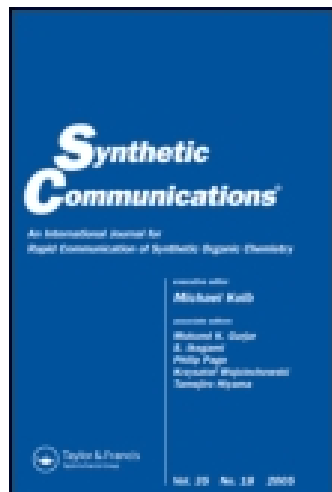


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Regioselective Synthesis of 1,5-Disubstituted 1,2,3-Triazoles by Reusable AlCl_3 Immobilized on $\gamma\text{-Al}_2\text{O}_3$

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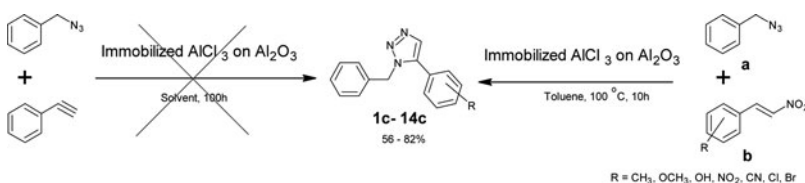
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REGIOSELECTIVE SYNTHESIS OF 1,5-DISUBSTITUTED 1,2,3-TRIAZOLES BY REUSABLE AlCl_3 IMMOBILIZED ON $\gamma\text{-Al}_2\text{O}_3$

Hemmaragala M. Nanjundaswamy and Heidi Abrahamse

Laser Research Centre, Faculty of Health Sciences, University of Johannesburg, Doornfontein, South Africa

GRAPHICAL ABSTRACT



Abstract There is rapidly growing interest in the synthesis and use of substituted 1,2,3-triazoles. We report an easy and interesting procedure that demonstrates the effectiveness of surface-modified $\gamma\text{-Al}_2\text{O}_3$, 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 for nine runs without losing its activity.

Keywords Azide; [3 + 2] cycloaddition; 1,5-disubstituted-1,2,3-triazoles; immobilized AlCl_3 on $\gamma\text{-Al}_2\text{O}_3$; nitroolefins

INTRODUCTION

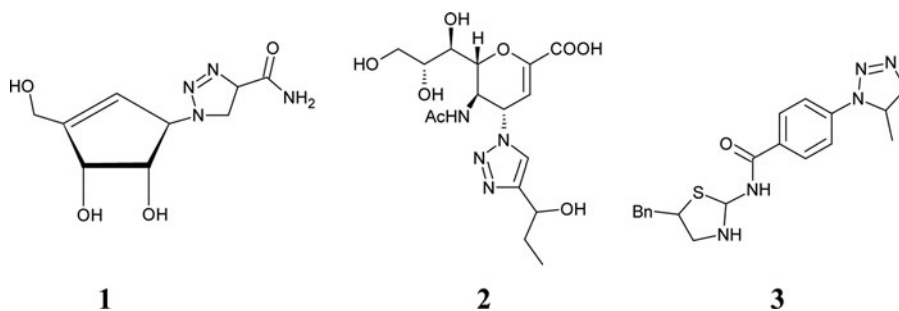
The 1,2,3-triazole family exhibit a broad spectrum of bioactivities such as antifungal,^[1] antiviral,^[2] antibacterial,^[3] and anticancer^[4] activities. 1,2,3-Triazoles and their derivatives have been of interest owing to their importance in contribution to the development of new drug candidates.^[5] The 1,2,3-triazole derivative, cyclopentenyl carbocyclic nucleosides **1**, has been demonstrated to be a potent antiviral agent against orthopoxviruses and SARS.^[6] The 1,2,3-triazole moiety is been manipulated with zanamivir derivatives **2** and studied for anti-AIV activities,^[7] and 3-arylethynyl-triazolyl ribonucleosides have been studied for successful anticancer activity on the

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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 be active against melanoma, colon, and breast cancer.^[9]

AlCl_3 is one of the prime members of Friedel–Craft 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 recently have been avoiding use of AlCl_3 because of drawbacks such as its corrosiveness, difficulty in separating the used and 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 and SiO_2 .



