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Sulfated tungstate a heterogeneous acid catalyst for synthesis of 4-aryl-*NH*-1,2,3-triazoles by 1,3-dipolar cycloaddition of nitroolefins with NaN₃

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ABSTRACT

A facile and new method for the synthesis of 4-aryl-NH-1,2,3-triazoles from nitroolefins and NaN_3 by 1,3-dipolar cycloaddition reaction, employing a mild solid inorganic acid sulfated tungstate as a heterogeneous catalyst, has been developed. The protocol emphasizes broad substrate scope with many functionalities, less reaction time, stability to open air, easy work-up, and with good to excellent yields.

GRAPHICAL ABSTRACT



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KEYWORDS

1,3-Dipolar cycloaddition; heterogeneous catalysis; nitrostyrenes; sulfated tungstate; 1,2,3-triazoles

Introduction

Five member nitrogen heterocyclic motifs are ubiquitous in useful organic compounds. Amongst them, 1,2,3-triazoles are an important class that finds widespread applications in the areas such as medicinal chemistry,^[1-6] agrochemistry, material chemistry, dyes, corrosion inhibitors, and photo stabilizers.^[1,7-9] For example, 1,2,3-triazoles show a broad spectrum of biological activities,^[10] including antibacterial, herbicidal, fungicidal, antiallergic, and anti-HIV. Specifically, 4-aryl-1*H*-1,2,3-triazoles were found as human methionine aminopeptidase (hMetAP2) and indoleamine 2,3-dioxygenase (IDO) inhibitors, and are expected to become medicines to treat cancers, AIDS, Alzheimer's disease, tristimania, cataracts, and some other serious diseases.^[11,12] The growing importance of 1,2,3-triazoles is highlighted with some examples such as 4-(2-chlorophenyl)-1H-1,2,3-triazole are indoleamine 2,3-dioxygenase (IDO) inhibitors; azahistidine, an unnatural amino acid; ML295, which is a monoacylglycerol lipase ABHD6 selective inhibitor; and 4-(3,4-dibromophenyl)-1H-1,2,3-triazole a hMetAP2 inhibitor (Fig. 1).^[11]

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ABHD6 selective inhibitor

Figure 1. Representative biologically active 1,2,3-triazoles.

An extensive range of chemosensors contains click-derived 1,2,3-triazoles where the triazole motif plays a functional role.^[9] Few other examples of 1,2,3-triazole derivatives are (1-benzyl-1*H*-1,2,3-triazole-4-yl)methanol (BTM) and (1-(pyridin-4-yl methyl)-1*H*-1,2,3- triazole-4-yl)methanol (PTM) are corrosion inhibitor for steel.^[13]

Development of methods for the synthesis of 1,2,3-triazoles has gained much attention.^[14-17] There are numerous methods for synthesis of 1,2,3-triazoles, like organo-catalyzed azide-ketone cycloaddition,^[18-21] I₂/TBPB oxidative cyclization of N-tosylhydrazones and anilines,^[15] the multi-component reaction involving aldehydes, nitroalkanes, and organic azides, [22,23] cyclization reactions of α, α -dichlorohydrazones and primary amines,^[24,25] the copper-catalyzed cyclization of hydrazones and azides^[26] using a catalyst, such as palladium in an inert atmosphere^[27] or p-TsOH.^[28] The pioneering work on synthesis of 1,2,3-triazole by 1,3-dipolar cycloaddition dates back to 1960s when Huisgen and coworkers disclosed route to make 1,2,3-triazole moiety through thermal induced dipolar cycloaddition between alkynes and azides.^[29-31] Alkyne-azide 1,3-dipolar cycloaddition reactions catalyzed by Cu^[32-35] and Ru^[36-39] are the most commonly utilized methods for the synthesis of N-substituted 1,2,3-triazoles and commonly referred as click chemistry. Ir-catalyzed azide-alkyne cycloaddition (IrAAC),^[40,41] are the other approaches. In the triazole synthesis, some multicomponent reactions to construct triazoles from terminal alkynes are reported.^[42-46] However, there are few papers discovering the synthesis of 1,2,3-triazoles from aldehydes^[22,47,48], which involves use of various catalysts such as proline,^[48] morpholine,^[22] Julia reagent,^[47] NaHSO₃/Na₂SO₃^[49] AlCl₃^[50] Al-MCM-41 and sulfated zirconia using a microwave.^[51] Cycloaddition of α,β -disubsituted nitroolefins and sodium azide^[2,52] using PTSA,^[53] Amberlyst-15^[54] microwave,^[55] sulfamic acid,^[56] and Bi₂WO₆ nanoparticles,^[57] carbon based biocatalyst^[58].

