Copper Triflate: An Efficient Catalyst for Direct Conversion of Secondary Alcohols into Azides

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Abstract: A simple, practical, and efficient strategy has been demonstrated for the direct synthesis of organic azides from alcohols using azidotrimethylsilane (TMSN₃) as azide source in the presence of copper(II) triflate [Cu(OTf)₂]. A variety of alcohols was converted into the corresponding azides in good to excellent yields. The formation of an intermediate carbocation was confirmed by the synthesis of bis(diphenylmethyl) ether.

Key words: azides, azidotrimethylsilane, copper triflate, Lewis acid

Organic azides are a versatile class of compounds frequently used in synthetic organic chemistry.¹⁻⁴ They are useful precursors for the preparation of amines,^{5,6} nitrenes,⁷ and heterocyclic compounds. For example, glycosyl azides are key intermediates in the synthesis of glycosyl amino acids.⁸ They are also substrates for the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction,^{9,10} which has received great attention in recent decades for the synthesis of druglike molecules, bioconjugation, and in areas of material science.^{11,12} The azide group itself is the key component of the HIV/AIDS drug, zidovudine.¹³

Transformation of alcohols to azides is an attractive procedure for the synthesis of a variety of organic compounds. The most common approach for this transformation involves a two-step protocol: conversion of the alcohol into the corresponding halide or sulfonate and subsequent nucleophilic substitution by azide anion.¹⁴ Direct conversion of alcohols into azides can be achieved by the Mitsunobu reaction.^{15,16} This is an attractive method for synthesis of azides in which the reaction can be conducted under mild and neutral conditions, and generally gives excellent yields of products. However, it involves the use of hydrazoic acid. Several modifications of this method have been reported using TPP/CBr₄/NaN₃,¹⁷ $TPP/DDQ/n-Bu_4NN_3$,¹⁸ 2,4,4,6-tetrabromo-2,5-cyclohexadienone/Ph₃P/Zn(N₃)₂·2py,¹⁹ bis(p-nitropheny)phosphorazidate/DBU,²⁰ diphenyl phosphorazidate/DBU,^{21,22} and TPP/I₂/imidazole/NaN₃.²³ Other methods for the direct conversion of alcohols into azides include the use of NaN₃/BF₃·OEt₂²⁴ 2,4,6-trichloro[1,3,5]triazine/ *n*-Bu₄NN₃,²⁵ 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (2-ADMP)/DBU,²⁶ TsIm/TBAI/NaN₃,²⁷

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and NaN₃/CCl₄–DMF.²⁸ Although the reported methods are effective, they suffer from limitations such as inaccessible and expensive reagents and long reaction times as well as cumbersome separation from the generated $Ph_3P=O$ and unreacted Ph_3P .

Thus, in this communication we wish to report our preliminary results for the direct conversion of alcohols into azides using azidotrimethylsilane (TMSN₃) and copper(II) triflate [Cu(OTf)₂, Scheme 1].

$$\begin{array}{c} \mathsf{R} & \overset{\mathsf{Cu}(\mathsf{OTf})_2, \mathsf{TMSN}_3}{\overset{\mathsf{P}}{\longrightarrow} & \mathsf{CH}_2\mathsf{Cl}_2} \xrightarrow{\mathsf{R}} \\ \mathsf{Ar} & \overset{\mathsf{P}}{\longrightarrow} & \mathsf{Ar} & \overset{\mathsf{R}}{\overset{\mathsf{N}_3}} \end{array}$$

Scheme 1 One-pot synthesis of azide from benzyl alcohols

Our study began with the direct reaction of 1-phenylethanol (1a) with TMSN₃ in the presence of InBr₃ (20 mol%) in dichloromethane to give (1-azidoethyl)benzene (2a) in 83% yield (Table 1, entry 1). The structure of 2a was determined by NMR and IR spectroscopy. A peak at 2096 cm⁻¹ in the IR spectrum of **2a** indicated the presence of the azide group. Encouraged with these results we screened different Lewis and Brønsted acids to improve the yields of 2a, and the results are summarized in Table 1. Among the catalysts screened, Cu(OTf)₂ was found to be most effective and produced 2a in an excellent isolated yield (94%) with 5 mol% of catalyst loading (Table 1, entry 6). Other copper salts such as CuSO₄·5H₂O, CuOTf, CuCl₂·2H₂O, CuCl, and CuBr also gave good yields of **2a** (Table 1, entries 3–8, 10, and 11), but a poor yield of 2a was observed with $Cu(OAc)_2 \cdot H_2O$ and no conversion was observed in the case of CuI, CuBr₂, and CuO (Table 1, entries 2, 12, and 13). Other Lewis acids such as $BF_3 \cdot OEt_2$, AlCl₃, FeCl₃ AgOTf, Yb(OTf)₃, Zn(OTf)₂, and In(OTf)₃ also resulted in good yields of 2a. Montmorillonite K10 gave good yields of 2a (Table 1, entry 14) whereas Brønsted acids such as PTSA and acetic acid were found not to be suitable for this conversion (Table 1, entries 15 and 16).

