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An approach toward the syntheses of triazolo benzoxazines, triazolo quinoxalines, triazolo benzodiazepines, triazolo benzoxazepines, and triazolo benzothiazines via a simple and convenient protocol using basic alumina as solid support

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ABSTRACT

A microwave assisted green protocol for the syntheses of triazole fused benzoxazines, benzoxazepines, quinoxalines, and benzothiazines was investigated using basic alumina as solid support. The one-pot reaction was carried out using Cu(phen)(PPh_3)Br as a catalyst. The protocol did not require the use of any additional ligands, base or the use of expensive and toxic palladiums.

Organic reactions performed under non-traditional reaction conditions by using inexpensive and recyclable mineral supports have attracted great attention in recent years primarily due to the growing environmental concerns.[1–3] The application of solid supports in a microwave-assisted reaction eliminates the use of solvents and the necessity of rigorous reaction conditions.[4] Besides, the homogenous dispersion of the active sites, simpler work-up procedure etc. makes the solid-supported reactions more useful than the conventional solution phase synthesis.[5] The use of solid support in a microwave-accelerated reaction also enables the reaction to execute at atmospheric pressure and thus it can be utilized for large scale synthesis of various organic compounds.[6,7]

Triazole fused benzoxazines showed a broad range of biological activities[8] and have wide clinical applications[9] (e.g., estazolam, alprazolam, etc.). 1,4-Benzoxazines or their modified scaffolds are present in a number of bioactive natural products,[10] as well as, in many medicinally significant compounds[11] (e.g., levofloxacin). Furthermore, there are many triazole fused 2,3-dihydro-1,4-benzoxazines[12] which have shown therapeutic potential based on in vitro and molecular modeling studies.[13] Similarly, 1,4-benzothiazines have also shown a wide range of pharmacological properties including anti-allergic, anti-aldoso-reductase, antifungal, anti-rheumatic, immunostimulating, vasorelaxant, anti-arrhythmic, anti-hypertensive, neuroprotective, and cytotoxic activities.[14] 1,4-/1,5-Benzodiazepines or benzoxazepines also have been well recognized for their wide array of biological activities, such as anti-insectant, antitumor, fibrinogenic receptor antagonist, human neurokinin NK1 receptors, muscarinic receptor ligands etc.[15] A number of triazoloquinoxaline derivatives can act as human A3 (hA3) adenosine receptor (AR) antagonists. Receptor-based SAR analysis also highlighted the versatility of the triazoloquinoxaline scaffold as potent and selective hA3 AR antagonists.[16] In addition 1,2,3-triazole derivatives showed strong antibacterial[17–19] and antifungal[20,21] properties.

Due to the varied biological activities of these heterocyclic scaffolds, several sequential and one-pot synthetic routes involving domino Sonogashira-azide–alkyne cycloaddition reactions in the presence of various transition-metal catalysts have been reported.[22a,22b] Chowdhury et al. had carried out the synthesis of triazolo-benzoxazines using $Pd(OAc)_2/PPh_3/CuI/K_2CO_3$ in DMF at 100 °C.[22c] These methodologies are no doubt quite efficient but may require both palladium and copper salts as catalysts and were carried out at elevated temperature. We have modified this

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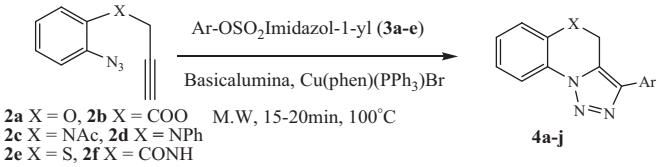
reaction using microwave heating, basic alumina as solid support and base, and aryl imidazol-1-yl-sulfonate as oxygen based electrophile.

