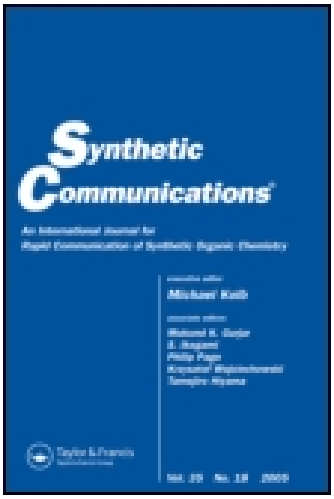

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$ZrCl_4$-Catalyzed C-O Bond to C-N Bond Formation: Synthesis of 1,2,3-Triazoles and Their Biological Evaluation

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$ZrCl_4$-CATALYZED C-O BOND TO C-N BOND FORMATION: SYNTHESIS OF 1,2,3-TRIAZOLES AND THEIR BIOLOGICAL EVALUATION

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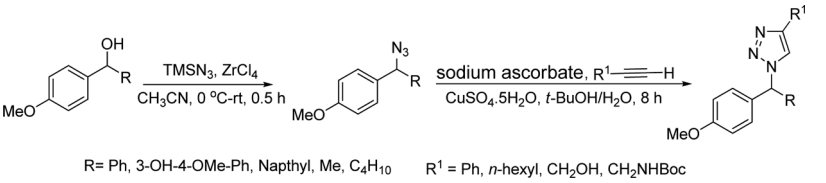
GRAPHICAL ABSTRACT



Abstract *A simple and efficient protocol was developed for the synthesis of aryl azides directly from aryl carbinols using $ZrCl_4$ as a Lewis acid catalyst. The azides were converted to novel triazoles under click reaction conditions, which were evaluated for their antimicrobial activity against various strains.*

Keywords Antimicrobial activity; click chemistry; 1,2,3-triazole; zirconium(IV) chloride

INTRODUCTION

Alcohol functionality, which is an attractive source of electrophile in view of green chemistry principles,[1a] is not a good leaving group. Hence, the derivatization becomes essential for its facile displacement.[1b] Though several methods were reported[2–4] for the direct nucleophilic substitution of alcohols, many of them suffer from elevated temperatures, longer reaction times, or stoichiometric use of the reagents. Thus, the development of newer methods for direct conversion of a C-OH bond into a C-N bond gains importance, because the amine group is very

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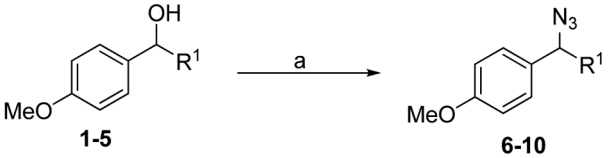


1-5 **6-10**

1 R^1 = Ph; **2** R^1= 3-OH-4-OMe-Ph
3 R^1 = Napthyl; **4** R^1 = Me; **5** R^1 = C_4H_{10},

6 R^1 = Ph (90%); **7** R^1= 3-OH-4-OMe-Ph (89%)
8 R^1 = Napthyl (90%); **9** R^1 = Me (87%)
10 R^1 = C_4H_{10} (82%)

Reagents and conditions: (a) $TMSN_3$, $ZrCl_4$, CH_3CN, 0 °C-rt, 0.5 h

Scheme 1. Conversion of aryl carbinols to azides.

common in many natural products as well as pharmaceutically important compounds.[5] Thus, the direct displacement of an alcohol group with an azide group gains prominence, because the azide group is a direct source of amines, in addition to its stability and reactivity in click chemistry[6] and bioconjugation.[7] The most common method for the synthesis of azide is by the Mitsunobu displacement[8] with HN_3 and its modifications.[9] The other C-N bond formation methods include a two-step conversion of alcohol to azide through mesylate,[10a] palladium-catalyzed hydroazidation of homoallyl alcohols,[10b] and gold-catalyzed direct amination of benzhydryl alcohols.[10c] In continuation of our interest in the catalytic applications of $ZrCl_4$ as a Lewis acid for various organic transformations,[11] we herein disclose $ZrCl_4$-catalyzed conversion of the known carbinols **1–5**[12] (Scheme 1), into the corresponding azides **6–10**, with $TMSN_3$ in CH_3CN at room temperature, click reaction of azides, and biological evaluation of the derived 1,2,3-triazoles (**6a–10d**).