After establishing Cu(OTf)₂ as catalyst of choice for this transformation, different solvents were screened and it was found that highest yield of **2a** was achieved in dichloromethane (Table 1, entry 6). Other solvents such as CHCl₃, CCl₄, and DMF gave good yields of **2a**, whereas THF and MeCN resulted in poor yields (Table 1, entries 24–28). It is worth to note that no conversion was observed in aqueous medium (Table 1, entry 29). The reac-

Table 1 Optimization of Reaction Conditions for Azidation of

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1-Phenylethanol ^a				
$\sum_{i=1}^{n}$	DH TMSN₃, catalyst	→N ₃		
	solvent, time			
1a		2a		
Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%) ^b
1	InBr ₃ (20)	$\mathrm{CH}_2\mathrm{Cl}_2$	30	83
2	CuI (20)	$\mathrm{CH}_2\mathrm{Cl}_2$	120	_c
3	$CuSO_4 \cdot 5H_2O(20)$	$\mathrm{CH}_2\mathrm{Cl}_2$	360	50
4	CuOTf (20)	CH_2Cl_2	30	80
5	Cu(OTf) (20) ₂	CH_2Cl_2	8	92
6	$Cu(OTf)_2(5)$	CH_2Cl_2	20	94
7	$CuCl_2 \cdot 2H_2O$ (20)	CH_2Cl_2	10	88
8	$CuCl_2 \cdot 2H_2O(5)$	CH_2Cl_2	20	82
9	$Cu(OAc)_2 \cdot H_2O(20)$	CH_2Cl_2	300	20
10	CuCl (20)	CH_2Cl_2	240	78
11	CuBr (20)	CH_2Cl_2	45	82
12	CuBr ₂ (20)	CH_2Cl_2	360	_c
13	CuO (20)	CH_2Cl_2	360	_c
14	Mont. K10 ^d (20)	CH_2Cl_2	45	60
15	PTSA (20)	CH_2Cl_2	180	c
16	AcOH (20)	CH_2Cl_2	360	c
17	$BF_3 \cdot OEt_2(20)$	CH_2Cl_2	30	80
18	AlCl ₃ (20)	CH_2Cl_2	30	82
19	FeCl ₃ (20)	CH_2Cl_2	120	57
20	AgOTf (20)	CH_2Cl_2	240	68

29 $Cu(OTf)_2(5)$ _c H₂O 20 ^a Reaction conditions: 1-phenylethanol (1.0 mmol), TMSN₃ (1.5 mmol), catalyst, solvent, r.t. (ca. 30 °C), time.

CH₂Cl₂

CH₂Cl₂

CH₂Cl₂

CHCl₃

 CCl_4

DMF

THF

MeCN

240

240

30

20

20

20

20

20

^b Isolated yield.

21

22

23

24

2.5

26

27

28

^c No conversion was observed.

Yb(OTf)₃ (20)

 $Zn(OTf)_2(20)$

In(OTf)₃ (20)

 $Cu(OTf)_{2}(5)$

 $Cu(OTf)_2(5)$

 $Cu(OTf)_{2}(5)$

 $Cu(OTf)_2(5)$

 $Cu(OTf)_2(5)$

tion failed to give the azido product when sodium azide was used as an azide source; albeit a trace amount of symmetrical ether was found after prolonged reaction times.

We then studied the scope of different alcohols for azidation reaction using TMSN₃ as azide source under the optimized conditions (Table 1, entry 6), and the results are summarized in Scheme 2. Alcohols with diverse substitutions on the aryl ring produced good to excellent yields of azides **2b–q**. For example, substrates bearing methoxy, hydroxy, fluoro, chloro, and bromo groups were well tolerated under the optimized conditions and gave good yields of the corresponding azides 2e-k. Biphenyl methanol and its derivatives also reacted smoothly to give biphenyl methyl azides in good yields (21,m). Substrates with heterocyclic rings such as pyridine, thiophene, and thiazole also participated in azidation and provided good yields of azides 2n-p. Gratifyingly, azidation proceeded smoothly with a tertiary alochol to give the corresponding azide in good yield (2q)²⁹ When allylic and propargylic alcohols were reacted under the standard azidation conditions, varying results were observed. For cinnamyl alcohol the symmetrical ether was also detected along with the azido product. Similarly, propargyl alcohol also resulted in a mixture of products, where the alkyne hydration product was also found along with propargyl azides. When cyclohexanol was reacted under the optimized conditions, no conversion was observed.

The mechanism for the reaction is believed to be through formation of the carbocation intermediate via heterolytic cleavage of the C-O bond of the alcoholic group with the assistance of TMSN₃/Cu(OTf)₂^{29,30} The catalyst simultaneously assists in the generation of azide from TMSN₃. The attack of azide to the carbocation intermediate results in the formation of the desired substitution product.

Formation of the intermediate carbocation is further supported by the fact that when diphenylmethanol (11) was treated with Cu(OTf)₂ under identical conditions in the absence of TMSN₃, bis(diphenylmethyl) ether (31) was obtained as the major product (Scheme 3). We further reacted 1j and 1p with $Cu(OTf)_2$ under TMSN₃-free conditions and obtained the corresponding ethers **3j**,**p** in good vields.

