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Synthesis of 1-substituted tetrazoles via the acid-catalyzed [3+2] cycloaddition between isocyanides and trimethylsilyl azide

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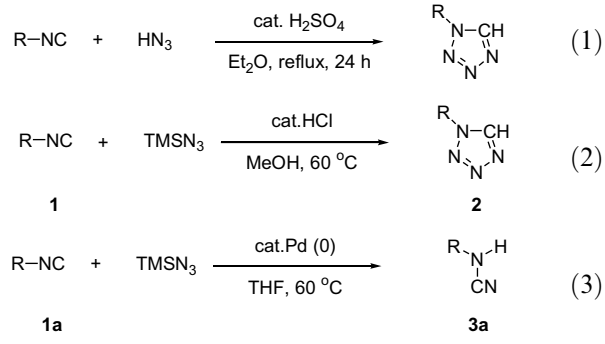
Abstract—1-Substituted tetrazoles were synthesized via the [3+2] cycloaddition between isocyanides and trimethylsilyl azide in the presence of an acid catalyst and MeOH. Various 1-substituted tetrazoles were obtained in good to high yields. The reaction probably proceeds through the in situ formation of hydrazoic acid, followed by a successive [3+2] cycloaddition with the isocyanide activated by an acid.

Tetrazoles are regarded as biologically equivalent to the carboxylic acid group, and extensive work on tetrazoles has been carried out in the field of medicinal chemistry.[1] Among them, *1-substituted* tetrazoles have received much attention because of their wide utility.[2] The acid-catalyzed cycloaddition between hydrazoic acid and isocyanides has long been one of the main routes to *1-substituted* tetrazoles. However, this standard procedure needs the direct addition of large excess amounts of dangerous and harmful hydrazoic acid (Eq. 1).[3] Therefore, it is desirable to develop a more efficient and convenient method for the synthesis of *1-substituted* tetrazoles. We now report that the acid-catalyzed [3+2] cycloaddition between isocyanides **1** and trimethylsilyl azide *in the presence of MeOH* gives the desired 1-substituted tetrazoles **2** in good to high yields (Eq. 2).

We previously reported that palladium-catalyzed cyanamide synthesis from the isocyanide **1a** and trimethylsilyl azide via cleavage of a Si–N bond gave the cyanamide **3a** in a high yield (Eq. 3).[4] During the course of this study, we found that the 1-substituted tetrazole **2a** was produced in a low yield when the reaction of **1a** with trimethylsilyl azide was carried out in the presence of a Lewis acid catalyst, instead of the Pd(0) catalyst. Accordingly it was expected that 1-substituted tetrazoles would be produced by a proper choice of the catalyst system. We examined the cycloaddition between *p*-methoxyisocyanobenzene **1a** and trimethylsilyl azide using several different catalysts and solvents (Table 1). When $YbCl_3$ was used as catalyst, the protic solvent (H_2O) gave a better result than the organic solvent (THF) (entries 1 vs 2) whilst MeOH gave the best result (entry 3).



Among the acid catalysts we tested, HCl gave the highest yield of **2a** (entry 6). Other Lewis acid catalysts such as $CeCl_3$ and $ZnCl_2$ were also effective (entries 4 and 5). The reaction without an acid catalyst gave a low yield of **2a** (entry 7).

The results of the [3+2] cycloaddition of various isocyanides **1** with trimethylsilyl azide are summarized in Table 2. When a mixture of *p*-methoxyisocyanobenzene **1a** and trimethylsilyl azide in MeOH was stirred at 60 °C for 6 h in the presence of 2 mol% of HCl (1.0 M in Et_2O solution), 1-(*p*-methoxyphenyl)tetrazole **2a** was formed

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Table 1. Effect of catalysts and solvents on the formation of tetrazole **2a**[a]

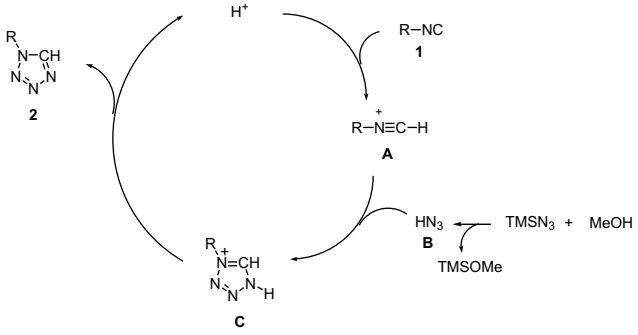
Entry	Catalyst	Solvent	Yield of **2a**,[b] %
1	$YbCl_3$	THF	24[c]
2	$YbCl_3$	H_2O	76
3	$YbCl_3$	MeOH	82 (77)
4	$CeCl_3$	MeOH	86
5	$ZnCl_2$	MeOH	82
6[d]	HCl	MeOH	87
7	None	MeOH	22

[a] The reaction of the isocyanide **1a** and $TMSN_3$ (2.0 equiv) was conducted in the presence of a catalytic amount of catalyst (5 mol%) at 60 °C for 24 h.
[b] ^{1}HNMR yield using *p*-xylene as an internal standard. Isolated yield is shown in parentheses.
[c] **1a** was recovered in 61% ^{1}HNMR yield.
[d] 1.0 M HCl in Et_2O solution was used.

