Conformational control in the regioselective synthesis of N-2-substituted-1,2,3-triazoles†

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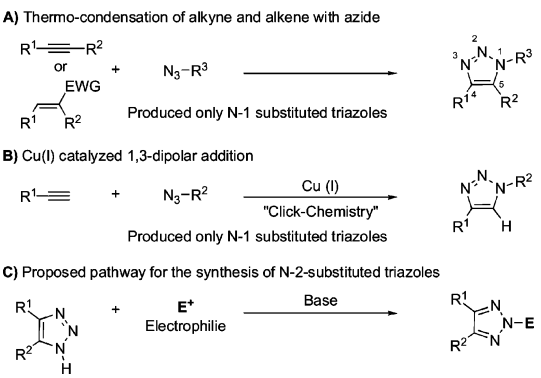
Received (in College Park, MD, USA) 31st March 2008, Accepted 23rd April 2008
First published as an Advance Article on the web 2nd June 2008
DOI: 10.1039/b805328f

An effective strategy for the synthesis of N-2-substituted-1,2,3-triazoles with excellent yields and regioselectivity has been developed.

Since the discovery of the copper-catalyzed alkyne–azide 1,3-dipolar addition for the synthesis of substituted 1,2,3-triazoles (often reported as "click-chemistry"),[1] these compounds have received considerable attention from scientists in many different fields.[2] Within the past six years, tremendous efforts have been made regarding the application of 1,2,3-triazoles in biological science,[3] medicinal chemistry[4] and material science.[5]

Currently, 1,2,3-triazoles are prepared by thermo- or copper-mediated 1,3-dipolar addition as shown in Scheme 1 (A and B). The thermo-condensation, which was first reported more than a century ago, required harsh reaction conditions with limited substrate scope. As a result, the 1,2,3-triazoles did not receive great attention until the remarkable discovery of Cu(I)-promoted "click-chemistry". In both approaches, only terminally substituted triazoles (N-1) can be obtained, due to the nature of azides. Therefore, any N-2 substituted triazoles can only be obtained by the conversion of non-substituted NH-triazoles with appropriate electrophiles (Scheme 1C). However, to the best of our knowledge, no effective strategy for regioselective N-2 substitution of 1,2,3-triazoles has been reported in the literature so far.[6]



Scheme 1

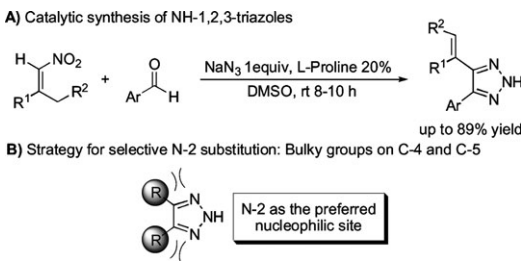
With a strong dipole moment and high electron density on the nitrogens, the NH-triazoles are good nucleophiles, which will react with electrophiles under suitable conditions. However, among the reported examples, including acetylation[7] and Michael addition,[8] the N-1 substituted triazoles were the dominant products. This is caused by the higher electron density associated with the two terminal nitrogens (N-1 and N-3) than the internal N-2 nitrogen. Therefore, selective N-2 substitution remains a big challenge in triazole derivatization.

Recently, we reported a metal-free synthesis of 4,5-disubstituted NH-1,2,3-triazoles through a three component cascade reaction (Scheme 2).[9] This new method produced various C-4, C-5 substituted NH-triazoles in good to excellent yields. Driven by the great desire to develop efficient synthetic strategies for functional triazole derivatives, we then investigated the substitution of this new class of compounds. Herein, we report a successful strategy for the regioselective synthesis of N-2 substituted-1,2,3 triazoles.

Our general hypothesis is that the C-4, C-5 substituent groups may provide the necessary steric hindrance to prevent nucleophilic substitution on the terminal nitrogens. The new triazole synthesis mentioned above allows for this investigation. To evaluate the effectiveness of this strategy, we first carried out an acetylation reaction on **1a**. As expected, the N-2 acetylation product was obtained as the only regioisomer in nearly quantitative yield and the structure of **2a** was characterized by X-ray crystallography (Scheme 3).

