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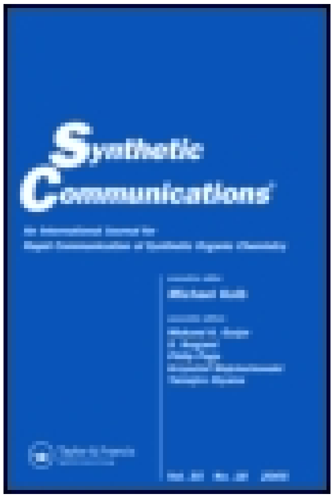

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Regioselective Synthesis of 1,5-Disubstituted 1,2,3-Triazoles by Reusable Immobilized $AlCl_3$ on γ-Al_2O_3

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Regioselective Synthesis of 1,5-Disubstituted 1,2,3-Triazoles by reusable immobilized $AlCl_3$ on γ-Al_2O_3

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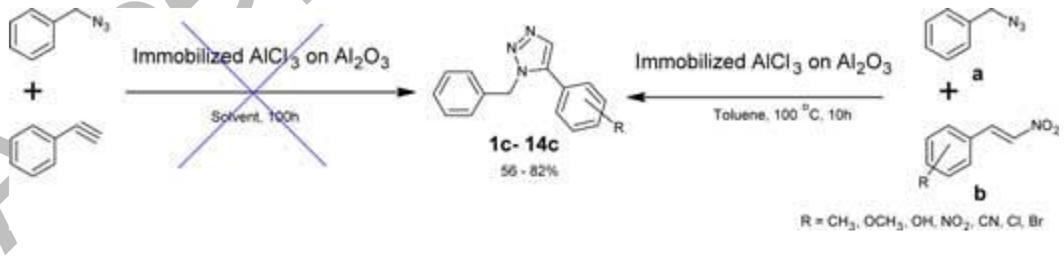
Abstract

There is rapidly growing interest in the synthesis and use of substituted 1,2,3-triazoles. We report the easy and interesting procedure demonstrating the effectiveness of the surface modified γ-Al_2O_3 which is reusable, efficient, catalytic, safe and environmentally acceptable for the regioselective synthesis of 1,5-disubstituted-1,2,3-triazoles *via* [3+2] cycloaddition of phenyl and benzyl azides with a series of aryl nitroolefins in good yields. No adverse effect on substituents such as nitro, cyano, hydroxy, ether linkage and halogens was observed. The catalyst could easily be recycled and was reused nine runs without losing its activity.

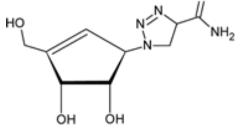


KEYWORDS: 1,5-disubstituted-1,2,3-triazoles; Immobilized $AlCl_3$ on γ-Al_2O_3; [3+2] cycloaddition; nitroolefins; azide

INTRODUCTION

The 1,2,3-Triazole family exhibit a broad spectra of bio-activities such as antifungal,[1] antiviral,[2] antibacterial[3] and anticancer activities.[4] 1,2,3-triazoles and the derivatives have been the current interest of research owing to their importance in contribution to the development of new drugs candidates.[5] The 1,2,3-triazole derivative of cyclopentenyl carbocyclic nucleosides **1** has been demonstrated to be a potent antiviral agent against orthopoxviruses and SARS.[6] 1,2,3-triazole moiety is been manipulated with zanamivir derivatives **2** and are studied for their anti-AIV activities[7] and 3-arylethylnyltriazolyl ribonucleosides have been studied for successful anticancer activity on the drug-resistant pancreatic cancer cell line MiaPaca-2.[8] Very recently, 1,2,3-triazoles attached with heterocyclic fragments **3** have been screened and found to active against melanoma, colon and breast cancer.[9]

$AlCl_3$ is one of the prime members of Friedel-Craft's catalysts that are widely used in petroleum refining and pharmaceutical industries. $AlCl_3$ plays a major role in alkylation, acylation, alkene isomerization, cracking, and polymerization processes. It should be noted that researchers of late, avoid using $AlCl_3$ because of drawbacks such as its corrosiveness, difficulty in separating the used/unreacted catalyst from products, and production of a large amount of waste. A promising improvement of traditional $AlCl_3$ catalysts is the immobilization of $AlCl_3$ on a support. Immobilization of $AlCl_3$ can easily be achieved on supports such as Al_2O_3, SiO_2, *etc*.