RESULTS AND DISCUSSION

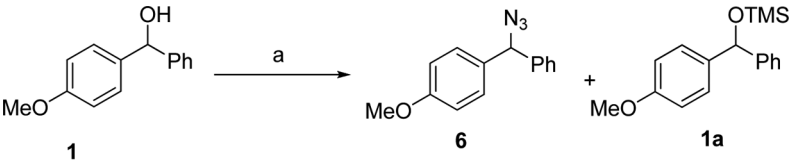
Accordingly, carbinol **1** on reaction with $TMSN_3$ in the presence of $ZrCl_4$ (5 mol%) in anhydrous CH_2Cl_2 (Scheme 2) gave **6** in 38% yield. Further, reaction of **1** in toluene or 1,4-dioxane afforded azide **6** in lower yields along with the respective tetramethylsilane (TMS) ether in **1a** in greater yields. However, reaction of **1** in acetonitrile or nitromethane was found to be good and gave **6** in excellent yields, with no traces of **1a**. Further, reaction of **1** in CH_3CN with different mol% of $ZrCl_4$ (10, 15, 20) revealed that 10 mol% is the optimum quantity.

A comparative study on the conversion of carbinol **1** to azide **6** was made using NaN_3 in the presence of $ZrCl_4$(10 mol%) in different solvents. The results, as tabulated in Scheme 2, evidently indicate that $TMSN_3$ is superior in the conversion of carbinol to azide.

Having established the reaction conditions, reaction of **1–5** in CH_3CN with $ZrCl_4$ (10 mol%) at room temperature for 0.5 h afforded the respective azides **6** (90%), **7** (89%), **8** (90%), **9** (87%), and **10** (82%) respectively (Scheme 1).

Antimicrobial Activity of Azides

Azides are energy-rich molecules with many applications[13] and are known for biocidal property. The synthesized azides **6–10** were evaluated for antibacterial



Reagents and conditions: (a) $TMSN_3$ or NaN_3, $ZrCl_4$, solvent, 0 °C-rt

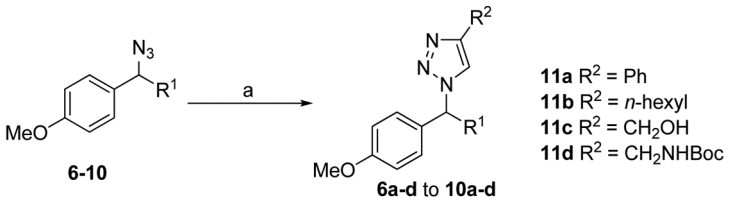
No.	Solvent	$TMSN_3$ / $ZrCl_4$		NaN_3 / $ZrCl_4$	
		Yield (%) **6**	Yield (%) **1a**	Yield (%) **6**	Yield (%) **1**
1	CH_2Cl_2	38	—	26	74
2	Toluene	24	68	22	78
3	1,4-dioxane	15	74	19	81
4	CH_3CN	80	—	20	80
5	CH_3NO_2	79	—	19	81

Scheme 2. Standardization of solvent/comparison of reagents.

activity by the agar well plate method against four bacterial cultures (viz., *Escherichia coli*, *Klebsiella pneumoniae*, *Bacillus subtilis*, and *Micrococcus luteus*) and compared with the antibacterial activity of streptomycin sulfate (Himedia) at 37 °C for 24 h. The data revealed that azides **7** and **8** were active against all the test cultures (Table 1), whereas the remaining azides **6, 9**, and **10** have showed no activity. Analysis of the inhibition zone data for **7** and **8** revealed that antibiotic activity is 50–55%, suggesting them to be only less potent with reference to streptomycin sulfate.

