Chinese Journal of Chemistry, **2004**, *22*, 1183—1186 **Article**

Novel Synthesis of 1,2,3-Triazoles via 1,3-Dipolar Cycloadditions of Alkynes to Azides in Ionic Liquid†

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2-Azido-3,5-dichloropyridine and 2-azido-5-chloro-3-fluoropyridine were given by reaction of sodium azide with 2,3,5-trichloropyridine, 3,5-dichloro-2-fluoropyridine or 5-chloro-2,3-difluoropyridine in ionic liquids. 1,3-Dipolar cycloaddition of 2-azido-3,5-dichloropyridine or 2-azido-5-chloro-3-fluoropyridine to alkynes in ionic liquids afforded the corresponding 1,4,5-trisubstituted [1,2,3]-triazoles in good yields and regioselectivities.

Keywords triazole, 1,3-dipolar cycloaddition, ionic liquid, trichloropyridine

Introduction

With the rapid advancement in the field of synthetic organic chemistry, more and more environmentally benign and eco-friendly processes are coming up at an overwhelming rate.[1] System of room temperature ionic liquids has been developed to a focal point of interest in both academy and industry.[2,3] This is because of not only their electrochemical properties,[2] but also their tremendous potential as solvents and phase-transition catalysts.[4] They are being used as green-solvents with unique properties such as a wide liquid range, good solvating ability, tunable polarity, high thermal stability, negligible vapor pressure and ease of recyclability.

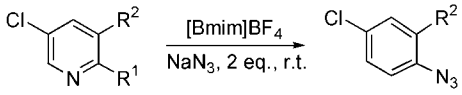
Their high polarity and ability to solubilize both organic and inorganic compounds can result in enhanced rates of chemical processes and can provide higher selectivities compared to conventional solvents.[5-9]

1-(2-Pyridyl)-1*H*-1,2,3-triazole derivatives were useful in pharmaceutical field and used as herbicidal agents.[10] Therefore, it is important to develop new and more efficient synthetic pathways to a diverse array of [1,2,3]-triazoles. The present paper will reveal that 2-azido-3,5-dichloropyridine and 2-azido-5-chloro-3-fluoropyridine were given by reaction of sodium azide with 2,3,5-trichloropyridine, 3,5-dichloro-2-fluoropyridine or 5-chloro-2,3-difluoropyridine in ionic liquids, and 1,3-dipolar cycloaddition of 2-azido-3,5-dichloropyridine or 2-azido-5-chloro-3-fluoropyridine to alkynes in ionic liquids afforded the corresponding 1,4,5-trisubstituted [1,2,3]-triazoles in good yields and regioselectivities.

Results and discussion

When reaction of NaN_3 with 1,2,3-trichloropyridine took place in DMF solvent at 80 ℃, the reaction time needed at least two days, and the yields were less than 30%. $[Bmim]BF_4$ is a common ionic liquid, where $[Bmim]^+$ is the 1-butyl-3-methylimidazolium cation, and has high polar and strong ability to dissolve organic or inorganic compounds. It could dissolve most of the NaN_3, so the reaction was accelerated. The yield was greatly increased to 65% when the reaction was completed after one day (Scheme 1 and Table 1**)**.

Scheme 1



1a — 1c
1a: $R^1 = R^2 = Cl$,
1b: $R^1 = F$, $R^2 = Cl$,
1c: $R^1 = R^2 = F$;

2a — 2c
2a=**2b**: $R^2 = Cl$,
2c: $R^2 = F$

Table 1 Synthesis of 2-azido-3,5-dichloropyridine and 2-azido-5-chloro-3-fluoropyridine

Entry	R^1	R^2	Melting point/℃	Product	Yield/%
1	Cl	Cl	80—82	**2a**	65
2[a]	Cl	Cl	80—82	**2a**	30
3	F	Cl	80—82	**2b**	68
4[a]	F	Cl	80—82	**2b**	41
5	F	F	66—68	**2c**	66

[a] without ionic liquids.

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With increasing quest for exploration of new reactions in ionic liquids, we report herein the use of ionic liquids as green solvents and catalyst for the 1,3-dipolar cycloaddition of azides to alkynes affording 1,2,3-triazoles in high to quantitative yields under mild and neutral conditions.