In 1961, Huisgen demonstrated the synthesis of 1,2,3-triazoles by 1,3-dipolar cycloaddition of azides and alkynes.^[10] 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 with 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 metal-mediated catalysts. Sasaki et al. also demonstrated the regioselective syntheses of adamantane derivatives of 1,2,3-triazoles via 1,3-dipolar cycloaddition reactions.^[16] $\text{Ce}(\text{OTf})_3$ has been recently employed to catalyze the cycloaddition to achieve 1,5-disubstituted-1,2,3-triazoles in excellent yields,^[17] and we are dedicated to making the route green and inexpensive and provide easy access to 1,5-disubstituted-1,2,3-triazoles.

RESULTS AND DISCUSSION

In view of the importance of 1,5-disubstituted-1,2,3-triazoles, we wanted to synthesize these compounds using an easily available, inexpensive, reusable catalyst and we set out to use immobilized AlCl_3 on $\gamma\text{-Al}_2\text{O}_3$.^[18] Initially the cycloaddition of terminal acetylenes and azides was tried, but we did not observe any trace of the corresponding product with the range of polar and nonpolar solvents such as MeOH, dichloromethane (DCM), dichloroethane (DCE), EtOH, MeCN, dimethylsulfoxide (DMSO), dimethylformamide (DMF), tetrahydrofuran (THF), benzene, and toluene, even at elevated temperatures. When the acetylenes were replaced by (2-nitroethenyl) benzene, surprisingly we could get the desired product as shown in Scheme 1.



Scheme 1.

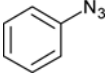
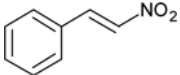
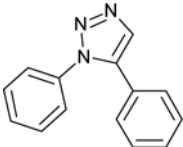
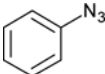
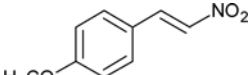
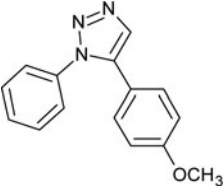
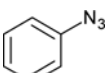
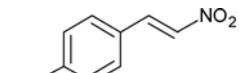
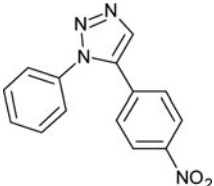
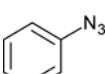
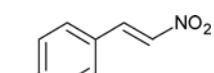
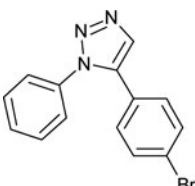
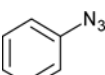
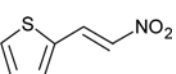
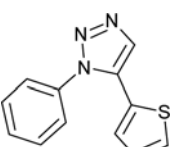
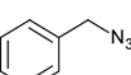
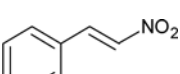
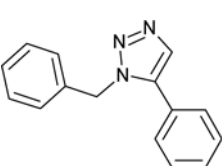
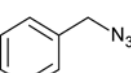
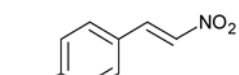
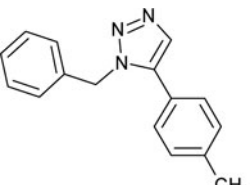
(2-Nitroethenyl)benzene (**1b**) afforded 56% (**1c**) in 12 h and other substituted (2-nitroethenyl)benzenes with both phenyl and benzyl azides gave the desired 1,5-diphenyl-1H-1,2,3-triazoles at 100 °C without any side reactions. The reaction of electron-withdrawing nitro and chloro substituents to (2-nitroethenyl)benzene **10b**, **11b**, and **13b** with benzyl azides afforded the products **10c**, **11c**, and **13c** in maximum yields of 82%, 79%, and 78% respectively, with less time than 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% yield. 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. The products obtained by this system were characterized by infrared spectroscopy, ¹H NMR and ¹³C NMR spectroscopy. The melting points/physical state were compared with authentic samples/literature; the isolated yields and the reaction timings of all products are summarized in Table 2.