The triazole acetate **2a** is stable under anhydrous, pH neutral conditions. However, treatment with acid or base causes hydrolysis of the amide. An attempt at reducing amide **2a** with $LiAlH_4$ led to the dissociation of the N–C bond, giving **1a** and ethanol. Although the relatively poor stability of **2a** limits the potential applications of this approach, the successful N-2 substitution confirmed our hypothesis.

Alkylation of **1a** was then performed in the expectation of forming a non-labile N–C bond. Treatment of **1a** with benzyl



Scheme 2

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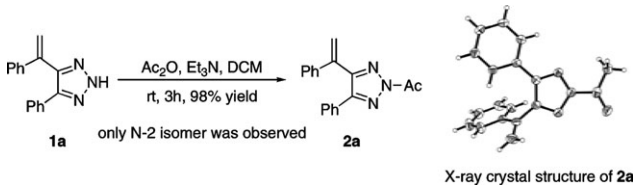
† Electronic supplementary information (ESI) available: Experimental details, X-ray measurement and ^1H and ^{13}C NMR spectra for all compounds. CCDC 682966–682970. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b805328f



Scheme 3

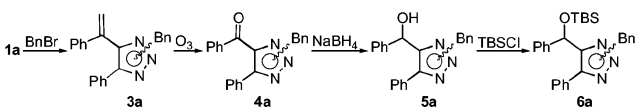
bromide gave *N*-benzyl triazoles in excellent yields (>95%). However, all three regioisomers were obtained (the three isomers can be readily separated by column chromatography. The N-2 product is of much lower polarity). One big challenge for further evaluation of the regioselectivity regarding different C-4, C-5 substituents is the characterization of all three isomers. This problem was overcome by the successful derivatization of the C-5 vinyl group in **3a** as shown in Scheme 4.

Notably, all three regioisomers were stable under the reaction conditions and alkyl rearrangement was not observed. Moreover, the *N*-benzyl bond was stable under acidic conditions (AcOH in DMSO, overnight) and basic conditions (K_2CO_3 in DMSO, overnight). Successful determination of N-1-**3a** and N-2-**4a** by X-ray crystallography provided the necessary characterization of all three N-isomers for these substrates. With this information in hand, we then investigated the optimal reaction conditions for the selective N-2 alkylation and the results are summarized in Table 1.

As shown in Table 1, N-3 alkylation was the least favored in almost all cases. From the crystal structures (N-1-**3a**, N-2-**4a**, N-1-**5a**), the C-4 aryl group adopted a nearly coplanar conformation with the triazole ring (the dihedral angle between the aryl and triazole rings is larger than 140°).[11] Therefore, the N-3 position was blocked for electrophilic addition. As a result, 4,5-diaryl triazoles should undergo preferred N-2 alkylation to give the dominant product, which is supported by the literature.[6] However, the regioselectivity from non-aryl substituted groups (more interesting derivatives) was complicated. The 5-vinyl substituted **1a** underwent N-1 substitution to give the major product, with the formation of a good amount of N-2 product.[12] Increasing the size of the C-5 group resulted in better N-2 selectivity (**1c** and **1e**).

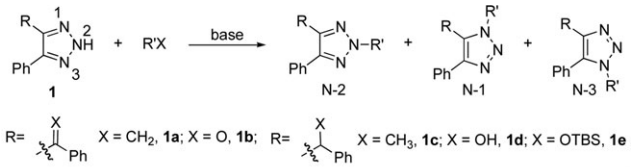
Screening of the reaction conditions revealed that the choice of solvent and base did change the reaction kinetics (different reaction rates). But the influence on the regioselectivity is subtle. Application of a stronger base, such as NaH, resulted in deprotonation of the N–H proton, favoring N-1 substitution (entries 7 and 8). The electrophiles, on the other hand, showed more influence on the regioselectivity. Application of the more hindered cyclohexanyl bromide, resulted in a slower reaction rate, and gave N-2 isomer as the only product (entry 14).