1,3-Dipolar cycloaddition reaction of azides to various alkynes to afford 1,2,3-triazoles have been widely studied in solution such as toluene, chloroform, methanol/H_2O and acetonitrile, using triethylamine as base and CuCl or CuI as catalyst, and refluxing one to seven days.[11,12] However, the limitation of typical methods is the poor regioselectivity normally found in the 1,3-dipolar cycloaddition of nonsymmetrical alkynes.[13] Also, long reaction time was required in the majority of the cases, and some azides would be decomposed by light or heat, releasing the gas of nitrogen. In this paper, we contribute new advances regarding the enhancement of the regio selectivity and the yields and shorten the reaction time.

Usually the addition of azides to terminal alkynes needs one week to finish in toluene catalyzed by copper(I) salts and the yields are not high, while in ionic liquids without any else catalyst the reaction was completed within three days at room temperature, and the ^1H and ^{13}C NMR proved that the regioselectivity was increased greatly (Scheme 2 and Table 2).

The ionic liquid can be typically recovered by extracting out the product first and followed by vacuum drying. The recovered solvent can be reused with no appreciable decrease in yield. The result is summarized in Table 3.

Experimental

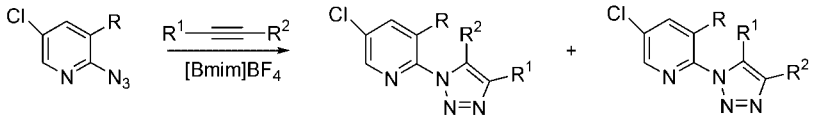
Melting points are uncorrected. TLC was performed using precoated silica gel 60 GF_{254} (0.25 mm), column chromatography was performed using silica gel (100—200 mesh), IR, ^1H and ^{13}C NMR spectra were recorded on an FT-Bruker AT-300 using TMS as an internal standard. Mass spectra were determined using a Finigan 8230 mass spectrometer. 2,3,5-Trichloropyridine, 3,5-dichloro-2-fluoropyridine, 5-chloro-2,3-difluoropyridine and 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) were prepared according to the procedures reported.[14-16]

Synthesis of 2-azido-3,5-dichloropyridine or 2-azido-5-chloro-3-fluoropyridine

A flask was charged with [Bmim]BF_4 (5 mL), 2,3,5-trichloropyridine (10 mmol) and sodium azide (12 mmol), heated at 60 ℃ with a stirrer and the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted four times with 20 mL of the dryed diethyl ether. The collected organic fraction was concentrated under vacuum, and the resulting product was directly charged on a small silica gel column, and eluted with a mixture of ethyl acetate and cyclohexane (1∶5) to give compound **2a**.

In the same way, reaction of sodium azide with 3,5-dichloro-2-fluoropyridine or 5-chloro-2,3-difluoropyridine gave compounds **2b** and **2c** (**2a**═**2b**).

Scheme 2



2a — 2c **3a — 3f** **4a — 4f**

3a, 4a: R = Cl, R^1 = Ph, R^2 = H; **3b, 4b**: R = Cl, R^1 = *n*-C_4H_9, R^2 = H;
3c, 4c: R = Cl, R^1 = *n*-C_5H_{11}, R^2 = H; **3d, 4d**: R = F, R^1 = Ph, R^2 = H;
3e, 4e: R = Cl, R^1 = Ph, R^2 = I; **3f, 4f**: R = Cl, R^1 = *n*-C_4H_9, R^2 = I

Table 2 Synthesis of 1,2,3-triazoles via 1,3-dipolar cycloadditions

Entry	R	R^1	R^2	Reaction time/d	Yield[b]/%	Product	**3**∶**4**[c]
1	Cl	Ph	H	2	65	**3a, 4a**	98∶2
2[a]	Cl	Ph	H	5	35	**3a, 4a**	65∶35
3	Cl	*n*-C_4H_9	H	2.5	58	**3b, 4b**	80∶20
4[a]	Cl	*n*-C_4H_9	H	7	34	**3b, 4b**	60∶40
5	Cl	*n*-C_5H_{11}	H	2.5	62	**3c, 4c**	80∶20
6	F	Ph	H	2	70	**3d, 4d**	99∶1
7	Cl	Ph	I	3	56	**3e, 4e**	95∶5
8	Cl	*n*-C_4H_9	I	3	51	**3f, 4f**	90∶10

[a] Without ionic liquids; [b] isolated yields; [c] determined by ^1H and ^{13}C NMR.

