A modified approach for the synthesis of biologically relevant 5-substituted-2-N-aryl-1,3-oxazole derivatives in mild conditions

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ABSTRACT
We herein report a modified approach for the synthesis of some pharmacologically relevant oxazole derivatives linked with amides under mild conditions. The utilization of polymer-supported triphenylphosphine (poly-TPP) as a phosphine ligand for generating the key iminophosphorane intermediate was found to be vital for achieving the synthesis of oxazole in room temperature. This alternative approach relying on the cyclization reaction of readily available phenacyl azide and phenyl isothiocyanate rendered the oxazole derivative 3a in excellent yield. This methodology has been applied for the synthesis of a more decorated oxazole derivative 3b having ester functionality and was further converted to different amides under microwave irradiation in good to excellent yields in the later stage.

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1. Introduction

The development of new leads in drug-discovery programme is always initiated by the synthesis of novel molecules which displays excellent and a wide array of biological profiles because of the presence of some critical structural features in them. Some heterocyclic frameworks act as highly functionalized scaffolds which play a pivotal role in developing new leads in drug discovery [1,2]. Among the diverse assortment of heterocyclic compounds, N-(hetero)aryl oxazole analogues (Figure 1) display a wide spectrum of applications and hence are considered as vital architectures in the area of medicinal chemistry, material science and agrochemicals [3]. Additionally, this class of compounds can be employed to construct complex ligands for various catalytic applications. Due to this high demand for N-aryl oxazoles in various fields, extensive research has been employed for the development of powerful and efficient synthetic strategies for this vital pharmacophore. The ability to bind with a wide range of enzymes and receptors via non-covalent interactions further warrants the development of greener and eco-friendly protocols for accessing diversely substituted N-aryl/heteroaryl oxazole based analogues [4].

The use of solid supported reagents in organic synthesis to construct different chemical frameworks has led to significant advances in the area of developing new chemical entities (NCE’s) for various drug-discovery programmes [5]. The use of some solid supported reagents in solution phase synthesis offers a key advantage in the ease of isolation of desired products through a simple filtration process. Among the solid supported reagents used in the area of chemical synthesis, polymer-supported triphenyl phosphine is a vital reagent that is widely employed in many chemical transformations [6].

Among the aforementioned pharmacologically relevant oxazole based moieties, 2-N-aryl-5-substituted-1,3-oxazole derivatives are important compounds developed by Dhar and Cho et al., independently which exhibited potent inosine monophosphate dehydrogenase (IMPDH) and 5-lipoxygenase (5-LOX) inhibitory
activities [7,8]. Even though the synthesis of 2-N-aryl-5-substituted-1,3-oxazole has been achieved by various methods hitherto [9,10], the most practiced one is by generating the iminophosphorane/heterocumulene in situ by treating isothiocyanate with triphenylphosphine (PPh₃) followed by the cyclization with β-keto azide which was initially reported by Froyen in 1991 [11]. In 1993, Molina and co-workers reported a similar approach by utilizing tributyl phosphine (PBu₃) ligand for the synthesis of analogous class of oxazole molecules bearing indole [12]. In 2015, Dhar and co-workers reported an alternative approach for the synthesis of these derivatives by heating phenacyl azide and phenyl isothiocyanate in PPh₃ at 90°C in dioxane [13]. Although the yield of this iminophosphorane/heterocumulene mediated methodology was excellent, the removal of triphenylphosphine oxide by-product from the reaction mixture requires tedious chromatographic separation and/or other crystallization techniques leading to tremendous problems in bulk process. This account points to some of our efforts in the synthesis of 2-N-aryl-5-substituted-1,3-oxazole analogues employing alpha azido ketones and isothiocyanates in presence of polymer-supported triphenylphosphine (poly-TPP) under exceptionally milder conditions (Scheme 1). In this letter, we report our modified approach for the synthesis of this oxazole derivative having ester functionality and its subsequent conversion to various amide derivatives of considerable pharmacological relevance under microwave irradiation.