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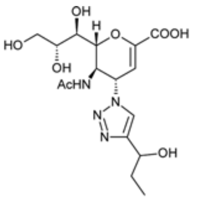

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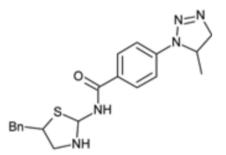

3

In the year 1961, Rolf Huisgen demonstrated the synthesis of 1,2,3-triazoles by 1,3-dipolar cycloaddition of azides and alkynes.[10] The Huisgen's reaction is generally carried out at elevated temperatures and unfortunately the reaction often produces a mixture of 1,4- and 1,5-disubstituted mixtures and there is was a lack of regioselectivity. Several modifications for Huisgen's reaction to achieve 1,4- disubstituted-1,2,3-triazoles[11-13] and 1,5-disubstituted 1,2,3-triazoles[14,15] have been reported using a variety of metals mediated catalysts. Sasaki et al. have also demonstrated the regioselective syntheses of adamantane derivatives of 1,2,3-triazoles *via* 1,3-dipolar cycloaddition reactions.[16] Ce(OTf)$_3$ is recently been employed to catalyze the cycloaddition to achieve 1,5-disubstituted-1,2,3-triazoles in excellent yields,[17] we are dedicated in making the route green and inexpensive and easy access to 1,5-disubstituted-1,2,3-triazoles.

RESULTS AND DISCUSSION

In view of importance of 1,5-disubstituted-1,2,3-triazoles, we wanted to synthesize these compounds using easily available inexpensive, reusable catalyst and we set out the experiments to use immobilized AlCl$_3$ on γ-Al$_2$O$_3$[18] and succeeded. Initially the cycloaddition of terminal acetylenes and azides were tried and did not observe any trace of the corresponding product with the range of polar and non-polar solvents such as

MeOH, DCM, DCE, EtOH, MeCN, DMSO, DMF, THF, benzene and toluene even at elevated temperatures. When the acetylenes were replaced by (2-Nitroethenyl)benzene, surprisingly we could able to get the desired product as shown in Scheme 1.

(2-Nitroethenyl)benzene (**1b**) afforded 56% (**1C**) in 12 hours and other substituted (2-Nitroethenyl)benzenes with both phenyl and benzyl azides gave the desired 1,5-Diphenyl-1H-1,2,3-triazoles at 100°C without any side reactions. The reaction of electron withdrawing nitro and chloro substituents to (2-Nitroethenyl)benzene 10b, 11b and 13b with benzyl azides afforded the products 10c 11c and 13c in maximum yields 82%, 79% and 78% respectively with lesser time compared to other examples. It is worth noting that, while the reaction of 1b, 4b and 8b with azides gave lower yields (56%, 58% and 57%) of the corresponding products, longer time was required to complete the reaction between (2-Nitroethenyl)thiophene with both phenyl and benzyl azides. In case of the reaction between 4-cyano-(2-Nitroethenyl)benzene (**Entry 12**) and benzyl cyanide, the mixture of products 4-(1-Benzyl-1H-1,2,3-triazol-5-yl)Benzonitrile and 4-(1-Benzyl-1H-1,2,3-triazol-5-yl)[5'-Phenyl-1'*H*-1',2',3',4'-tetrazole] were expected but, we could only able to isolate 4-(1-Benzyl-1H-1,2,3-triazol-5-yl)Benzonitrile in 34%. Further, the reaction of phenyl azide with (2-Nitroethenyl)benzene was chosen to survey the efficiency of the catalyst and to standardize the amounts of catalyst to be employed and it was found that 40 mg is enough to complete the reaction to obtain maximum yield. Results of a range of amounts of immobilized catalyst are shown in Table 1; in the absence of catalyst we could not isolate any product.