Table 3 Results obtained using recycled ionic liquid

Entry	Product	Cycle	Yield/%	**3**∶**4**
1	**3a**, **4a**	1	65	98∶2
2	**3a**, **4a**	2	63	98∶2
3	**3a**, **4a**	3	64	98∶2

2-Azido-3,5-dichloropyridine (2a): A white solid. m.p. 80—82 ℃. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 8.25 (d, J =2.1 Hz, 1H), 7.80 (d, J=2.1 Hz, 1H); IR (KBr) ν_{max}: 3414 (m), 3103 (m), 2117 (s), 1710 (w), 1622 (w), 1548 (s), 1477 (s), 1291 (m), 1223 (m), 1142 (m) cm^{-1}. Anal. calcd for $C_5H_2Cl_2N_4$: C 31.77, H 1.07, N 29.64; found C 31.91, H 1.15, N 29.13.

2-Azido-3-fluoro-5-chloropyridine (2c): A white solid. m.p. 66—68 ℃. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 8.66 (d, J=2.0 Hz, 1H), 7.16 (d, J=2.0 Hz, 1H); IR (KBr) ν_{max}: 3123 (m), 2110 (s), 1620 (w), 1550 (s), 1479 (s) cm^{-1}. Anal. calcd for $C_5H_2ClFN_4$: C 34.80, H 1.17, N 32.47; found C 34.96, H 1.21, N 32.13.

General procedure for synthesis of 1,2,3-triazoles

In a 25 mL flask were placed 1 mmol of **2**, 1 mmol of alkyne and 3 mL of [Bmim]BF_4, the mixture was stirred at room temperature for an appropriate time (Table 2). After completion of the reaction as indicated by TLC, the reaction mixture was washed with toluene (3 ×15 mL), the combined toluene extracts were concentrated *in vacuo*, and the residual yellow solid was washed with diethyl ether three times and then recrystallized in toluene to give **3a—3f** and **4a—4f**.

3,5-Dichloro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine (3a): A white solid, m.p. 142—145 ℃. ^{1}H NMR (DMSO-d_6, Me_4Si) δ: 9.96 (s, 1H), 9.56 (s, 1H), 8.65 (s, 1H), 8.06 (d, J=8.04 Hz, 2H), 7.54 (m, 2H), 7.44 (t, J =7.04 Hz, 1H); ^{13}C NMR (DMSO-d_6, Me_4Si) δ: 147.69, 142.34, 129.50, 129.23, 129.10, 128.85, 125.84, 125.00, 124.21, 124.01, 121.90; IR (KBr) ν_{max}: 3069 (m), 1626 (m), 1567 (s), 1481 (s), 1240 (w), 1197 (s), 1013 (s) cm^{-1}. MS *m/z*: 290 (M^+). Anal. calcd for $C_{13}H_8Cl_2N_4$: C 53.63, H 2.77, N 19.24; found C 53.26, H 2.62, N 19.13.

3,5-Dichloro-2-(4-butyl-1*H*-1,2,3-triazol-1-yl)pyridine (3b): A white solid, m.p. 116—117 ℃. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 9.03 (s, 1H), 8.10 (d, J=1.75 Hz, 1H), 7.91 (d, J=1.75 Hz, 1H), 2.97 (t, J=6.7 Hz, 2H), 1.76 (m, 2H), 1.48 (m, 2H), 0.99 (t, J=6.0 Hz, 3H); IR (KBr) ν_{max}: 2930 (s), 1670 (m), 1432 (m), 1230 (w), 1132 (s), 1024 (s) cm^{-1}. Anal. calcd for $C_{11}H_{12}Cl_2N_4$: C 48.73, H 4.46, N 20.66; found C 48.56, H 4.31, N 20.45.

3,5-Dichloro-2-(5-butyl-1*H*-1,2,3-triazol-1-yl)pyridine (4b): ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 9.15 (s, 1H), 8.04 (d, J=1.75 Hz, 1H), 7.87 (d, J=1.75 Hz, 1H), 2.83 (t, J=6.7 Hz, 2H), 1.73 (m, 2H), 1.43 (m, 2H), 0.9 (t, J=6.0 Hz, 3H).