2. Results and discussions

As a model reaction to start our initial screening studies, we treated phenacyl azide and phenyl isothiocyanate in PPh₃ as reported by Dhar et al [13]. We obtained the desired oxazole product 3a in 93% isolated yield which is almost consistent with their results (Table 1, entry 1). In our continuous efforts to simplify the overall methodology (work-up and removal of phosphorus oxide by-product), we decided to screen the reaction with different phosphine ligands at room temperature (Table 1). Although the utilization of other phosphine ligands simplified the purification process, it significantly reduced the yield of the desired product (Table 1, entries 3–7). However, we could obtain the required product in acceptable yield when polymer-bound triphenylphosphine dichloride (poly-TPPCl₂) was used as the iminophosphorane precursor. Gratifyingly, the expected product was procured in excellent yield (96% isolated yield) when polymer-supported triphenylphosphine (poly-TPP) was employed. The corresponding oxide by-product could be easily removed by filtration through celite bed.

Our next attention was to apply this modified methodology in the synthesis of more specialized pharmacologically relevant 2-N-aryl-5-substituted-1,3-oxazole derivatives. Accordingly, we designed our two-step synthesis for the target molecules by applying our modified protocol for oxazole synthesis (Scheme 2). In our successful trials, the desired oxazole derivative 3b was obtained in 94% yield. The adopted purification
procedure (filtration) was facile and efficient in terms of yield and time consumption.

We then decided to treat the intermediate 3b with different primary and secondary amines 4a-h in view of synthesizing more decorated oxazole based target molecules. Microwave irradiation reactions are always considered to be superior to conventional heating methodologies owing to its rapid product formation with lesser side-products [14–20]. Accordingly, we decided to utilize microwave irradiation for the synthesis of our target molecules. We initially took intermediate 3b and 4-tert-butyl aniline 4a as model substrates for the control experiments (Table 2). Different lithium salts and solvents were screened to identify the suitable reaction condition for our optimization studies. To our delight, we obtained the desired product 5ba in reasonable yield when lithium chloride (LiCl) was employed in N,N-dimethylformamide (DMF) at 100°C under microwave irradiation (Table 2, entry 2). The best yield of 5ba was obtained when LiCl was used in 1,2-dichloroethane (DCE) as a solvent at 100°C under microwave irradiation (Table 2, entry 5).

The above-optimized protocol for the conversion of ester to amides was then extended to evaluate the substrate scope. Accordingly, we treated 3b and different amines with LiCl in 1,2-dichloroethane (DCE) as solvent at 100°C in a microwave reactor. To our delight, all the amines rendered the desired target molecules

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**Scheme 1.** Synthesis of oxazole derivative 3a.

**Table 1.** Optimization of reaction parameters for the synthesis of 3a.

| Entry | Phosphine Ligand | Product isolation method | Yield\(^b\) 3a (%) |
|-------|-----------------|--------------------------|-----------------|
| 1\(^c\) | PPh\(_3\) | Column | 93 (96) |
| 2 | PPh\(_3\) | Column | 20 |
| 3 | PCy\(_3\) | Column | 25 |
| 4 | P(o-tolu)\(_3\) | Column | 22 |
| 5 | P(t-Bu)\(_3\) | Column | 15 |
| 6 | PBu\(_3\) | Filtration | 50 |
| 7 | P(Oct)\(_3\) | Filtration | 40 |
| 8 | Poly-TPPCl \(_2\) | Filtration | 60 (70) |
| 9 | Poly-TPP | Filtration | 96 (99) |

\(^{a}\)Reaction conditions: Azide 1a (1 mmol), isothiocyanate 2a (1.2 mmol), phosphine ligand (1 mmol), dioxane, 3 h, RT.

\(^{b}\)Isolated yield, GC-MS yield in parenthesis.

\(^{c}\)Reaction carried out at 90°C for 15 min.