CONCLUSION

In summary, we have demonstrated an elegant method for the synthesis of a wide variety of 1,5-disubstituted-1,2,3-triazoles in the presence of immobilized $AlCl_3$ on γ-Al_2O_3. The products of this environmentally friendly procedure, that allowed reuse of the catalyst, were analytically pure. In addition, this reaction is convenient, affording good yields and therefore we believe the procedure is very versatile and will increase the accessibility of 1,5-disubstituted-1,2,3-triazoles to the synthetic chemistry and biology community.

Experimental

Nitroolefins are prepared according to the previous report [19] and purified, all other solvents were of analytical grade and purified wherever necessary according to standard procedures prior to use. TLC was run on pre-coated silica gel on aluminium plates obtained from Whatmann Inc. All reactions were performed at 100 ºC. Melting points were obtained with Büchi B-540 apparatus. IR spectra were recorded on Bruker-TENSOR-FTIR spectroscopy. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 and 100 MHz spectrometer respectively, chemical shifts were reported in (ppm) with TMS as internal standard. Elemental analyses were performed on Perkin Elmer – 2004. Yields refer to the isolated products after purification by column chromatography using 70–230 mesh silica gel.

Typical Procedure To The Preparation Of Azides

In a typical experiment, (2-Nitroethenyl)benzene (150 mg, 1.0 mmol) is taken in to 10 mL round bottomed flask, 5 mL of toluene, phenyl azide (155 mg, 1.3 equiv.) were added and started stirring meanwhile, immobilized $AlCl_3$ on γ-Al_2O_3 (40 mg) is added into the reaction flask and the mixture is gradually heated and maintained the temperature at 100 °C, after 12 h, the disappearance of starting material (2-Nitroethenyl)benzene was observed on thin layer chromatography, the mixture was cooled, filtered and the catalyst was removed off and preserved for recycling. The filtrate was evaporated off under reduced pressure to get the crude which was purified by column chromatography over silica gel using eluent (1.5: 8.5 :: ethyl acetate: hexane) to afford 124 mg (56% yield) of pure 1,5-Diphenyl-1H-1,2,3-triazole (entry 1c) as white solid which melted at 113−114 °C (lit. 113−114 °C)[20]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.47−7.41 (m, 3H), 7.40−7.32 (m, 5H), 7.24−7.21 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.6, 133.4, 129.4, 129.2, 128.9, 128.6, 126.8, 125.2 ppm.

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

ACKNOWLEDGEMENTS

Authors are grateful to the University of Johannesburg for the financial assistance.

Full experimental details, procedures for the preparation of 1,5-Diphenyl-1H-1,2,3-triazoles, preparation of azides, preparation of catalyst, recycling of the spent catalyst, physical constants, copies of ^{1}H NMR, ^{13}C NMR and the data can be found via the "supplementary content" section of the article's web page.