The antibacterial activity was evaluated by measuring the inhibition zone formed around the wells at a concentration of 100 µg. Wells containing sterile water and solvent (DMSO) were used as controls.

Having found two of the five azides with antibacterial activity, it was proposed to convert them in to 1,2,3-triazoles and evaluate their antibacterial activity.



Reagents and conditions: (a) sodium ascorbate, acetylene, $CuSO_4.5H_2O$, *t*-BuOH/H_2O, 8 h

Scheme 3. Conversion of aryl azides to 1,2,3-triazole.

Table 1. Antimicrobial activity of azides

Entry	Aryl azides	R^1	*E. coli*	*M. luteus*	*K. pneumoniae*	*B. subtilis*
1	**6**	Phenyl	00	00	00	00
2	**7**	Isovanillyl	14	16	16	15
3	**8**	Napthyl	15	17	15	14
4	**9**	Methyl	00	00	00	00
5	**10**	Isobutyl	00	00	00	00
	Control (DMSO)		00	00	00	00
	Streptomycin sulfate		32	31	30	33

1,2,3-Triazoles, prepared by Huisgen 1,3-dipolar cycloaddition reaction[14] and their wide range of biological applications in research, made them very attractive targets. Click chemistry reaction conditions, using Cu(I) as a catalyst, were adopted in the present study to obtain the 1,4-regioisomers[15] of triazoles.

Accordingly, azide **6** was treated with phenyl acetylene **11a** in the presence of sodium ascorbate and $CuSO_4 \cdot 5H_2O$ in *t*-BuOH-H_2O at room temperature for 8 h to give **6a** in 95% yield. Having established the reaction conditions for the conversion of azide to 1,2,3-triazole to create diverse triazoles, each of the five azides **6**–**10** were independently treated with four acetylenes (viz., **11a–d**) to afford the triazoles **6a**–**d** to **10a**–**d** respectively. All the triazoles were characterized by spectral and analytical methods.

Antimicrobial Activity of Triazoles

Because triazoles are known to be powerful antimicrobial agents,[16] the synthetic triazoles were evaluated for their antibacterial behavior (Table 2) against Gram-negative (*E. coli* and *K. pneumoniae*) and Gram-positive (*B. subtilis* and *M. luteus*) microbial strains, by adopting the same methodology used for the azides.

All the synthetic triazoles showed significant antibacterial activity against the tested cultures. Maximum activity was indicated for triazole **9b** against *B. subtilis* (25 mm) and *M. luteus* (24 mm), whereas minimum activity was indicated for observed for triazole **8d**. The SAR (structure–activity relationship) studies revealed that the parent azide moieties (phenyl, methyl, and isobutyl) have no activity but also have exhibited good antibacterial activity when they were converted into triazoles (**6a–d, 9a–d**, and **10a–d**). Further observations revealed that among the triazoles, compounds with NHBoc and *n*-hexyl side chains (**6b, 6d, 9b, 9d, 10b**, and **10d)** showed good intensity of antibacterial activity compared with the other two side chains (phenyl and -CH_2OH). SAR studies on **7a**–**d** and **8a**–**d** prepared from active azide moieties **7** and **8** showed an increase in the antibacterial activity of **7c** and **7d**, whereas triazoles from **8** displayed diminished activity.

