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Improvement of the Van Leusen reaction in the presence of β-cyclodextrin: a green and efficient synthesis of oxazoles in water

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Abstract: An efficient approach for the synthesis of oxazoles through the Van Leusen reaction in the presence of β-cyclodextrin is described. In aqueous medium using β-cyclodextrin as a supramolecular catalyst, tosylmethyl isocyanide was deprotonated by triethylamine and subsequently underwent an addition/cyclization reaction with aldehydes to produce corresponding oxazoles in excellent yields. This protocol improves the Van Leusen reaction with the use of catalytic amounts of base at low temperature in green media.

Keywords: aldehydes; β-cyclodextrin; oxazoles; tosylmethyl isocyanide (TosMIC); Van Leusen reaction.

1 Introduction

Oxazoles are common substructures in numerous synthetic intermediates, biologically active compounds, and pharmaceuticals [1–4]. Remarkably, many macrocyclic compounds from bacteria or of marine origin with oxazole units display significant cytotoxic, antitubuline, and antitumor activity and also act as β_3 adrenergic receptor agonists [5]. Another example is a series of phenyloxazoles as dopamine receptor binding profiles [6]. A wide variety of biologically important oxazoles have been isolated including compound **1**, which is a potent PTP-1B inhibitor that shows antihyperglycemic activities (Fig. 1) [7].

These significant prevalences of oxazoles have stimulated the need for efficient routes to the preparation of these heterocycles. Numerous synthetic protocols have been developed for this goal such as intermolecular cycloadditions [8–10], condensations [11], and intramolecular cyclization of amino acids [12], which sometimes suffer in their versatility, convenience, and yield. One of the best choices to improve synthetic efficiency is the Van Leusen oxazole synthesis in which an aldehyde reacts with tosylmethyl isocyanide (TosMIC) to form an oxazole [13–17].

Nowadays, green chemistry has attracted great attention in organic reactions with the concern to design environmentally friendly products and chemical processes [18–22]. Water, as an economically available and environmentally benign solvent, is an excellent alternative to carcinogenic and toxic organic solvents. However, the fundamental disadvantage in carrying out the reaction in water is the insolubility of organic substrate in water [23, 24]. Cyclodextrins, having a hydrophobic inside and a hydrophilic outside, can enhance the solubility and form reversible host-guest complexes with organic compounds [25–27].

2 Results and discussion

The classic Van Leusen conditions have significant drawbacks such as the use of excess amounts of base, harsh reaction conditions, relatively long reaction times, and difficult workup [13, 14]. Although various methodologies of the Van Leusen reaction have been reported, many drawbacks still exist in these methods [15–17]. Hence, the improvement of Van Leusen reaction through low cast and easy reaction condition and workup with excellent yield is desirable.

According to the pharmacological significance of oxazoles and the importance of green chemistry, we sought to develop a novel improvement of the Van Leusen reaction using β-cyclodextrin (β-CD) as a recyclable supramolecular promoter, which would offer an efficient formation of desired oxazoles. Thus, the reaction between TosMIC **1** and benzaldehyde **2a** was investigated in the presence of various amounts of Et_3N and β-CD at different temperatures in water. As is shown in Table 1,

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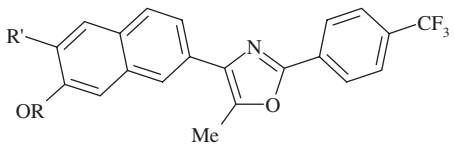


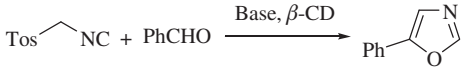
1 (PTP-1B inhibitor)

Fig. 1: An example of biologically active oxazoles.