To our surprise, the benzyl ketone triazole **1b**, which is expected to be a less hindered substrate than **1a**, gave excellent N-2 selectivity (entry 15). This result significantly improves the



Scheme 4 Derivatization of *N*-benzyl triazoles.[10]

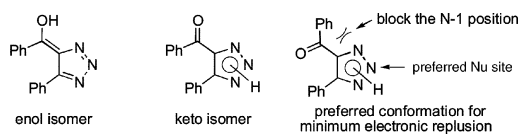
Table 1 Screening of reactions for NH-triazole alkylation[a]



	Triaz-ole	Electrophile	Sol.	Base	Time (h)	Conv. (%)[b]	N2:N1:N3[b]	Yield (%)[c]
1	**1a**	BnBr	Acetone	K_2CO_3	5	100	1.7:1:0.5	>98
2			CH_2Cl_2	K_2CO_3	30	60	0.6:1:0.4	50
3			DMSO	K_2CO_3	1	100	1.6:1:0.5	>98
4			THF	K_2CO_3	72	65	0.5:1:0.6	60
5			MeOH	K_2CO_3	30	45	1.5:1:1.0	40
6			Acetone	Et_3N	30	50	1.8:1:1.3	45
7			DMF	NaH	4	100	1.6:1:0.2	95
8			THF	NaH	30	100	0.2:1:0.3	95
9			Acetone	Cs_2CO_3	5	100	2.0:1:0.2	>98
10		Allyl-Br	Acetone	K_2CO_3	5	100	1.8:1:0.3	>98
11		BnCl	Acetone	K_2CO_3	5	65	2.0:1:0.2	85[e]
12		CH_3I	Acetone	K_2CO_3	5	100	1.5:1:0.4	>98
13		DCE	Acetone	K_2CO_3	72	75	2.8:1:0.2	85[e]
14		Br-Cy	Acetone/DMSO(2:1)	K_2CO_3	14	70	Only N-2	90[e]
15	**1b**	BnBr	Acetone	K_2CO_3	5	100	7.6:1:0.4	>98
16	**1c**	BnBr	Acetone	K_2CO_3	5	100	10.3:1:0.6	>98
17	**1d**	BnBr	Acetone	K_2CO_3	5	100	2.2:1:0.1	>98
18	**1e**	BnBr	Acetone	K_2CO_3	5	100	4.7:1:1.4	>98
19[d]	**1b**	DCE	-	K_2CO_3	14	100	Only N-2	95
20		DCE	DCE/Acetone (4:1)	K_2CO_3	14	100	21.5:1:0	91

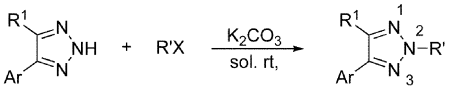
[a] The reaction was carried out by mixing triazole **1** (1.0 equiv.), base (2.0 equiv.) and R′X (1.5 equiv.) with solvent (0.2 M of **1**) at room temperature unless otherwise noted. [b]Ratios and conversions were determined by ^{1}H NMR integration. [c]Yields (combination of all three isomers) were determined by NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. [d]Heating at 45 °C. [e]Yields based on the consumption of the **1**. [f]DCE = 1,2-dichloroethane.

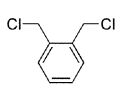
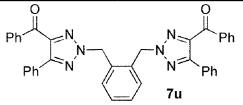
potential application of this strategy, since the ketone functionality can be readily converted into other functional groups. The 5-keto-triazole **1b** may adopt two conformations, the keto and enol forms. Since hydroxy-triazole **1d** (entry 17) gave only moderate N-2 selectivity (even with potential intramolecular H-bonding), the keto isomer was likely the active conformation under the reaction conditions, considering that triazole nitrogens are better nucleophiles. Therefore, to avoid the electronic repulsion between the keto oxygen and the triazole nitrogen, the benzoyl on C-5 would like to be coplanar with the triazole ring as shown in Scheme 5.[13] As a result, the phenyl group effectively blocked the N-1 position, leaving N-2 as the preferred nucleophilic site. By taking advantage of our understanding of the influences of electrophiles, C-5 substituted groups and reaction conditions on the course of the



Scheme 5 Electronic repulsion resulted in conformational control for selective N-2 substitution.