MIC by Tube Dilution Method

Out of the several synthetic triazoles, 10 triazoles (Table 3) were selected for MIC (minimum inhibitory concentration) studies. From the studies, it is evident that triazole **9b** showed MIC of 15.625 μg/mL concentration to inhibit the growth of the organism against *B. subtilis* and *K. pneumoniae*. All the new triazoles showed

Table 2. Antimicrobial activity of triazole derivatives

Entry	Triazoles	R^1	R^2	*E. coli*	*M. luteus*	*K. pneumoniae*	*B. subtilis*
1	**6a**	Phenyl	Phenyl	12	12	12	15
2	**6b**	Phenyl	*n*-Hexyl	13	15	16	15
3	**6c**	Phenyl	CH_2OH	13	16	12	11
4	**6d**	Phenyl	CH_2NHBoc	18	18	16	15
5	**7a**	Isovanillyl	Phenyl	20	11	15	16
6	**7b**	Isovanillyl	*n*-Hexyl	17	0	16	14
7	**7c**	Isovanillyl	CH_2OH	20	20	20	20
8	**7d**	Isovanillyl	CH_2NHBoc	20	15	22	22
9	**8a**	Napthyl	Phenyl	0	0	17	17
10	**8b**	Napthyl	*n*-Hexyl	11	14	12	0
11	**8c**	Napthyl	CH_2OH	17	15	17	14
12	**8d**	Napthyl	CH_2NHBoc	0	10	0	0
13	**9a**	Methyl	Phenyl	14	24	16	15
14	**9b**	Methyl	*n*-Hexyl	15	24	21	25
15	**9c**	Methyl	CH_2OH	12	15	12	12
16	**9d**	Methyl	CH_2NHBoc	12	19	13	16
17	**10a**	Isobutyl	Phenyl	11	15	11	17
18	**10b**	Isobutyl	*n*-Hexyl	12	17	15	16
19	**10c**	Isobutyl	CH_2OH	12	11	12	13
20	**10d**	Isobutyl	CH_2NHBoc	13	18	16	18
	Control			0	0	0	0
	standard			32	31	30	33

Table 3. MIC studies

Entry	Compound	*E. coli*	*B. subtilis*	*K. pneumoniae*	*M. luteus*	*P. putida*
1	**6b**	31.25	31.25	31.25	31.25	31.25
2	**6d**	31.25	31.25	31.25	62.5	62.5
3	**7a**	31.25	62.5	31.25	31.25	>125
4	**7c**	15.625	62.5	62.5	31.25	62.5
5	**7d**	31.25	62.5	62.5	62.5	62.5
6	**8c**	62.5	31.25	31.25	31.25	62.5
7	**9a**	31.25	62.5	62.5	31.25	62.5
8	**9b**	>125	15.625	15.625	>125	>125
9	**9d**	62.5	62.5	62.5	62.5	62.5
10	**10d**	31.25	62.5	62.5	62.5	125
	Streptomycin	6.25	6.25	6.25	6.25	150

moderate MIC values with a concentration of 31.25 and 62.5 μg/mL. Further, it was also observed that the synthetic triazoles showed lesser MIC values than the standard (streptomycin) against *P. putida*.

EXPERIMENTAL

Solvents were dried over standard drying agents and freshly distilled prior to use. All commercially available chemicals were used without further purification. All reactions were performed under nitrogen. ^1H NMR and ^{13}C NMR spectra were measured with Varian Gemini FT 200-MHz, Bruker Avance 300-MHz, Unity

400-MHz, and Inova 500-MHz spectrometers with TMS as internal standard for solutions in $CDCl_3$. *J* values are given in hertz. Chemical shifts were reported in parts per million (ppm) relative to solvent signal. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. Infrared (IR) spectra were recorded on a fourier transform (FT) IR (Perkin-Elmer IR-683) spectrophotometer with NaCl optics. Jasco DIP 300 digital polarimeter was used for measurement of optical rotations at 25 °C. Mass spectra were recorded on direct inlet system or liquid chromatography (LC) by MSD trap SL (Agilent Technologies). The high-resolution mass spectrometry (HRMS) data were obtained using Q-TOF mass spectrometry.