In spite of these several methods, there is scope for new methods especially considering the use of expensive metals like Rh, Ir, Pd as a catalyst, need of inert atmosphere, and use of hazardous reagents. Combination of Bronsted acid and NaN₃ forms hydrazoic acid which is toxic in nature and also susceptible to explosion. Hence, triazole synthesis is mainly conducted under neutral or basic conditions.^[59] But, under these conditions, competitive cyclotrimerization of arylnitroolefins was observed giving 1,3,5triarylbenzenes as undesired byproducts.^[52] in the recent attempt by Xue-Jing Quan, to use acid catalyzed condition resulted in inhibition of the undesired cyclotrimerization but the acid is used under homogeneous condition,^[28] use of acid in homogeneous format has its own disadvantages. Also other acid catalyzed conversions suffers from limitations such as the use of microwave conditions, high temperature, and requirement of high catalyst loading. Therefore, there is a need to develop a practically simple heterogeneous mild acid catalyzed method for synthesis of 1,2,3-triazoles.

Recently our research group has introduced sulfated tungstate as a heterogeneous green catalyst and successfully shown its applications in many useful transformations. Sulfated tungstate is mildly acidic, non-corrosive, reusable, easy to prepare and has established its effectiveness in amidation, Ritter, Biginelli, Kindler, Strecker, Willgerodt–Kindler reactions, *N*-formylation, transamidation, *N*-monoalkylation of primary amines, etherification, synthesis of amidine, and 1,3,5-triarylbenzenes.^[60] In this paper, we describe a new application of sulfated tungstate in 1,3-dipolar cycloaddition of nitroolefins with NaN₃.

Result and discussion

Sulfated tungstate was prepared by the well-established procedure in our laboratory and is described in our earlier publication.^[61,62] Preliminary investigations were conducted using 1:1.2 mole ratio of (E)-(2-nitrovinyl) benzene (1a) and sodium azide as building blocks in the presence of 25 wt% of a sulfated tungstate and DMF as a solvent at 100 °C and the expected product 3a was obtained in 95% yield. Encouraged with this result experiments were conducted to optimize various parameters. To fix the reaction temperature reactions were conducted at different temperatures of 70, 60 and 50 °C. The reaction proceeded efficiently to afford the target **3a** in 95% at 60 °C (Table 1, entry 3). To screen the suitability of different solvents reactions were performed in polar solvents like DMSO, ACN and nonpolar solvents like toluene and xylene (Table 1, entries 5–8). All the solvents were viable for the reaction but the reaction rates were slow as indicated by the lower yields for the same reaction time of 1 h. The reaction in DMSO was found to be equally good as a solvent but the reaction was bit slower giving 80% in 3 h (Table 1, entry 6). Towards optimization of catalyst loading reactions were conducted using different wt% of catalyst such as 30, 15, 10 and 5 wt%.

There was no significant improvement in yield even after increasing the catalyst loading to 30 wt% (Table 1, entry 9). With, a decrease in the catalyst loading up to 10 wt% the reaction rate and yield remained the same (Table 1, entry 11). With further decrease to 5% reaction slowed down giving 72% yield in 2h (Table 1, entry 12). Therefore 10 wt% of catalyst loading with the reaction time of 1 h was considered to be adequate. With these optimized conditions in hand, we turned our focus to study the substrate scope of the new method. Changing the electronic nature of the substituents on nitrostyrene has almost no effect on the overall course of the reaction.

This may be attributed to the high efficiency of this protocol. Nitrostyrenes containing electron-donating groups (OCH₃) works well to offers the respective product with good yield (Table 2. Entries 8, 9). Electron-withdrawing groups such as NO_2 and -CN

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1a			2a		
Entry	Solvent	Sulfated Tungstate (wt%)	Temp. (°C)	Time (h)	Yield (%) ^b
1	DMF	25	100	1	95
2	DMF	25	70	1	94
3	DMF	25	60	1	95
4	DMF	25	50	2	81
5	ACN	25	Reflux	3	10
6	DMSO	25	100	3	80
7	Toluene	25	100	2	46
8	Xylene	25	100	2	43
9	DMF	30	60	1	94
10	DMF	15	60	1	94
11	DMF	10	60	1	95
12	DMF	5	60	2	72
13	DMF	0	60	12	0

^aReaction conditions: **1a** (1 mmol), **2** (1.2 mmol), sulfated tungstate, solvent and temperature; ^bisolated yield of 3a.



	NO_2 Sulfated T	ungstate (10 wt%)	N=N NH	
	R ¹ DMF	$;$ 60 °C, 1h \mathbf{R}^2		
_	1	R ¹ 2		
Entry	R	Product	Yield (%) ^b	
1	$R^1 = H, R^2 = H$	2a	95	
2	$R^1 = 4$ -Br, $R^2 = H$	2b	88	
3	$R^1 = 4$ -Cl, $R^2 = H$	2c	92	
4	$R^1 = 4$ -F, $R^2 = H$	2d	90	
5	$R^1 = 2$ -Cl, 4-Cl, $R^2 = H$	2e	91	
6 ^c	$R^1 = 4 - NO_2, R^2 = H$	2f	89	
7 ^d	$R^1 = 4$ -CN, $R^2 = H$	2g	81	
8	$R^1 = 4$ -OCH ₃ , $R^2 = H$	2h	82	
9	$R^1 = 3$ -OCH ₃ , 4-OCH ₃ , $R^2 = H$	2i	79	
10	$R^1 = 4$ -OCH ₃ , $R^2 = CH_3$	2j	81	
11	$R^1 = H, R^2 = -CH_2CH_3$	2k	76	
12	2-CH ₃ furan, $R^2 = H$	21	89	
13	2-thiophene, $R^2 = H$	2m	83	
14	2-naphthalene, $R^2 = H$	2n	84	

