0–25	Trace
10	CH ₂ Cl ₂	2.0	6	0–25	30
11	EtOAc	2.0	3	40	86
12	EtOAc	2.0	2	50	82
13	EtOAc	2.0	2	60	73
14	EtOAc	2.0	1	70	75

^a Isolated yield.

diverse advantages and applications of [®]T3P show its potential as a reagent in organic synthesis. Though, [®]T3P has been identified as a mild water scavenger, the wider scope and synthetic utility of this reagent for oxidation and cyclodehydration has not been explored.

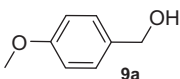
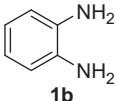
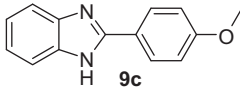
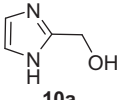
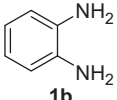
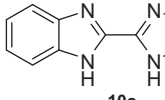
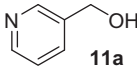
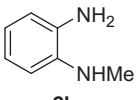
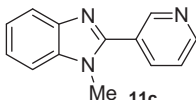

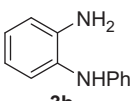
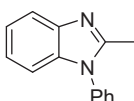
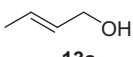
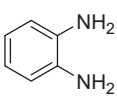
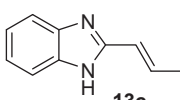
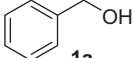
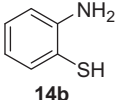
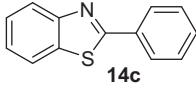
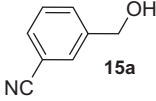
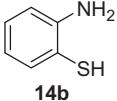
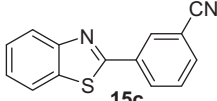
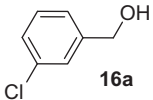
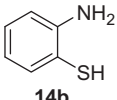
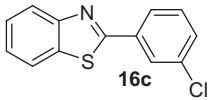
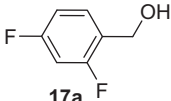
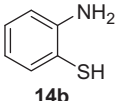
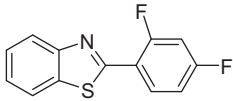
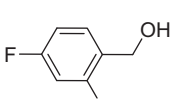
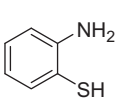
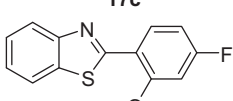
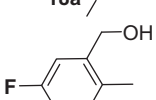
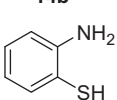
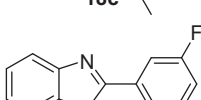
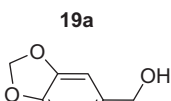
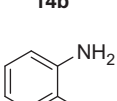
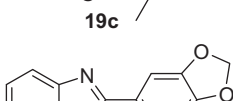
" Structure of propylphosphonic anhydride ([®]T3P)"

Here, we report a novel, direct approach for synthesis of benzimidazoles and benzothiazoles starting from various alcohols, *o*-diamine, and *o*-aminothiophenol without the need for an additional oxidant.²⁶ The tandem process involves oxidation, cyclization and [®]T3P mediated dehydrogenation under mild conditions at 0–25 °C (Scheme 1).

**Scheme 2.** General approach for the synthesis of benzimidazoles.**Table 2**
Synthesis of benzimidazoles from alcohols, using *o*-diaminoarenes

Entry ^a	Alcohol	Substrate	Product ^{b,c}	Time (h)	Yield%
1				4	90
2				3	93
3				3	95
4				2.5	88
5				2.5	97
6				2.5	92
7				3	94
8				3	88

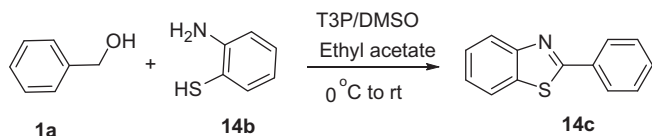
Table 2 (continued)

Entry ^a	Alcohol	Substrate	Product ^{b,c}	Time (h)	Yield%
9	 9a	 1b	 9c	4	85
10	 10a	 1b	 10c	3	94
11	 11a	 2b	 11c	3	90
12	 12a	 3b	 12c	4	87
13	 13a	 1b	 13c	2.5	94
Synthesis of benzothiazoles from different alcohols, using aminothiophenol					
14	 1a	 14b	 14c	2.5	92
15	 15a	 14b	 15c	4	85
16	 16a	 14b	 16c	2	93
17	 17a	 14b	 17c	2	95
18	 18a	 14b	 18c	3	93
19	 19a	 14b	 19c	3.5	91
20	 8a	 14b	 20c	3	90

^a ®T3P (2 equiv) was used.^b Reaction time was 2.5–4 h.^c Purified by crystallization or column chromatography.