In summary, we have developed a simple and efficient method for the preparation of organic azides via direct azidation of alcohols using TMSN₃ as azide source and Cu(OTf)₂ as catalyst. A variety of benzylic alcohols can be converted into the corresponding azides in short reaction time (20 min) with good to excellent yields. Formation of intermediate carbocation was confirmed by the synthesis of bis(diphenylmethyl) ether. The protocol can be used for in situ generation of azides for further transformations.

General Procedure for Azidation

To a stirred solution of alcohol 1 (1.0 mmol) and azidotrimethylsilane (TMSN₃; 1.5 mmol) in CH₂Cl₂ (2.0 mL) was added Cu(OTf)₂ (5 mol%), and the reaction mixture was stirred at r.t. (ca. 30 °C) for

^d Montmorillonite K10.



Scheme 2 Direct azidation of alcohols using TMSN₃



Scheme 3 Synthesis of bis(diarylmethyl) ether

20 min. On completion of the reaction as indicated by TLC, the reaction was diluted with H_2O and extracted with EtOAc. The organic layers were dried with anhydrous Na_2SO_4 , filtered, and evaporated under vacuum. The crude residue was purified by column chromatography (60–120 mesh silica gel, 1:9; EtOAc–hexane).

Spectroscopic Data for Selected Compounds

(Azidomethylene)dibenzene (2l)

Colorless liquid; yield 91%. ¹H NMR (300 MHz, CDCl₃): δ = 7.38–7.34 (m, 2 H), 7.32–7.25 (m, 8 H), 5.70 (s, 1 H). ¹³C NMR (75 MHz, CDCl₃): δ = 139.6, 128.7, 128.1, 127.4, 68.6. IR (NaCl): 2939, 2098, 1650, 1496, 1450, 1388, 1249, 1095 cm⁻¹.

4-{Azido[3-(benzyloxy)phenyl]methyl}-1-(benzyloxy)-2-methoxybenzene (2m)

White solid; yield 94%; mp 95–96 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.43–7.33 (m, 7 H), 7.32–7.28 (m, 2 H), 7.28–7.19 (m, 2 H), 6.91 (dd, *J* = 4.3, 1.7 Hz, 2 H), 6.87 (d, *J* = 2.1 Hz, 1 H), 6.81 (dd, *J* = 7.1, 5.1 Hz, 2 H), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1 H), 5.58 (s, 1 H), 5.11 (s, 2 H), 5.00 (s, 2 H), 3.81 (s, 3 H). ¹³C NMR (75 MHz, CDCl₃): δ = 159.0, 149.8, 148.1, 141.37, 137.1, 136.8, 132.5, 129.8, 128.6, 128.6, 128.1, 127.9, 127.6, 127.3, 119.95, 119.94, 114.2, 114.0, 113.7, 111.0, 71.0, 70.0, 68.2, 56.1. IR (NaCl): 2962, 2931, 2098, 1643, 1604, 1512, 1458, 740, 694, 647 cm⁻¹.

2-(1-Azidoethyl)thiazole (2p)

Yellow liquid; yield 94%. ¹H ŃMR (300 MHz, CDCl₃): δ = 7.62 (d, J = 3.4 Hz, 1 H), 7.22 (d, J = 3.4 Hz, 1 H), 5.14–5.04 (m, 1 H), 1.57 (d, J = 6.5 Hz, 3 H). ¹³C NMR (75 MHz, CDCl₃): δ = 174.5, 140.2, 117.0, 65.9, 22.2. IR (NaCl): 2977, 2931, 2106, 1650, 1504, 1434, 1195, 1149, 1110, 1064 cm⁻¹.

Bis(diphenylmethyl) Ether (31)

White solid; yield \$7%; mp 104–105 °C (lit.³¹ 109 °C). ¹H NMR (300 MHz, CDCl₃): \$ = 7.37 (t, J = 1.9 Hz, 2 H), 7.35–7.33 (m, 8 H), 7.30 (d, J = 1.7 Hz, 4 H), 7.28 (d, J = 1.4 Hz, 2 H), 7.26 (t, J = 1.6 Hz, 2 H), 7.24–7.20 (m, 2 H), 5.40 (s, 2 H). ¹³C NMR (75 MHz, CDCl₃): \$ = 142.2, 129.2, 128.4, 127.5, 127.3, 80.0. IR (NaCl): 2931, 2846, 1643, 1546, 1488, 1450, 1180, 1118, 1049 cm⁻¹.

Bis[(thiazol-2-yl)ethyl] Ether (3p)

Yellow liquid; yield 79%. ¹H NMR (300 MHz, CDCl₃): δ = 7.72 (d, J = 3.1 Hz, 2 H), 7.30 (d, J = 3.1 Hz, 2 H), 5.17 (q, J = 6.5 Hz, 2 H), 1.65 (d, J = 6.5 Hz, 6 H). ¹³C NMR (75 MHz, CDCl₃): δ = 176.0, 142.2, 118.9, 68.0, 24.1. IR (NaCl): 2970, 2923, 1650, 1504, 1195, 1103, 1072, 790 cm⁻¹.

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