^aReaction conditions: 1 (1 mmol), sodium azide (1.2 mmol), DMF, time; ^bisolated yield; ^ctime required 2 h; ^dtime required 1.5 h.

reacted with equal ease (Table 2, entries 6–7). Different halogens such as fluoro, chloro and bromo substituted nitrostyrenes were well tolerated in the transformation (Table 2, entry 1–4). The method was also found to be suitable for the synthesis of sterically challenging o-substituted nitrostyrenes providing good yield under the optimized reaction conditions (Table 2, entry 5).

Stearic factors were also introduced α - to nitro group as in case of substrates (E)-1methoxy-4-(2-nitroprop-1-en-1-yl)benzene and (E)-(2-nitrobut-1-en-1-yl)benzene, both the substrates reacted smoothly under the optimized reaction conditions to give products in 81% and 76% yield respectively indicating the tolerance of stearic factors and showing wider substrate scope (Table 2, entries 10 and 11).

In addition, reaction with acid labile heterocyclic nitrostyrene such as (E)-2-(2-nitrovinyl) furan and (E)-2-(2-nitrovinyl) thiophene also proceeded smoothly to give products in 89 and 83% yields, respectively (Table 2, entries 12 and 13). With substrate (E)-2-(2-nitrovinyl) naphthalene having fused ring system, the reaction was facile giving 84% yield (Table 2, entry 14).

To explore the applicability of the method on a preparative scale, with substrate (E)-(2-nitrovinyl) benzene, the reaction was successfully scaled up to 1.49 g, getting the yield of without any significant decrease in the efficiency (92% as against 95% in 10 mmol scale). The gram-scale reaction was performed in the usual laboratory setup with a two-neck round-bottomed flask fitted with a reflux condenser. This example clearly establishes the practical feature of this newly developed method.

To understand the reaction mechanism following studies were carried out. Tungsten trioxide (WO₃), a material close to sulfated tungstate but lacking acidity was screened. However, no reaction was observed at 60 °C even after 12 h in DMF as a solvent. This result indicates that sulfated tungstate plays a catalytic role and not just acts as a solid surface. In the next experiment, the catalyst was suspended in nitrostyrene and DMF mixture and stirred for 15 min at 60 °C. Then hot filtered, washed with chloroform, and dried in an oven and recorded FT-IR. The IR spectrum showed peaks corresponding to nitrostyrene (1333 cm⁻¹ and 1516 cm⁻¹), indicating its adsorption on the catalyst. Similarly, in another experiment, the catalyst was suspended in a mixture of sodium azide and DMF, stirred for 15 min at 60 °C filtered. Hot filtered wash with water and chloroform dried in an oven and recorded FT-IR. In the IR spectrum, there were no peaks corresponding to azide and only peaks attributed to the catalyst were observed. Indicating that, sodium azide was not adsorbed on the catalyst.

Based on these experimental results a mechanism is postulated for the reaction involving activation of nitrostyrene through H-bonding as well as activation of double bond and formation of transition state A as depicted in Figure 2 followed by [3+2] cycloaddition and aromatization driven elimination of NO₂ group leading to the formation of triazole 2a.

In conclusion, the present work described a new protocol for the synthesis of 1,2,3triazoles through 1,3 dipolar cycloaddition in presence of sulfated tungstate, a mild and easy to synthesize, the heterogeneous acid catalyst has been developed. The method is operationally simple and can be performed under aerobic conditions in the usual laboratory setup. Mild reaction conditions and tolerance of a wide variety of functional groups and potential for use in preparative scale are some noteworthy features of this newly developed method.



Figure 2. Postulated mechanism.

Experimental

Procedure for synthesis of 4-phenyl-1H-1,2,3-triazole (2a)

To a stirred solution of nitrostyrene 1 (1 mmol) and sulfated tungstate (10 wt%) in DMF (2 mL), NaN₃ (1.2 mmol) was added and the mixture was stirred at 60 °C for 1 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled down to rt. Then the mixture was diluted by adding ethyl acetate (10 ml) with stirring. Filtered off the catalyst. The filtrate was washed with 10 mL of water, the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (100–200 mesh) and petroleum ether/EtOAc mixture as an eluent to afford pure product 4-phenyl-NH-1,2,3-triazole with 95% yield.

White solid, mp =150–151 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.07 (s, 1 H), 7.86 (d, J=7.5 Hz, 2 H), 7.49 (t, J=7.5 Hz, 2 H), 7.43 (d, J=7.3 Hz, 1 H), 7.29 (s, 1 H). ¹³C NMR (101 MHz, DMSO-d₆) δ 167.77 (s), 133.30 (s), 131.19 (s), 129.71 (s), 129.37 (s), 129.01 (s), 126.01 (s).

General procedure, ¹H and ¹³C NMR of compounds are provided in the supplementary information.

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