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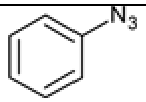
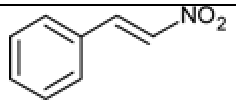
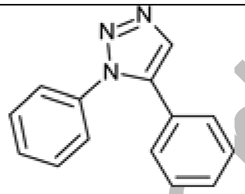
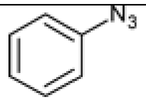
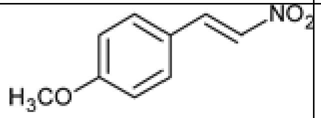
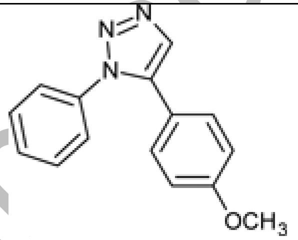
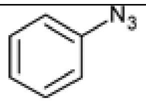
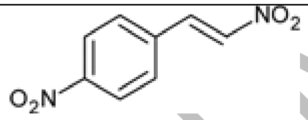
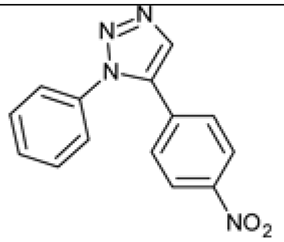
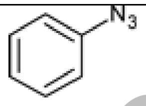
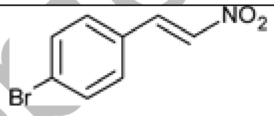
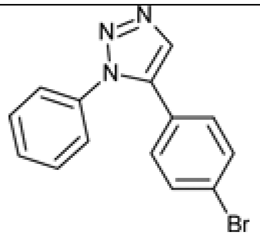
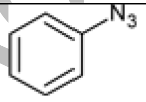
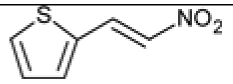
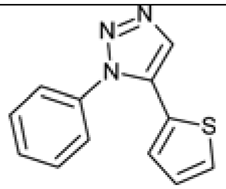
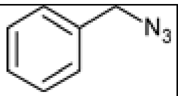
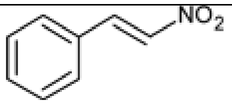
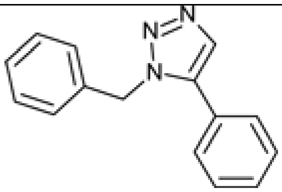
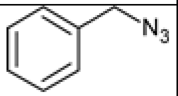
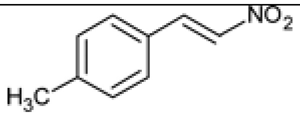
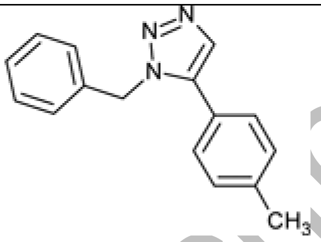
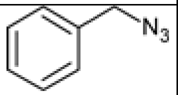
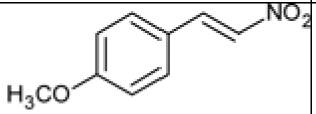
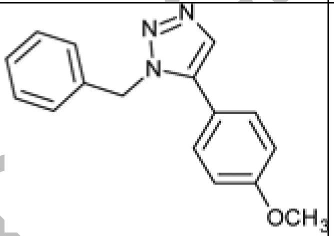
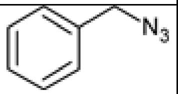
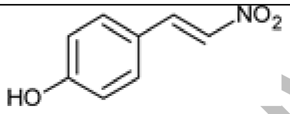
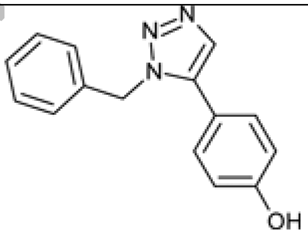
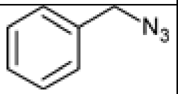
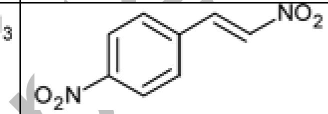
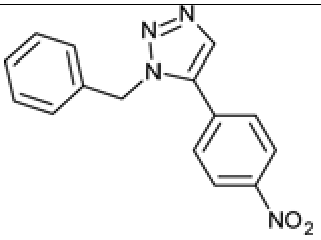
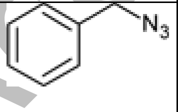
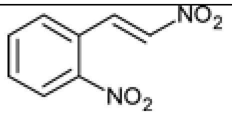
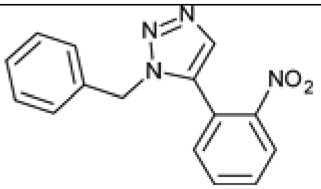
Table 1 Results of the amounts of immobilized $AlCl_3$ on γ-Al_2O_3 at 100 °C[a]