in 92% yield (entry 1).[5] We investigated the reaction of the other arylisocyanides **1b–f**. The isocyanobenzenes **1b** and **1c**, bearing electron-donating groups at the *ortho* positions of the aromatic rings, gave the corresponding tetrazoles **2b** and **2c** in high yields, respectively, although a prolonged reaction time was required in the case of sterically hindered *ortho* disubstituted isocyanobenzene **1c** (entries 2 and 3). The reaction of isocyanobenzene **1d** was complete in 5 h to afford 1-phenyltetrazole **2d** in good yield (entry 4). The reactions of the isocyanides **1e** and **1f**, having electron-withdrawing groups at the *para* position of the aromatic ring, also produced the corresponding tetrazoles **2e** and **2f** in 58% and 77% yields, respectively (entries 5 and 6). The above results indicate that the tetrazole-forming reaction tolerates a wide range of functional groups and the [3+2] cycloaddition proceeds well, irrespective of the position and electronic nature of the substituents on the aromatic ring. We next investigated the reactivity of the alkyl isocyanides **1g–k**. The reaction of *n*-butyl isocyanide **1g**, sterically bulky cyclohexyl isocyanide **1h** and *t*-butyl isocyanide **1i** furnished the desired tetrazoles **2g–i** in good to high yields, although longer reaction times were needed (entries 7–9). The reaction of (trimethylsilyl)methyl isocyanide **1j** containing the TMS functional group also produced the corresponding tetrazole **2j** in 81% yield (entry 10). The 1-substituted tetrazole-forming reaction was applicable to a substrate having two reactive sites, such as 1,4-diisocyanobutane **1k**, and the corresponding product **2k** was obtained in high yield (entry 11).

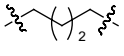
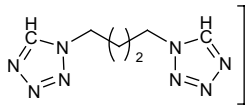
A proposed mechanism for the 1-substituted tetrazole-forming reaction in the presence of an acid catalyst and MeOH is shown in Scheme 1. At the initial stage of the catalytic cycle, the reaction of isocyanides **1** with H^+ would produce the intermediate **A**; HN_3 **B** would be formed in situ via the reaction of $TMSN_3$ and MeOH.[6] The [3+2] cycloaddition between the N–C bond of the intermediate **A** and HN_3 **B** takes place readily to form the intermediate **C**. Deprotonation of the intermediate **C** finally affords the 1-substituted tetrazoles **2**.

We are now in a position to synthesize 1-substituted tetrazoles **2** with a wide range of substituents in very good to high yields through the efficient and convenient acid-catalyzed cycloaddition reaction between isocyanides **1** and trimethylsilyl azide in MeOH. Further studies on the application of the present methodology to the synthesis of biologically active compounds and the extension of the present finding to 5-substituted tetrazole synthesis are under investigation.



Scheme 1. Proposed mechanism for the formation of tetrazoles **2**.

Table 2. Synthesis of tetrazoles **2** under acid catalysis[a]

Entry	R	**1**	Time, h	**2**	Yield,[b] %
1	*p*-MeO–C_6H_4	**1a**	6	**2a**	92
2	*o*-MeO–C_6H_4	**1b**	6	**2b**	85
3	2,6-Dimethyl-C_6H_3	**1c**	24	**2c**	87
4	C_6H_5	**1d**	5	**2d**	67
5	*p*-CO_2Me–C_6H_4	**1e**	10	**2e**	58
6	*p*-NO_2–C_6H_4	**1f**	4	**2f**	77
7	$CH_3(CH_2)_3$	**1g**	24	**2g**	57
8	Cyclohexyl	**1h**	24	**2h**	78
9	*t*-Bu	**1i**	24	**2I**	92
10	Me_3SiCH_2	**1j**	24	**2j**	81
11		**1k**	24	**2k** 	90

[a] The reaction of isocyanides **1** and $TMSN_3$ (1.5 equiv) was conducted in MeOH (0.5 M) in the presence of a catalytic amount of HCl (2 mol%, 1.0 M in Et_2O solution) at 60 °C for the time shown in Table 2.
[b] Isolated yield.

Acknowledgements

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5. The procedure for the synthesis of tetrazole **2a**: to a mixture of MeOH (1 mL), a solution of HCl (0.01 mL, 1.0 M in Et_2O solution) and *p*-methoxyisocyanobenzene **1a** (66.5 mg, 0.5 mmol) was added trimethylsilyl azide (0.1 mL, 0.75 mmol) in a pressure vial. The reaction mixture was stirred at 60 °C for 6 h. After consumption of **1a**, the mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography (*n*-hexane/AcOEt = 5:1 to 1:1) to afford 1-(*p*-methoxyphenyl)-tetrazole **2a** in 92% yield (81.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (3H, s), 7.09–7.05 (2H, m), 7.62–7.57 (2H, m), 8.90 (1H, s); ^{13}C NMR (100.40 MHz, $CDCl_3$): 55.67, 115.06, 122.80, 126.77, 140.40, 160.51; IR (KBr) 3130, 1614, 1517, 1253, 1020, 827 cm^{-1}. Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.57; N, 31.80. Found: C, 54.50; H, 4.76; N, 31.53; HRMS (EI) Calcd for $C_8H_9N_4O$ (M^++H) 177.0771. Found 177.0770.
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