Table 2 Reaction substrate scope[a]



	Electrophile	Product	Time (h)	Yield of **N-2** (%)[b]
1	BnBr	**7a** R'=Bn	5	**82**[c]
2	BuCl	**7b** R'=Bu	14	**90**
3	Br-Cy	**7c** R'=Cy	14	**90**
4[d]	$ClCH_2CH_2Cl$	**7d** R'=CH_2CH_2Cl	14	**95**[c]
5	Allyl-Br	**7e** R'=Allyl	5	**74**
6	$ClCH_2COOEt$	**7f** R'=CH_2COOEt	10	**84**
7	BnBr	**7g** X=Me,R'=Bn	5	**85**
8	Allyl-Br	**7h** X=Me,R'=Allyl	5	**76**
9	BnBr	**7i** X=OH,R'=Bn	5	**63**
10[e]	$ClCH_2CH_2Cl$	**7j** X=OH, R'=CH_2CH_2Cl	5	**90**
11	$ClCH_2COOEt$	**7k** X=OH, R'=CH_2COOEt	10	**93**
12	BnBr	**7l** X=OTBS,R'=Bn	5	**62**
13	BnBr	**7m** Ar=4-OMePh	5	**80**
14	$ClCH_2COOEt$	**7n** Ar=4-OMePh	10	**65**
15	BnBr	**7o** Ar=4-NO_2Ph	5	**87**
16[d]	$ClCH_2CH_2Cl$	**7p** Ar=4-NO_2Ph	14	**90**
17	$ClCH_2COOEt$	**7q** Ar=4-NO_2Ph	10	**92**
18	BnBr	**7r** Ar=1-naphthalenyl	5	**62**
19[d]	$ClCH_2CH_2Cl$	**7s** Ar=1-naphthalenyl	14	**81**
20[d]	BnBr	**7t** Ar=Ph, R=$HO(CH_2)_5CO$-	5	**83**
21		 **7u**	14	**85**

[a] Reactions were carried out by mixing triazole **1** (1.0 equiv.) and R′X (1.5 equiv.) with solvent (0.2 M of **1**) at room temperature unless otherwise noted. [b]Separated yield of N-2 isomers. [c]Structures have been confirmed by X-ray diffraction. [d]Heating at 45 °C. [e]Refluxing. [f]Cy = cyclohexanyl.

reactions, various N-2 substituted triazoles have been synthesized in excellent yields and the results are summarized in Table 2.

Notably, the N-2 isomers usually have much lower polarity than the N-1/N-3 isomers, which allowed the easy separation of the desired N-2 isomers. The applications of versatile electrophiles, such as allyl halide, α-chloro esters and DCE, provide good synthetic handles, which permit further functional group transformations. In addition, besides the 5-aryl-keto triazoles, the 5-alkyl-keto triazoles also gave excellent N-2 selectivity (**7t**), thus extending the scope of our strategy. Finally, the successful preparation of bis-triazole **7u** indicated the great potential of these compounds as ligands in the formation of a new class of transition metal complexes.

In conclusion, we have successfully developed a general approach for the selective N-2 substitution of 1,2,3-triazoles. To the best of our knowledge, this is the first example of the selective preparation of N-2 triazole compounds with clear characterization of the different N-isomers. With the continuously growing interest in 1,2,3-triazoles, we believe this strategy will greatly benefit researchers in various fields. Studies of triazole analogues as peptide mimics and transition metal ligands are currently under investigation in our group and will be reported in due course.

We greatly appreciate the C. Eugene Bennett Department of Chemistry, the Eberly College of Arts and Science, WVU research co-op and WV-Nano Initiative at West Virginia University for financial support.

Notes and references

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10. NMR NOE experiments were performed and the results were not clear enough for regioisomer assignment. Therefore the X-ray structures were applied for final characterization.
11. Based on the crystal structures of N-1-**3a**, N-1-**5a** and N-2-**4a**(**7a**), the dihedral angles between C-4 Ar and the triazole ring are 157.4°, 148.3° and 143.1°,respectively.
12. The crystal structure of N-1-**3a** revealed a dihedral angle of 91.4° between the triazole ring and the C-5 vinyl group. Since the C-5 vinyl is perpendicular to the triazole ring, less steric hindrance will be observed at the N-1 position. Therefore, poor regioselectivity has been obtained, as shown.
13. The crystal structure of **7a** revealed a dihedral angle of 169° between the triazole ring and C-5 keto group.