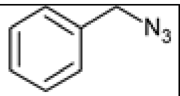
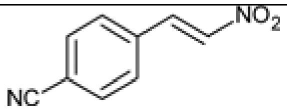
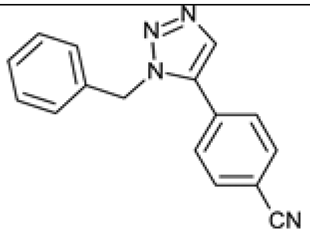
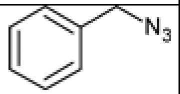
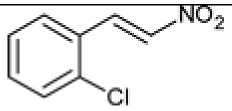
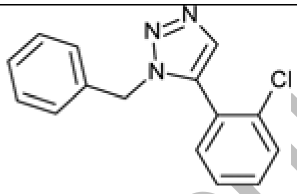
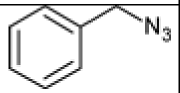
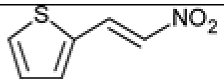
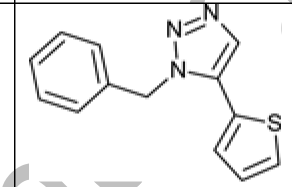
Entry	Catalyst (mg)	Reaction time (h)	Yield (%)
1	No catalyst	100	trace
2	10	18	6
4	20	18	15
6	30	18	41
7	40	12	56
8	50	12	56
9	60	12	56
10	70	12	56
11	80	12	56
12	90	12	56
13	100	12	56

[a] Reaction of 1 mmol of (2-Nitroethenyl)benzene with 1.1 mmol of phenyl azide in 5 mL of toluene at 100 °C in presence of various quantities of immobilized $AlCl_3$ on γ-Al_2O_3.

Table 2 Immobilized $AlCl_3$ on Al_2O_3 catalyzed synthesis of 1,5-disubstituted-1,2,3-triazoles by the reaction of nitroolefins and azides in toluene at 100 ˚C

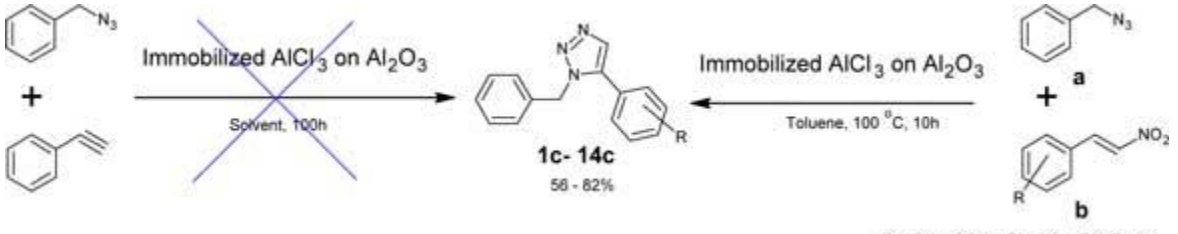
Entry	Azide	Nitrolefin	Reaction time	Product (h)	Yield^a (%)
1			12		56
2			12		61
3			10		70
4			10		58
5			14		62

6			9		73
7			9		67
8			9		57
9			9		63
10			8		82
11			8		79

12			9		34
13			8		78
14			10		64

[a] Isolated yields after column purification

Scheme 1.


N3
+
Immobilized AlCl3 on Al2O3
Solvent, 100h
N
N
N
R
1c- 14c
56 - 82%
Immobilized AlCl3 on Al2O3
Toluene, 100 °C, 10h
N3
a
+
NO2
R
b
R = CH3, OCH3, OH, NO2, CN, Cl, Br