Table 1. Results of the amounts of immobilized AlCl₃ on γ-Al₂O₃ 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

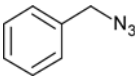
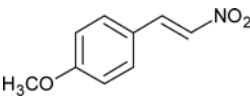
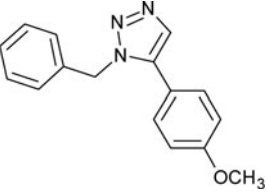
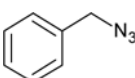
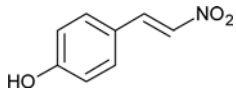
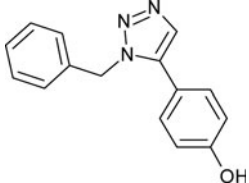
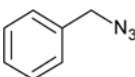
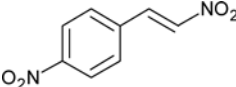
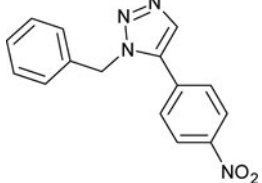
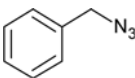
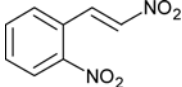
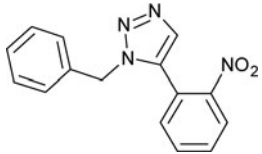
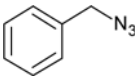
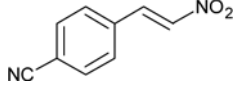
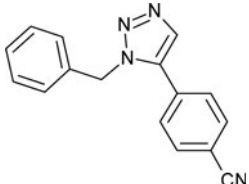
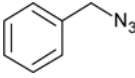
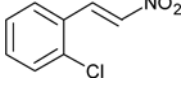
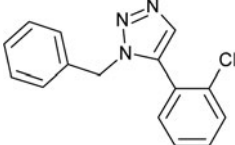
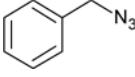
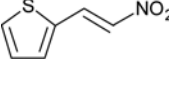
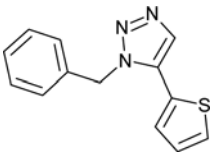
^aReaction of 1 mmol of (2-nitroethenyl)benzene with 1.1 mmol of phenyl azide in 5 mL of toluene at 100 °C in the presence of various quantities of immobilized AlCl₃ on γ-Al₂O₃.

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	Nitroolefin (h)	Reaction time	Product yield ^a (%)
1			12	 56
2			12	 61
3			10	 70
4			10	 58
5			14	 62
6			9	 73
7			9	 67

(Continued)

Table 2. Continued

Entry	Azide	Nitroolefin (h)	Reaction time	Product yield ^a (%)
8			9	 57
9			9	 63
10			8	 82
11			8	 79
12			9	 34
13			8	 78
14			10	 64

^aIsolated yields after column purification.

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 $\gamma\text{-Al}_2\text{O}_3$. The products of this environmentally friendly procedure, which allowed reuse of the catalyst, were analytically pure. In addition, this reaction is convenient and affords 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 communities.

EXPERIMENTAL

Nitroolefins were 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. Thin-layer chromatography (TLC) was run on pre-coated silica gel on aluminium plates obtained from Whatmann. All reactions were performed at 100 °C. Melting points were obtained with Büchi B-540 apparatus. IR spectra were recorded on Bruker-Tensor-FTIR spectroscope. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 and 100 MHz spectrometers respectively, with chemical shifts were reported in parts per million (ppm) and TMS as internal standard. Elemental analyses were performed on a Perkin-Elmer 2004 instrument. Yields refer to the isolated products after purification by column chromatography using 70- to 230-mesh silica gel.

Typical Procedure for the Preparation of Azides

In a typical experiment, (2-nitroethenyl)benzene (150 mg, 1.0 mmol) was taken in a 10-mL round-bottomed flask, 5 mL of toluene and phenyl azide (155 mg, 1.3 equiv.) were added and stirred, while immobilized AlCl_3 on $\gamma\text{-Al}_2\text{O}_3$ (40 mg) was added into the reaction flask. The mixture was gradually heated and maintained at 100 °C; after 12 h, the disappearance of starting material (2-nitroethenyl)benzene was observed on TLC. The mixture was cooled and filtered, and the catalyst was removed 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. This was melted at 113 – 114 °C (lit. 113 – 114 °C)^[20]. ^1H 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.

FUNDING

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SUPPORTING INFORMATION

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, and copies of ^1H NMR and ^{13}C NMR data can be accessed on the [publisher's website](#).

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