the oxazole was not formed in the absence of Et_3N (entry 1), but was produced in good yield (78%) in the presence of 2.3 equiv. of Et_3N at 90°C after 5 h without the use of β-CD (entry 3). However, this reaction has a difficult workup to achieve the pure product. As a consequence, we used β-CD as promoter and it was found that the best yield of oxazole **3a** was obtained in the presence of 40 mol% of Et_3N and 15 mol% of β-CD at 50°C in water after 2 h (96%, entry 8). Consequently, the use of β-CD proved to be essential to achieve excellent yields and lead to lower reaction times and temperatures, as well as lower amounts of the required base. In addition to Et_3N, several bases such as DBU, pyridine, ^{t}BuOK, K_2CO_3, and NaOH were also examined (entries 9–13). Organic bases gave better results, presumably as a consequence of the hydrophobic insides of β-CD. Finally, Et_3N was chosen because of the high yields of the desired products and its relatively lower cost. The reaction did not proceed cleanly in the absence of additional base. Also, the reaction was carried out in various solvents including CH_3CN, CH_2Cl_2, $CHCl_3$, toluene, DMF, THF, DMSO, dioxane, and 1,2-dichloroethane (DCE) (entries 14–22), and water was found to be the best solvent under these conditions.

Consequently, the reaction of TosMIC and benzaldehyde **2a** was selected as the model reaction for monitoring the recoverability of β-CD. After the completion of the reaction, the reaction mixture was cooled to 10°C and β-CD was filtered off, washed with ice-cold water, and dried. The recovered β-CD was further used in the same reaction and its catalytic activity and the product yields were determined. We found that the yields of the desired product **3a** decreased slightly after four to five cycles (Table 2).

Table 1: Optimization of the Van Leusen oxazole synthesis in the presence of β-CD.[a]



1 **2a** **3a**

Entry	Base (mol%)	β-CD (mol%)	Temperature (°C)	Solvent	Time (h)	Yield of 3a (%)[b]
1	–	–	90	Water	5	No reaction
2	Et_3N (100)	–	90	Water	5	49
3	Et_3N (230)	–	90	Water	5	78
4	Et_3N (50)	20	r.t.	Water	5	13
5	Et_3N (50)	20	50	Water	2	96
6	Et_3N (45)	20	50	Water	2	95
7	Et_3N (40)	20	50	Water	2	96
8	Et_3N (40)	15	50	Water	2	96
9	DBU (40)	15	50	Water	2	93
10	Pyridine (40)	15	50	Water	2	89
11	^{t}BuOK (40)	15	50	Water	2	57
12	K_2CO_3 (40)	15	50	Water	2	53
13	NaOH (40)	15	50	Water	2	49
14	Et_3N (40)	15	50	CH_3CN	2	16
15	Et_3N (40)	15	50	CH_2Cl_2	2	Trace
16	Et_3N (40)	15	50	$CHCl_3$	2	Trace
17	Et_3N (40)	15	50	Toluene	2	Trace
18	Et_3N (40)	15	50	DMF	2	43
19	Et_3N (40)	15	50	THF	2	19
20	Et_3N (40)	15	50	DMSO	2	45
21	Et_3N (40)	15	50	Dioxane	2	30
22	Et_3N (40)	15	50	DCE	2	Trace

[a]Reaction conditions: equimolar ratio of TosMIC and benzaldehyde, appropriate amount of base and β-CD; solvent (3 mL); temperature and time.

[b]Isolated yield.

Table 2: Recoverability study of β-CD.[a]

β-CD	Recovered β-CD (%)	Yield of 1a (%)[b]
Fresh	97	96
1	96	96
2	95	95
3	94	95
4	94	94
5	91	90

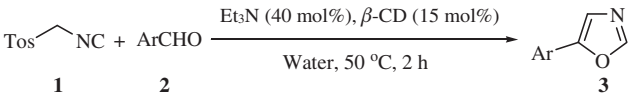
[a]Reaction conditions: TosMIC (1 mmol), benzaldehyde (1 mmol), Et_3N (40 mol%), β-CD (15 mol%); 50°C; water as solvent; 2 h.
[b]Isolated yields.

To show the generality and scope of this protocol, the reactions were performed using various aldehydes **2** in the presence of 40 mol% of Et_3N and 15 mol% of β-CD at 50°C in water. All the reactions proceeded to completion within 2 h. ^1H NMR analysis of the reaction mixtures clearly indicated the formation of the oxazoles **3a**–**m** in excellent yields of 89–96% (Table 3).