1-(Azido(phenyl)methyl)-4-methoxybenzene (6)

A stirred solution of alcohol **1** (2.0 g, 9.35 mmol) in acetonitrile (10 mL) at 0 °C was sequentially treated with azidotrimethylsilane (3.0 mL, 23.38 mmol) and $ZrCl_4$ (0.22 g, 0.93 mmol) and stirred for 30 min. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Solvent was evaporated and the residue purified by column chromatography (60- to 120-mesh silica gel, 3% EtOAc in petroleum ether) to afford **6** (2.02 g, 90%) as a yellow liquid; IR ($CHCl_3$): 3030, 2091, 1609, 1510, 1243, 1174, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): (7.37–733 (m, 2H, ArH), 7.32 (m, 3H, ArH), 7.21 (d, 2H, $J = 8.7$ Hz, ArH), 6.88 (dt, 2H, $J = 2.1$, 8.8 Hz, ArH), 5.67 (s, 1H, ArCH), 3.97 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ159.2, 139.7, 131.6, 128.6, 128.5, 127.8, 127.1, 113.9, 67.9, 55.1.

1-((4-Methoxyphenyl)(phenyl)methyl)-4-phenyl-1H-1,2,3-triazole (6a)

A solution of azide **6** (0.20 g, 0.84 mmol) and phenyl acetylene **11a** (0.09 mL, 0.84 mmol) in *t*-BuOH (1 mL) and water (1 mL) was treated with sodium ascorbate (0.01 g, 0.04 mmol) followed by $CuSO_4 \cdot 5H_2O$ (0.02 g, 0.08 mmol) at room temperature and stirred for 8 h. Solvent was evaporated from the reaction mixture, and the residue was diluted with water (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (5 mL) and dried (Na_2SO_4). Solvent was evaporated and the residue purified by column chromatography (60- to 120-mesh silica gel, 15% EtOAc in petroleum ether) to afford **6a** (0.27 g, 95%) as a white solid; mp 157–159 °C; IR ($CHCl_3$): 3032, 2928, 1609, 1512, 1456, 1250, 1178, 1030, 763, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): (7.81 (d, 2H, $J = 7.2$ Hz, ArH), 7.60 (s, 1H, CH), 7.45–7.21 (m, 6H, ArH), 7.17–7.07 (m, 5H, ArH, ArCH), 6.91 (d, 2H, $J = 8.7$ Hz, ArH), 3.82 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$): (129.6, 128.8, 128.7, 128.4, 128.1, 127.7, 125.6, 119.5, 114.3, 67.6, 55.3. HRMS (ESI+) *m/z* calcd. for $C_{22}H_{20}N_3O$ ($M^+ + H$) 342.16009; found 342.16022.

Experimental Procedure for MIC Studies

All the test strains (*E. coli*, *B. subtilis*, *K. pneumonia*, *M. luteus*, and *P. putida*), each 1 mL volume (OD equal to match the turbidity of a MacFarland 0.5 standard

tube) were inoculated in nutrient (1 mL) broth with final compound concentrations of 250 to 0 μg/mL and standard drug (streptomycin) concentration from 400 to 6.25 μg/mL. All the tubes were incubated at 37 °C for 12–16 h. The turbidity of each tube is measured with respect to control tube. MIC values are defined as the lowest concentration of compound at which growth is completely inhibited for at least for 8 h.

CONCLUSION

In conclusion, an efficient method for the conversion of C-O bond (carbinols) to C-N bond (to azide) catalyzed by $ZrCl_4$ has been developed. The method reported is not only simple to operate but also affords the product azides in short duration of time with good yields. The azides were converted into 1,2,3-triazoles by click chemistry. The azides and derived triazoles were evaluated for their antimicrobial activity against Gram-positive and Gram-negative bacteria. The study revealed some of the triazoles with interesting antibacterial activity. Further SAR studies to derive better compounds with better activity are in progress.

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SUPPORTING INFORMATION

Full experimental details, spectral data of the products, and ^{1}H NMR, ^{13}C NMR, and HRMS spectra of all the new compounds can be accessed on the publisher's website.

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