Microwave heating at controlled temperature and pressure may considerably reduce reaction time without promoting any side reactions.[23] Solid support like alumina, possesses excellent ability to absorb the organic compounds on their surface, and transmits microwave irradiation without absorbing or restricting it. Literature also revealed that the basic oxides, like alumina, serve as a suitable alternative for palladium catalyzed heteroannulation reactions due to its role as a base and the presence of oxide ion in the solid framework.[24] Oxygen based electrophiles[25a,25b] have also attracted attention of the synthetic organic chemists, due to their high stability and easy accessibility through functional group interconversion from readily available hydroxylated compounds. These prompted us to explore an efficient yet simple and one-pot green protocol using basic alumina and microwave irradiation with aryl imidazol-1-yl-sulfonate as electrophile. Herein, we describe (Scheme 1) the synthesis of triazolo benzoxazines, triazolo quinoxalines, triazolo benzodiazepines, triazolo benzoxazepines, and triazolo benzothiazines involving various azido alkynes (**2a–f**) and aryl imidazol-1-yl-sulfonate as oxygenated electrophilic compounds (**3a–e**) with basic alumina as a solid support using only Cu(phen)(PPh_3)Br (**1h**) as a catalyst under microwave irradiation (100 °C, 250 W). In all cases the products were obtained in high yield. The use of solid support serves dual role; it eliminates the use of hazardous and costly Pd-catalyst and also restricts the use of organic solvents. The new protocol does not require additional base and can be carried out efficiently in a short time.



Scheme 1. One-pot reaction under microwave irradiation using basic alumina as solid support.

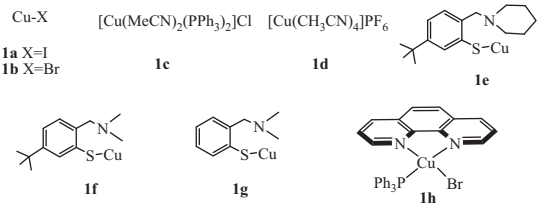


Figure 1. Copper catalysts used in the study.

We used **2a** and **3a** to synthesize triazole fused benzoxazine **4a** for the initial studies. Our first objective was to develop the optimal condition for the one-pot reaction under solid support without using Pd salts. Systematic studies of the reaction conditions in the presence of copper(I) catalysts[23b,26] (Fig. 1) and various solid supports (basic alumina, TiO_2, MgO) revealed that basic alumina provided better yield (Table 1), even in the absence of any added base (triethyl amine or DBU). Copper(I) iodide or bromide (**1a–b**), yielded [1,2,3]triazolo[5,1-c][1,4]benzoxazines (**4a**) in 61% and 58%, respectively, (Table 1, entry 5 & 6), whereas, the use of catalysts **1c** and **1d** gave yields of 54% and 57% (Table 1, entry 7 & 8). Similar observations were noted for thio-copper complexes (**1e–g**) (Table 1, entry 9–11). Use of catalyst **1h** was found to be very effective for the reaction with an excellent yield of 77% (Table 1, entry 12). No additional base was required as basic alumina acts as base and also as solid support.

To evaluate the effect of microwave irradiation in comparison with conventional reaction conditions, a pre-heated oil-bath was used as heat source. Reaction in an oil bath of the same reactants **2a, 3a**, and catalyst **1h** gave **4a** in significantly lower yield (60%). This clearly indicates that the effect of microwave is not purely thermal. It could be expected that the application of microwave irradiation causes easy excitation of electronic energy levels and thus leads to better yield.

