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ZrCl₄ Catalyzed C-O bond to C-N bond formation: synthesis of 1,2,3-triazoles and their biological evaluation

Gangavaram V. M. Sharma¹, Kandikonda Suresh Kumar^{1,3}, Buddana Sudheer Kumar², Sheri Venkata Reddy¹, Reddy Shetty Prakasham², Helmut Hugel³,

¹Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, India ²Biochemical and Environmental Engineering Sciences, CSIR-Indian Institute of Chemical Technology, Hyderabad, India ³Royal Melbourne Institute of Technology, Melbourne, VIC, Australia

Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500007, India E-mail: esmvee@iict.res.in
Biochemical and Environmental Engineering Sciences, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500007, India. E-mail: prakasam@iict.res.in
Royal Melbourne Institute of Technology, Melbourne VIC 3001, Australia. Email: hugel@rmit.edu.au

Abstract

A simple and efficient protocol was developed for the synthesis of aryl azides directly from aryl carbinols using ZrCl₄ 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.

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 HN₃ 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 ZrCl₄ as a Lewis acid for various organic transformations,^[11] we herein, disclose ZrCl₄ catalyzed conversion of the known carbinols **1-5**^[12] (Scheme 1), into the corresponding azides **6-10**, with TMSN₃ in CH₃CN 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 TMSN₃ in the presence of ZrCl₄ (5 mol%) in anhydrous CH₂Cl₂ (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 CH₃CN with different mol% of ZrCl₄ (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 NaN₃ in the presence of ZrCl₄ (10 mol%) in different solvents. The results, as tabulated in the Scheme 2, evidently indicate that TMSN₃ is superior in the conversion of carbinol to azide.

Having established the reaction conditions, reaction of **1-5** in CH₃CN with ZrCl₄ (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 CuSO₄.5H₂O in *t*-BuOH-H₂O 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 characterised 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 -CH₂OH). 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. ^1H 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 °C 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 (Na₂SO₄). 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 (CHCl₃): 3030, 2091, 1609, 1510, 1243, 1174, 1031 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.37-7.33 (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); ¹³C NMR (75 MHz, CDCl₃): 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 CuSO₄·5H₂O (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 (Na₂SO₄). 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 °C; IR (CHCl₃): 3032, 2928, 1609, 1512, 1456, 1250, 1178, 1030, 763, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₂₂H₂₀N₃O (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 °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, ¹H NMR, ¹³C 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 ZrCl₄ 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	<i>E. coli</i>	<i>M. luteus</i>	<i>K. pneumoniae</i>	<i>B. subtilis</i>
1	6	Phenyl	00	00	00	00
2	7	Isovanillyl	14	16	16	15
3	8	Naphthyl	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	<i>E. coli</i>	<i>M. luteus</i>	<i>K. pneumoniae</i>	<i>B. subtilis</i>
1	6a	Phenyl	Phenyl	12	12	12	15
2	6b	Phenyl	<i>n</i> -hexyl	13	15	16	15
3	6c	Phenyl	CH ₂ OH	13	16	12	11
4	6d	Phenyl	CH ₂ NHBoc	18	18	16	15
5	7a	Isovanillyl	Phenyl	20	11	15	16
6	7b	Isovanillyl	<i>n</i> -hexyl	17	0	16	14
7	7c	Isovanillyl	CH ₂ OH	20	20	20	20
8	7d	Isovanillyl	CH ₂ NHBoc	20	15	22	22
9	8a	Naphthyl	Phenyl	0	0	17	17
10	8b	Naphthyl	<i>n</i> -hexyl	11	14	12	0
11	8c	Naphthyl	CH ₂ OH	17	15	17	14
12	8d	Naphthyl	CH ₂ NHBoc	0	10	0	0
13	9a	Methyl	Phenyl	14	24	16	15
14	9b	Methyl	<i>n</i> -hexyl	15	24	21	25
15	9c	Methyl	CH ₂ OH	12	15	12	12
16	9d	Methyl	CH ₂ NHBoc	12	19	13	16
17	10a	Isobutyl	Phenyl	11	15	11	17
18	10b	Isobutyl	<i>n</i> -hexyl	12	17	15	16
19	10c	Isobutyl	CH ₂ OH	12	11	12	13
20	10d	Isobutyl	CH ₂ NHBoc	13	18	16	18

	Control			0	0	0	0
	standard			32	31	30	33

Table 3 MIC studies

Entry	Compound	<i>E. coli</i>	<i>B. subtilis</i>	<i>K. pneumoniae</i>	<i>M. luteus</i>	<i>P. putida</i>
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 R¹ = Ph; **2** R¹ = 3-OH-4-OMe-Ph **6** R¹ = Ph (90%); **7** R¹ = 3-OH-4-OMe-Ph (89%)
3 R¹ = Naphthyl; **4** R¹ = Me; **5** R¹ = C₄H₁₀, **8** R¹ = Naphthyl (90%); **9** R¹ = Me (87%)
 10 R¹ = C₄H₁₀ (82%)

Reagents and conditions: (a) TMSN₃, ZrCl₄, CH₃CN, 0 °C-rt, 0.5 h

Scheme 2

Reagents and conditions: (a) TMSN₃ or NaN₃, ZrCl₄, solvent, 0 °C-rt

Scheme 3

Reagents and conditions: (a) sodium ascorbate, acetylene, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, $t\text{-BuOH}/\text{H}_2\text{O}$, 8 h