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A novel method for the highly efficient synthesis of 1,2-benzisoxazoles under neutral conditions using the Ph_3P/DDQ system

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Abstract—The use of Ph_3P/DDQ offers a novel, neutral and highly efficient method for the efficient conversion of 2-hydroxyaryl aldoximes and ketoximes to 1,2-benzisoxazoles in excellent yields at room temperature.

Isoxazoline ring systems are an important class of nitrogen–oxygen heterocycles with many synthetic applications as structural units of many molecules of biological interest that has made them useful intermediates in medicinal chemistry.[1] Due to their biological activities, they have been the subject of extensive experimental studies[2] and many synthetic methods have been employed in the synthesis of these compounds including reactions of 2-hydroxy aryl aldoximes and ketoximes with, (i) thionyl chloride in pyridine,[3] (ii) trichloroacetyl isocyanate,[4] (iii) Ac_2O and K_2CO_3,[5] (iv) Ac_2O in pyridine[6] or the reaction of hydroxylamine-*O*-sulfonic acid with 2-hydroxyphenyl carbonyl compounds,[7] etc.

The methods developed so far have limitations and drawbacks such as; they are usually two-step procedures including the conversion of the hydroxyl group of the oximes to leaving groups such as halides or acetates followed by the base-catalyzed cyclization reaction to the 1,2-benzisoxazoles[3,5–7] and are usually temperature dependent needed heating[5,6] or cooling.[3,7,8] Both elevated temperatures and alkaline conditions may cause unwanted secondary processes such as cyclization to 1,3-benzoxazoles[4,7,9] which occurs through a Beckmann rearrangement of the intermediate carbamoyl oxime and subsequent ring closure or hydrolysis of the oxime derivatives. In continuation of our work on the use of Ph_3P/DDQ,[10] we now report that this mixed reagent system offers the possibility of preparing 1,2-benzisoxazoles under mild and neutral reaction conditions at room temperature without the formation of any side products.

We first optimized the reaction conditions for cyclization of salicylaldoxime to its corresponding 1,2-benzisoxazole. The reaction was carried out by mixing Ph_3P and DDQ in dichloromethane as solvent at room temperature. The addition of the oxime immediately produced the corresponding benzisoxazole in an excellent yield.

The optimized molar ratio of Ph_3P/DDQ/oxime was found to be 1.5/1.5/1.0. In this reaction, salicylaldoxime on treatment with Ph_3P/DDQ was cyclized without the need to add any base.

The successful synthesis of 1,2-benzisoxazole derivatives via the cyclization of different aldoximes prompted us to investigate the applicability of this procedure for the generation of other 1,2-benzisoxazoles. A similar behaviour was also observed in the cyclization of 2-hydroxy aryl ketoximes to the corresponding 1,2-benzisoxazoles (Scheme 1).

The results of this study are summarized in Table 1. As shown in this table, the use of this method at room temperature and under neutral conditions prevents the formation of any 1,3-benzoxazoles, and 1,2-benzisoxazoles are the only products obtained.

Keywords: Triphenylphosphine; DDQ; Oxime; 1,2-Benzisoxazole.
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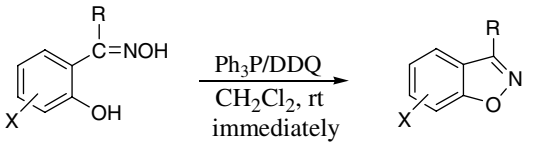


R = H, alkyl, aryl

X = H, CH_3, C_2H_5, OH, OCH_3, Br

Scheme 1.

A mixture of Ph_3P (1.5 mmol, 0.392 g) and DDQ (1.5 mmol, 0.34 g) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 1 min. Salicylaldoxime (1 mmol, 0.137 g) was then added. The green color of the reaction mixture changed to brown after 1 min. GC or TLC monitoring showed completion of the reaction. The solvent was evaporated. Column chromatography of the crude mixture on silica gel using *n*-hexane and ethyl acetate (3:1) as eluent gave the desired 1,2-benzisoxazole in a 95% yield. Bp 91–92 °C/15 mmHg. Lit.[7] bp 35–38 °C/2 mmHg; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 8.71 (1H, s), 7.28–7.87 (4H, m); ^{13}C NMR (250 MHz, $CDCl_3$): δ (ppm) = 109.70, 121.27, 121.99, 123.72, 130.02, 146.18, 162.20.

In order to show the advantages of the present work in comparison with other recently reported protocols, we compared the reaction conditions of this method with those reported previously (Table 2).

As shown in Table 2, the highest yield, shortest reaction time, and the most neutral reaction conditions are achieved using the present methodology.