In order to explore the scope and optimal conditions for T3P-DMSO mediated synthesis of benzimidazoles and benzothiazole, benzyl alcohol **1a** was selected as a model. The reaction of **1a** (1.1 equiv), 1,2-phenylenediamine (1.0 equiv), ®T3P (2.0 equiv, 50% solution in EtOAc), and 2:1 volume of EtOAc:DMSO at

0–25 °C for 4 h yielded 90% of **1c** (Table 1, entry 3). The influence of DMSO, various solvents and temperature on the synthesis of benzimidazole **1c** was studied and the results are summarized in Table 1. We tried the reaction **1a** with **1b** using ®T3P (2.0 equiv) alone without DMSO both at 0–25 °C and 70 °C but no reaction



Scheme 3. General approach for the synthesis of benzothiazoles.

was observed. Increasing the volume of DMSO in the ratio (EtOAc/DMSO) to 1:1, 1:2, 1:3, and 1:4 did not improve the yield. The optimization studies of the experiments are provided in Table 1, (entries 5–10) which shows the effect of various solvents such as EtOAc (entry 3, 90%), toluene (entry 5, 75%) and CH₃CN (entry 8, 60%), in which ethyl acetate was chosen as the appropriate solvent with consideration to yield. The optimum temperature of the reaction was determined by conducting the experiments at 40, 50, 60, and 70 °C. The results showed that at these temperatures the reaction time was drastically reduced, but with no significant increase in the yield of benzimidazole **1c**.

The reactions were carried out using ethyl acetate at 0–25 °C by taking 1:1.1 mol ratio mixture of *o*-phenylenediamine, and different alcohols in the presence of [®]T3P to get the desired product in excellent yield (Scheme 2) the results in Table 2 show that aromatic, aliphatic, and heterocyclic alcohols react without any significant difference to provide their corresponding benzimidazoles and benzothiazoles in good yield. This method can tolerate protecting group like Boc and other functional groups such as ester, halide, nitrile, allylic, and methoxy. The scope and the generality of this procedure is illustrated with respect to various aliphatic, aromatic, and heterocyclic alcohols and the results are summarized in Table 2.

To generalize our reagent system, the applicability of the [®]T3P/DMSO system was examined for their reactions with a series of aromatic, aliphatic, and heterocyclic alcohols with 1,2-phenylenediamines under the optimized conditions (Table 2). As shown, a variety of alcohols bearing electron-donating (entries 8–9) and electron withdrawing (entries 4–7), heterocyclic (10–11), and aliphatic (12–13) substituents were successfully employed to prepare the corresponding benzimidazole derivatives in excellent yields. This procedure is applicable to substituted 1,2-phenylenediamines, which produced the corresponding 2-arylbenzimidazoles simply in excellent yields. 2-Aminothiophenol also underwent the reaction, affording the corresponding 2-arylbenzothiazoles (Scheme 3) in excellent yields (Table 2, entries 14–20). The 2-aminophenol did not produce the desired products in the reaction.

In conclusion, we have developed an expedient and direct method for the synthesis of benzimidazoles and benzothiazoles in excellent yields, starting directly from a variety of alcohols 1,2-phenylenediamine and 2-aminothiophenol derivatives. The protocol involves [®]T3P-DMSO mediated oxidation of alcohols to aldehydes followed by cyclocondensation with 1,2-phenylenediamine and *o*-aminothiophenol, to afford benzimidazoles and benzothiazoles in one-pot operation with excellent yield. [®]T3P is low in toxicity, and commercially available at moderate price. The range of benzimidazoles and benzothiazoles were produced in high yields without the need for any additional oxidants.

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- General procedure for the one-pot synthesis of benzimidazoles and benzothiazoles: to a solution of alcohol (1.1 mmol) in a mixture of solvents ethyl acetate (4 mL) and DMSO (2 mL), was added [®]T3P (2 mmol, 50% solution in ethyl acetate) at 0 °C and the resulting reaction mixture was stirred at room temperature for 1–2 h under nitrogen atmosphere. The reaction was monitored by TLC, 1,2-phenylenediamine (1 mmol) was added and stirred further for 1–2 h. After completion of the reaction, the mixture was diluted with water (20 mL) and neutralized with 10% NaHCO₃ solution. The product was extracted with ethyl acetate (10 mL) and the combined organic phase was washed with water (10 mL) and brine solution. The organic phase was dried over anhydrous Na₂SO₄. The solvent was dried under reduced pressure to afford a crude product, which was purified on silica gel using ethyl acetate and petroleum ether. For the conversion of alcohols to benzothiazoles the same procedure as above was followed except the use of *o*-aminothiophenol, instead of 1,2-phenylenediamine.