**Table 2.** Optimization of reaction parameters for the conversion of ester to amida.

| Entry | Lithium salt | Solvent | Yield\(^b\) 5ba (%) |
|-------|--------------|---------|------------------|
| 1 | LiBr | DMF | 40 |
| 2 | LiCl | DMF | 65 |
| 3 | LiI | DMF | 25 |
| 4 | LiCl | Dioxane | 50 |
| 5 | LiCl | DCE | 90 |

\(^{a}\)Reaction conditions: Ester 3b (1 mmol), amine 4a (1.2 mmol), lithium salt (2 mmol), solvent (2 mL), microwave irradiation at 100°C for 1 h.

\(^{b}\)Isolated yield.

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**Scheme 2.** Synthesis of targeted oxazole derivatives.
Table 3. Synthesis of target molecules$^{a,b}$.

| Ester 3b + Amines 4a-h | LiCl | DCE | Microwave 100°C, 1h. | 5b(a-h) |
|------------------------|------|-----|----------------------|---------|
| $\text{3b} \quad \text{F-} \quad \text{O_NO_} \quad \text{H} \quad \text{N} \quad \text{O} \quad \text{R}^2 \quad \text{R}^1 \quad \text{H} \quad \text{C} \quad \text{O-} \quad \text{3b}$ | $\text{F-} \quad \text{O_NO_} \quad \text{H} \quad \text{N} \quad \text{O} \quad \text{R}^2 \quad \text{R}^1 \quad \text{H} \quad \text{C} \quad \text{O-} \quad \text{5b(a-h)}$ |

$\text{5ba (90%)} \quad (60%)^c$ $\text{5bb (87%)}$

$\text{5bc (95%)}$ $\text{5bd (89%) (45%)^c}$

$\text{5be (86%)}$ $\text{5bf (85%)}$

$\text{5bg (93%)} \quad (50%)^c$ $\text{5bh (95%)}$

$^{a}$Reaction conditions: Ester 3b (1 mmol), amine 4a-h (1.2 mmol), LiCl (2 mmol), DCE, microwave irradiation at 100°C for 1 h.

$^{b}$Isolated yield in parenthesis.

$^{c}$Reaction carried out by conventional heating for 6 h.

$\text{5b(a-h)}$ in good to excellent yields (Table 3). The primary amines, both aromatic and aliphatic, furnished the desired products in good yields whereas the secondary aliphatic cyclic amines gave the required products in excellent yields (Table 3). For substantiating the advantages of microwave irradiation, we also performed the same reaction for synthesizing $\text{5ba}$, $\text{5bd}$ and $\text{5bg}$ by standard heating methodologies (Table 3). Microwave irradiation proved to be superior in terms of yield and reaction time.

A plausible mechanism for the conversion of ester 3b to amides $\text{5b(a-h)}$ has been depicted herein. We speculate that the oxophilic lithium salt binds with the oxygen atom of the carbonyl group in ester, thereby increasing its reactivity. The subsequent attack of amine to the carbon atom of carbonyl group followed by elimination of alcohol yield the desired products.

The synthetic procedure for accessing the intermediate 3a is detailed below. To the weighed quantity of $\beta$-keto azide 1a (1 mmol, 1 equiv) in dioxane (3 mL) in a two-necked Round Bottomed (RB) flask, isothiocyanate 2a (1.2 mmol, 1.2 equiv) and 3 mmol/g loaded poly-TPP (1 mmol, 1 equiv) was added and stirred at RT for 3 h. After the completion of reaction monitored by TLC, the reaction mixture was filtered through celite and the filtrate was collected and distilled under reduced pressure. The resulting solid was recrystallized from ethanol to obtain the titled compound 3a as white solid in 96%
yield (227 mg). The melting point (170-172 °C) and the spectral details of the product were found to be matching with the reported values [21].

3. Conclusion

We have developed an exceptionally mild, facile and modified approach for the synthesis of some pharmacologically relevant 2-amino-5-substituted-1,3-oxazole derivatives under microwave irradiation. The developed methodology paved the way for the synthesis of some biologically relevant oxazole derivatives and can be extended for the synthesis of other densely functionalized heterocycles in the future. The pharmacological screening of the newly synthesized molecules will be carried out in our laboratory in due course and will be reported in future.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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