3,5-Dichloro-2-(4-pentyl-1*H*-1,2,3-triazol-1-yl)pyridine (3c): A white solid, m.p. 120—122 ℃. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 9.06 (s, 1H), 8.14 (d, J=1.70 Hz, 1H), 7.93 (d, J=1.70 Hz, 1H), 2.93 (t, J=7.1 Hz, 2H), 1.77 (m, 2H), 1.39 (m, 4H), 0.91 (t, J=6.7 Hz, 3H); IR (KBr) ν_{max}: 2934 (s), 1674 (m), 1435 (m), 1234 (w), 1130 (s) cm^{-1}. Anal. calcd for $C_{12}H_{14}Cl_2N_4$: C 50.54, H 4.95, N 19.65; found C 50.78, H 4.77, N 19.38.

3,5-Dichloro-2-(5-pentyl-1*H*-1,2,3-triazol-1-yl)pyridine (4c): ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 9.22 (s, 1H), 8.08 (d, J=1.70 Hz, 1H), 7.89 (d, J=1.70 Hz, 1H), 2.50 (t, J=7.0 Hz, 2H), 1.75 (m, 2H), 1.28 (m, 4H), 0.90 (t, J=6.6 Hz, 3H).

5-Chloro-3-fluoro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine (3d): A white solid, m.p. 132—134 ℃. ^{1}H NMR (DMSO-d_6, Me_4Si) δ: 9.66 (s, 1H), 9.23 (s, 1H), 8.32 (s, 1H), 7.76 (d, J=7.80 Hz, 2H), 7.26 (m, 2H), 7.16 (t, J=7.00 Hz, 1H). ^{13}C NMR (DMSO-d_6, Me_4Si) δ: 146.58, 143.27, 142.14, 128.60, 128.03, 127.90, 127.50, 125.90 125.15, 124.72, 121.90; IR (KBr) ν_{max}: 3050 (m), 1622 (m), 1564 (s), 1476 (s), 1220 (w), 1175 (s), 1010 (s) cm^{-1}. Anal. calcd for $C_{13}H_8ClFN_4$: C 56.84, H 2.94, N 20.40; found C 56.52, H 2.88, N 20.54.

3,5-Dichloro-2-(4-phenyl-5-iodo-1*H*-1,2,3-triazol-1-yl)pyridine (3e): An orange solid, m.p. 162—165 ℃. ^{1}H NMR (DMSO-d_6, Me_4Si) δ: 10.13 (d, J=1.29 Hz, 1H), 8.71 (d, J =1.29 Hz, 1H), 8.01 (d, J=8.25 Hz, 2H), 7.60 (m, 2H), 7.51 (t, J=7.62 Hz, 1H); ^{13}C NMR (DMSO-d_6, Me_4Si) δ: 149.66, 144.74, 134.24, 129.83, 129.12, 129.08, 128.35, 128.09, 127.34, 123.85, 123.56; IR (KBr) ν_{max}: 3073 (m), 1628 (w), 1564 (m), 1483 (s), 1230 (m), 1039 (m) cm^{-1}. MS *m/z*: 416 (M^+). Anal. calcd for $C_{13}H_7Cl_2IN_4$: C 37.44, H 1.69, N 13.43; found C 37.14, H 1.61, N 13.39.

3,5-Dichloro-2-(4-butyl-5-iodo-1*H*-1,2,3-triazol-1-yl)pyridine (3f): An orange solid, m.p. 136—138 ℃. ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 8.01 (d, J=1.88 Hz, 1H), 7.87 (d, J=1.88 Hz, 1H), 2.94 (t, J=6.5 Hz, 2H), 1.77 (m, 2H), 1.50 (m, 2H), 0.99 (t, J=6.1 Hz, 3H); IR (KBr) ν_{max}: 2935 (s), 1674 (m), 1443 (m), 1235 (w), 1135 (s), 1035 (s) cm^{-1}. Anal. calcd for $C_{11}H_{11}Cl_2IN_4$: C 33.28, H 2.79, N 14.11; found C 33.12, H 2.64, N 14.02.

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