We suggest a mechanism for the reaction which occurs through the formation of the adduct **(I)** from the reac-

Table 1. The conversion of 2-hydroxyaryl aldoximes and ketoximes to 1,2-benzisoxazoles using Ph_3P/DDQ in dichloromethane at room temperature[a]

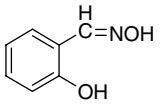
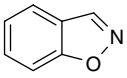
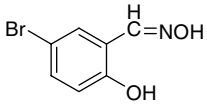
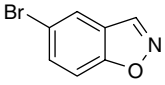
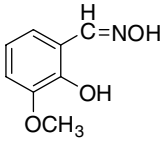
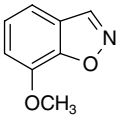
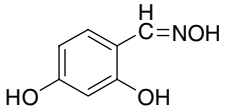
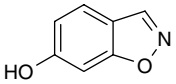
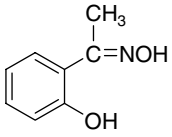
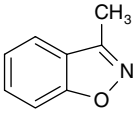
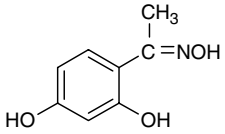
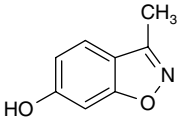
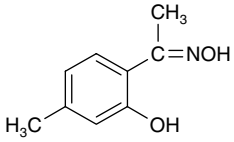
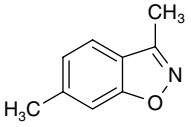
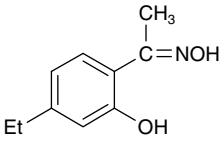
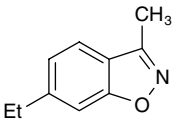
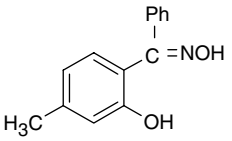
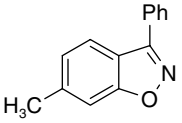
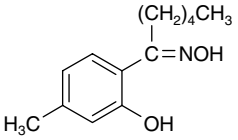
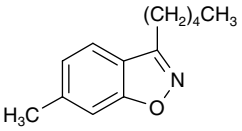
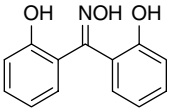
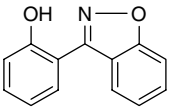
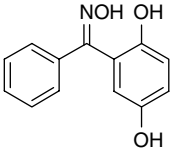
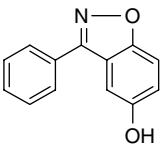
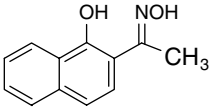
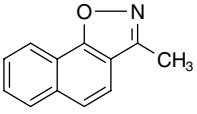
Entry	Compound	Product	Isolated yield (%)
1			95
2			93
3			93
4			92
5			95
6			95
7			93

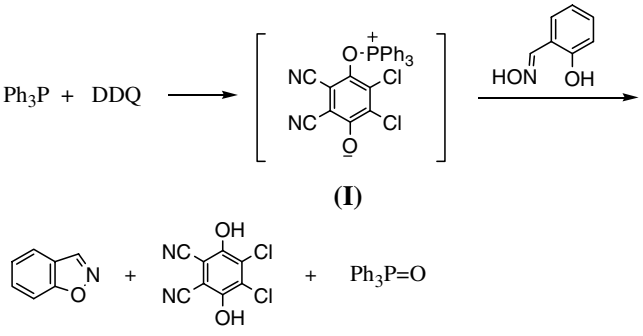
Table 1 (*continued*)

Entry	Compound	Product	Isolated yield (%)
8			92
9			90
10			94
11			93
12			95
13			91

[a] Quantitative conversion was obtained after 1 min.

Table 2. Comparison of the reaction conditions of the present method with those reported in the literature

Entry	Reagent	Conditions	Time	Yield (%)
1	Ph_3P/DDQ	CH_2Cl_2/rt	1 min	90–95
2	$Cl_3CCONCO$	THF/rt	30 min	33–90
3	$SOCl_2$/pyridine	Et_2O/0 °C	2 h	—
4	Hydroxylamine-*O*-sulfonic acid	H_2O/0 °C	1 h	88–95
5	Ac_2O/K_2CO_3	C_6H_6/reflux	5 h	43–61



Scheme 2.

tion between Ph_3P and DDQ.[11] The reaction of the hydroxyl group of the oxime with the positively charged phosphorus atom in this intermediate is followed by cyclization and the formation of the corresponding 1,2-benzisoxazole and triphenylphosphine oxide (Scheme 2).

In conclusion, we have introduced a highly efficient protocol for the preparation of 1,2-benziosxazoles from 2-hydroxyaryl aldoximes and ketoximes under mild and neutral conditions using a mixture of Ph_3P and DDQ as commercially available, cheap, chemicals. Excellent yields, fast reactions and the absence of any rearranged products are worthy of mention for the presented method.

Acknowledgements

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