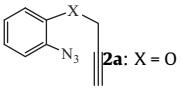
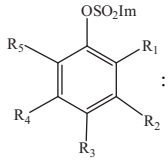
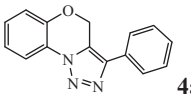
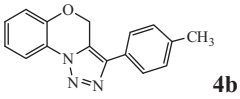
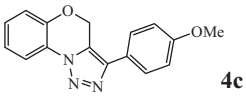
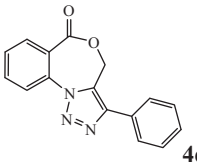
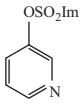
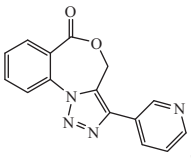
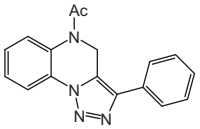
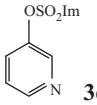
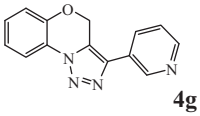
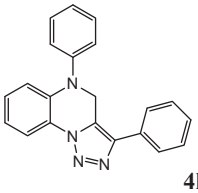
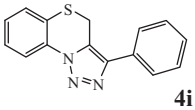
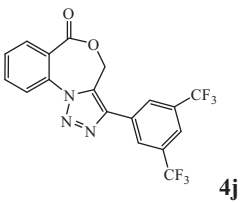
To establish the scope and generality of this approach, reaction of various aryl imidazol-1-yl-sulfonates (**3a–e**) was carried out following the same reaction condition. The results are summarized in Table 2. It was observed that a wide variety of aryl imidazol-1-yl-sulfonates possessing different functional groups reacted successfully. All the products were characterized by spectral and analytical methods. To ensure the recyclability of the solid support, the residue was washed thoroughly with acetone and water, calcined at

Table 1
Optimization of Cu(I) catalysts on various solid supports and bases

Entry[a]	Solid support	Catalyst used	Catalyst (mol %)	Time (min)	Yield[b] (%)
A. Without additional base					
1	TiO_2	**1a**	2.0	10	27
2	TiO_2	**1a**	2.5	10	30
3	TiO_2	**1a**	2.5	15	30
4	TiO_2	**1a**	3.0	15	30
4	MgO	**1a**	2.5	15	36
5	Basic alumina	**1a**	2.5	15	61
6	Basic alumina	**1b**	2.5	15	58
7	Basic alumina	**1c**	2.5	15	54
8	Basic alumina	**1d**	2.5	15	57
9	Basic alumina	**1e**	2.5	15	54
10	Basic alumina	**1f**	2.5	15	48
11	Basic alumina	**1g**	2.5	15	57
12	Basic alumina	**1h**	2.5	15	77
B. With Et_3N as additional base					
13	Basic alumina	**1h**	2.5	15	77
C. With DBU as additional base					
14	Basic alumina	**1h**	2.5	15	75

[a] All reactions were performed using 1-azido-2-(prop-2-ynyloxy)benzene (**2a,** 1 equiv) and arylimidazol-1-yl-sulfonate (**3a**, 1.2 equiv), with copper catalysts (**1a–h**) under microwave irradiation (250 W, 100 °C).
[b] Isolation of pure product, **4a**.

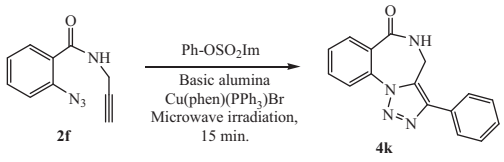
Table 2
Basic alumina supported reactions of aryl imidazol-1-yl-sulfonates (**3a**–**e**) with various azido alkynes (**2a**–**f**) leading to triazole fused derivatives (**4a**–**j**)

Entry[a]	Azide	Arylimidazol-1-yl-sulfonates	Product	Yield (%)[b]	Ref.
1	 **2a**: X = O 2a: X = O	 : $R^1 = R^2 = R^3 = R^4 = R_5 = H$	 **4a**	77	22c
2	**2a**	**3b**: $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = CH_3$	 **4b**	82	22c
3	**2a**	**3c**: $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = OMe$	 **4c**	81	22c
4	**2b**: X = COO	**3a**	 **4d**	72	21b
5	**2b**	 **3d** **3d**	 **4e**	84	25c
6	**2c**: X = NAc	**3a**	 **4f**	67	27a
7	**2a**	 **3d**	 **4g**	64	22c
8	**2d**: X = NPh	**3a**	 **4h**	66	27a
9	**2e**: X = S	**3a**	 **4i**	58	28
10	**2b**	**3e**: $R^2 = R^4 = CF_3$; $R^1 = R^3 = R^5 = H$	 **4j**	62	25c

[a] Reactions were performed using (**2a**–**f**) (1.0 equiv), basic alumina (500 mg–1 gm), (**3a**–**e**) (1.2 equiv), **1h** (2.5 mol %), under microwave irradiation (250 W, 100 °C) for 15–20 min.
[b] Isolated yield (some losses during purification were unavoidable in certain cases).