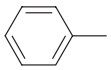
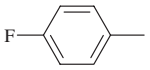
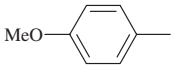
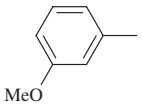
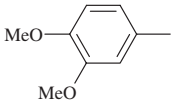
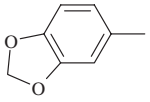
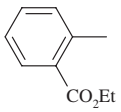
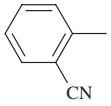
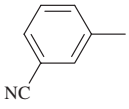
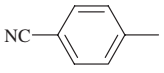
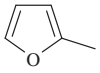
The general procedure for the preparation of oxazoles **3** is given in the Supporting Information, which is available online. The identity of the oxazoles **3** was further deduced from their ^1H and ^{13}C NMR spectral data, which were consistent with the literature values [28–30] (see Supporting Information), and finally proved by melting point determination [28–30].

A plausible mechanism for the formation of the oxazoles **3** is depicted in Scheme 1. At first, deprotonation of TosMIC **1** by Et_3N yields intermediate ion **4**. Nucleophilic addition of ion **4** to aldehyde **2** would form intermediate **5**, which cyclizes into intermediate **6**. Then, protonation of this compound by triethylammonium affords dihydroxazole **7**, which undergoes deprotonation of the β-proton of the sulfinyl group to give ion **8**. Finally, elimination of the sulfinyl group leads to the formation of stable oxazole **3**. In this mechanism, β-CD covers all the organic substances, which leads to the availability of triethylamine and triethylammonium in the desired steps. Taken altogether, this resulted in lower reaction times and temperatures.

Table 3: The green method for the Van Leusen synthesis of oxazoles **3a–m.**[a]



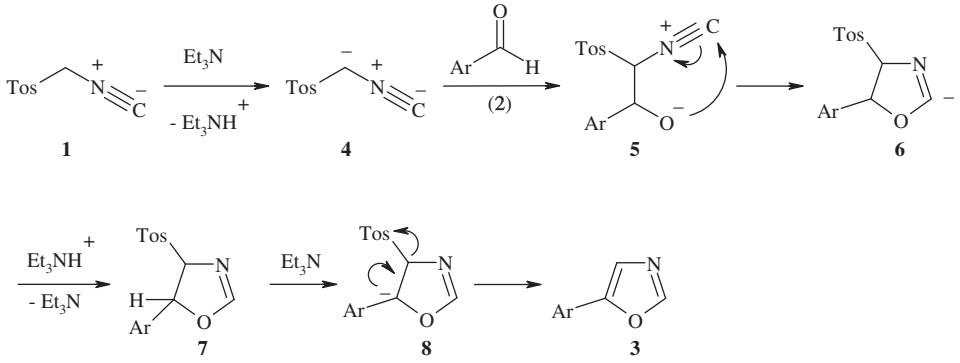
1 2 3

Product	Ar	Yield (%)[b]	M. p. (°C)	M. p. (°C) [Lit.]
3a		96	38	37–38 [28]
3b		93	38–39	37–39 [28]
3c		90	57–58	58 [29]
3d		92	Oil	
3e		91	101–103	100–102 [30]
3f		91	89–90	88–90 [30]
3g		94	Oil	
3h		95	100–101	100 [29]
3i		93	134–135	135 [29]
3j		95	133–134	133 [29]
3k		89	93–95	92–94 [28]
3l		92	65	64–65 [28]
3m		90	Oil	

[a]Reaction conditions: TosMIC (1 mmol), aldehydes (1 mmol), Et_3N (40 mol%), β-CD (15 mol%); 50°C; in 3 mL of water; 2 h.
[b]Isolated yields.

3 Conclusion

In summary, we have developed a green and efficient method for the Van Leusen reaction to produce oxazoles of potential synthetic and pharmacological interest. The use of β-CD/water as an inexpensive and environmentally benign promoter and reaction medium, the simple procedure, relatively short reaction times, easy workup, and high yields provide a very useful route for the synthesis of differently substituted oxazoles in the Van Leusen reaction.



Scheme 1: Plausible reaction mechanism.

4 Supporting information

The general procedure for the preparation of oxazoles **3**, their ^{1}H and ^{13}C NMR spectroscopic data, as well as copies of these spectra are given as Supporting Information, which is available online (DOI: 10.1515/znb-2017-0005).

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