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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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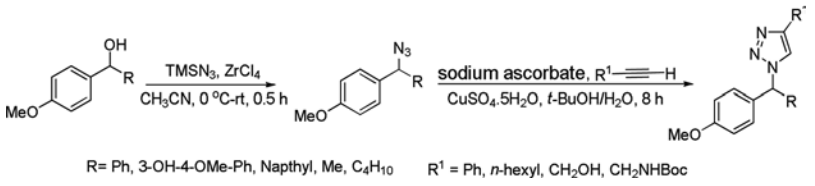
Abstract

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 and evaluated the resulting triazoles for their antimicrobial activity against various strains.



R= Ph, 3-OH-4-OMe-Ph, Napthyl, Me, C_4H_{10} R^1 = Ph, *n*-hexyl, CH_2OH, CH_2NHBoc

KEYWORDS: Zirconium(IV) chloride, Click chemistry, 1,2,3-Triazole, antimicrobial activity

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, since the amine group is very 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, since 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 on 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 TMS ether in **1a** in higher 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 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 the 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 (Scheme1).

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 activity by 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 sulphate (Himedia) at 37 °C for 24 h. The data revealed that azides **7** and **8** were active against all the test cultures (Table 1), while 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. 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 $CuSO_4.5H_2O$ 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 charcterised by spectral and analytical methods.

Antimicrobial Activity Of Triazoles

Triazoles, since are known to be powerful antimicrobial agents,[16] the synthetic triazoles were evaluated for their antibacterial behaviour (Table 2) against gram -ve (*E. coli* and *K. pneumoniae*) and gram +ve (*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**. SAR (structure activity relationship) studies revealed that the parent azide moieties (phenyl, methyl and isobutyl) having no activity, also have exhibited good antibacterial activity when they were converted into triazoles (**6a-d**, **9a-d** and **10-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** inferred an increase in the antibacterial activity of **7c** and **7d**, while, triazoles from **8** displayed diminished activity.

MIC By Tube Dilution Method

Out of the several synthetic triazoles, ten 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 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 Section:

General Experimental Details

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. ^{1}H NMR and ^{13}C NMR spectra were measured with Varian Gemini FT 200 MHz spectrometer, Bruker Avance 300 MHz, Unity 400 MHz and Inova 500 MHz with tetramethylsilane as internal standard for solutions in $CDCl_3$. *J* values are given in Hz. Chemical shifts were reported in 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 ºC in *vacuo*. IR-spectra were recorded on 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 LC by MSD trap SL (Agilent Technologies), the 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 x 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 (60-120 mesh Silica gel, 3% EtOAc in pet. 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, $CDCl_3$): δ 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, $CDCl_3$): δ 159.2, 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 $CuSO_4.5H_2O$ (0.02 g, 0.08 mmol) at room temperature and stirred for 8 h. Solvent was evaporated from the reaction mixture, residue diluted with water (5 mL) and extracted with EtOAc (2 x 10 mL). Combined organic layer were washed with brine (5 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, 15% EtOAc in pet. ether) to afford **6a** (0.27 g, 95%) as a white solid; mp 157-159 ^oC; IR ($CHCl_3$): 3032, 2928, 1609, 1512, 1456, 1250, 1178, 1030, 763, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 Mac Farland 0.5 standard tube) were inoculated in nutrient (1 mL) broth with final compound concentrations of 250 µg/mL to 0 µg/mL and standard drug (Streptomycin) concentration from 400 µg/mL to 6.25 µg/mL. All the tubes were incubated at 37 ^{o}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.

SUPPORTING INFORMATION

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

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 in high 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 +ve and -ve 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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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

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

Scheme 1

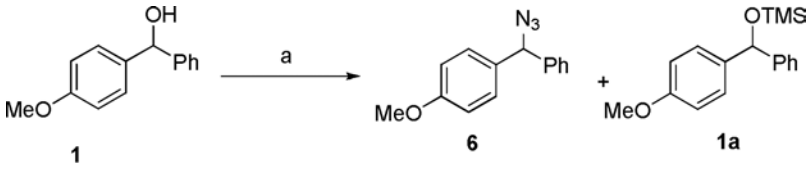
1-5 6-10

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%)

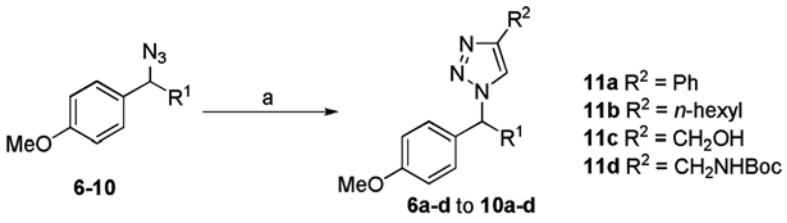
Reagents and conditions: (a) $TMSN_3$, $ZrCl_4$, CH_3CN, 0 °C-rt, 0.5 h

Scheme 2



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

Scheme 3



6-10 → **6a-d** to **10a-d**

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