150 °C, and the material was reused three times without any noticeable change in the yield of the products (data not shown).

It is interesting to note that the new protocol was successfully employed for the synthesis of fused benzodiazepines **4k** using



Scheme 2. Synthesis of fused benzodiazepines **4k** from 2-azido-*N*-(3-phenylprop-2-ynyl)benzamide (**2f**).

2-azido-*N*-(3-phenylprop-2-ynyl)benzamide (**2f**), where nitrogen atom of the amide backbone is unprotected (Scheme 2). Similar cyclization reactions have been reported earlier where nitrogen was suitably protected.[27a] Under the new reaction condition, the compound was produced in good yield (63%). No by-products resulting from *endo*- or *exo*-cyclization due to the presence of NH and alkyne functionality in immediate vicinity were observed.

To establish the pathway we carried out the reaction with compounds **2b** and **3a** and tried to isolate the intermediate products [I (path A) and II (path B), Scheme 3], but without success. This could be due to rapid formation of the final product **4d** under microwave irradiation in the presence of basic alumina as solid support. When the reaction was carried out stepwise and in the absence of electrophile (path B, Scheme 3), the intermediate **II**[21b] could be isolated. Subsequent addition of the electrophile in the same reaction vessel under the same reaction condition afforded the final product **4d**. Recently, Benton et al.[27b] have shown that a similar type of reaction using Cu(I), base, and solvent at elevated temperature proceeds via cycloaddition followed by C–H arylation (path B). Since, Path A and Path B utilize different reagents and keeping in mind that Sonogashira reaction cannot take place in the absence of electrophile, the exact pathway could not be ascertained.

In summary, we have demonstrated an efficient, economical, environmentally benign, and rapid process for the synthesis of triazole fused benzoxazines, benzothiazines, benzodiazepines, benzoxazepines, and quinoxalines. The method eliminates the use of hazardous and expensive palladium salts, additional ligands. No additional base and solvent are required as basic alumina acts as solid support and base. The exact reaction mechanism could not be ascertained, as no intermediate compound could be isolated. Cu(phen)(PPh_3)Br is used as the only catalyst and plays a dual role in cycloaddition reaction and activation of C–H bond. Moreover, application of microwave reduces the time of the reaction considerably with improved yield of the product. The uniqueness of the methodology lies in its eco-friendly operation, reusability of the solid support, and excellent yield.

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra of all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.080.

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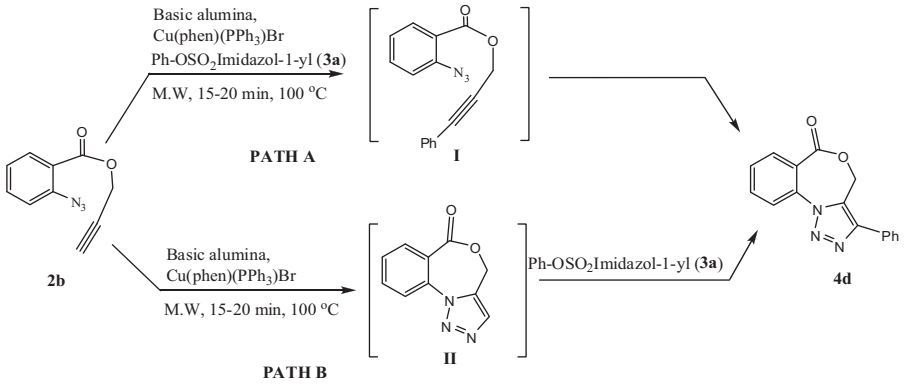

Scheme 3. Possible pathways for the formation of the product **4d**.

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