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SYNTHESIS OF BITRIAZOLYL COMPOUNDS *VIA* HUISGEN REACTION

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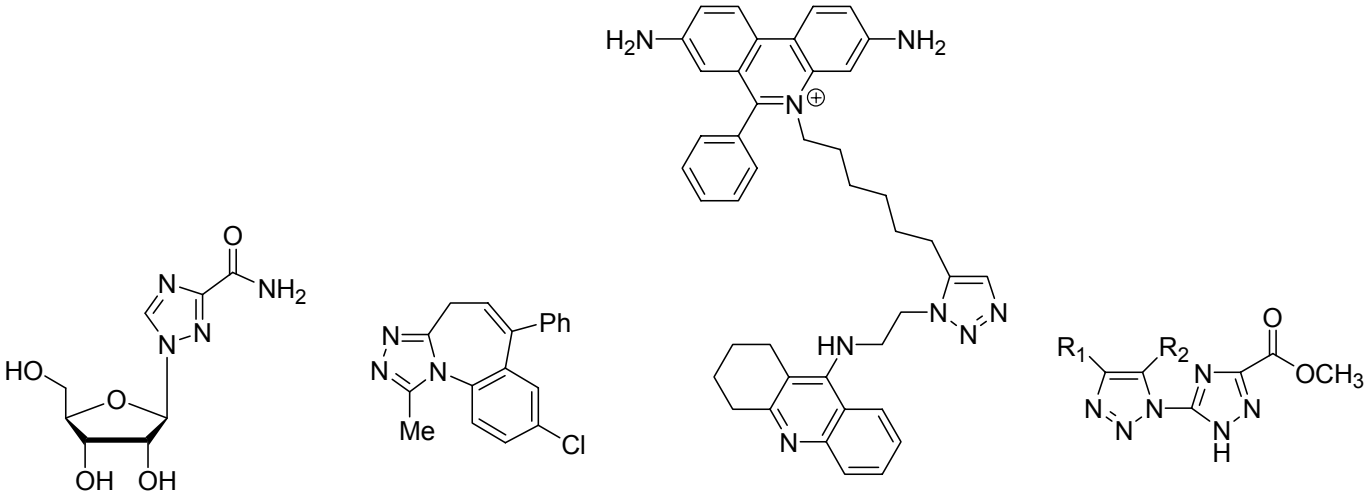
Abstract – Bitriazolyl compounds were synthesized *via* Huisgen 1,3-cyclcoaddition starting with an azidotriazole and various alkynes. Good yields were obtained with terminal alkynes using copper(I) as a catalyst in the THF/H_2O system.

INTRODUCTION

Triazoles are attractive construction units because of their unique structure and properties. Although they are not present in the natural products, they are of considerable significance in medicinal chemistry and in material sciences. Ribavirin[1] (Scheme 1) is the first synthetic nucleoside showing a broad-spectrum of antiviral activity against many RNA and DNA viruses. Alprazolam[2] (Scheme 1), a member of the benzodiazepines drug family, is one of the main drugs used at present for the treatment of anxiety and panic disorders. A 1,2,3-triazole ligand (***syn*-1** in Scheme 1) was recently found to be the most potent acetylcholinesterase inhibitor.[3] Triazoles also provide useful components for constructing molecular memory devices[4] and fuel cell drives.[5] However, triazole compounds have not received as much attention as they deserve, propably because of the lack of convenient and practical methods of synthesis.

We are interested in the potential applications of triazole compounds in the fields of medicine and material sciences. For this purpose, we wanted to obtain bitriazolyl unit (**1**) (Scheme 1) for use as a surrogate for the current biaryl motif, which is being widely applied in a range of pharmaceutics, herbicides, and natural products, as well as in conducting polymers, molecule wires and liquid-crystalline materials.[6] One of the most convenient and attractive approach to the synthesis of the 1,2,3-triazoles is the Huisgen 1,3-dipolar cycloaddition using azides and alkynes.[7] In a recent attempt to synthesize

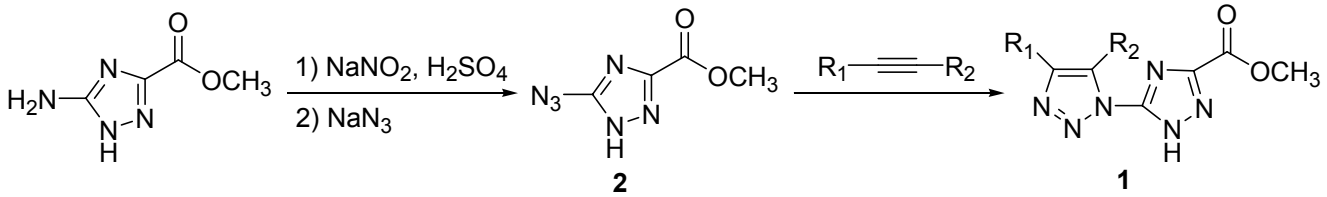
photolabeling probes of ribavirin, we developed a convenient and practical method of synthesizing azidotriazole (**2**) (Scheme 2) on a large scale.[8] We are interested in using this molecule as the starting material for synthesizing bitriazolyl compounds (**1**) with various alkynes *via* the Huisgen reaction. Here we report on the synthesis and characterisation of these bitriazolyl compounds.



Scheme 1: Ribavirin, Alprazolam, the most potent AChE inhibitor ***syn*-1** and bitriazolyl compound (**1**).

RESULTS AND DISCUSSION

Scheme 2 shows the synthesis of the bitriazolyl constructs. Methyl 5-azido-1,2,4-triazole-3-carboxylate (**2**) was synthesized from methyl 5-amino-1,2,4-triazole-3-carboxylate by diazotization with HNO_2 at –3 °C followed by substitution with NaN_3. This two-step procedure yields readily **2** in a scale of 20 g, which can serve as the starting material for Huisgen reaction to obtain the bitriazolyl building blocks.

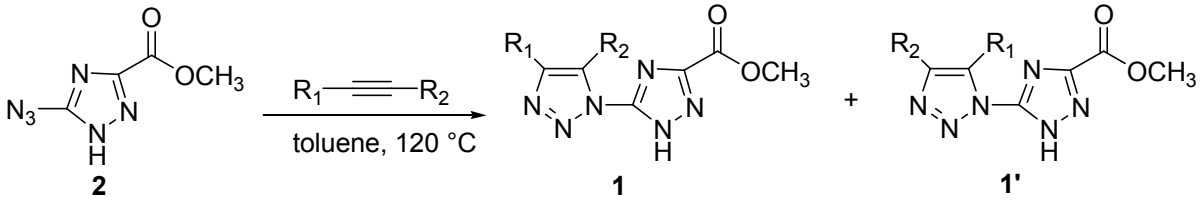


Scheme 2: Synthesis of bitriazolyl units (**1**)**,** starting with 5-amino-1,2,4-triazole-3-carboxylate, using the Huisgen reaction *via* **2**.

When the Huisgen reaction was carried out with **2** and various alkynes by simply heating, the results were not very satisfactory (Table 1), since low yields and several by-products were obtained. Most of the reactions were not complete, with the starting materials being recovered in yields of up to 90% (data not shown). There was one exception in the case of methyl propiolate, which gave a yield of 74.6%, and only 1,4-disubstituted 1,2,3-triazole isomer was isolated and identified (Entry 1 in Table 1). It is known that

strong electron-withdrawing substituents on the alkynes and strong electron-donating substituents on the azides favor the reaction.[9] However, the triazole ring is highly electron-deficient, which makes **2** less reactive in Huisgen reactions. Only the most electron-deficient and least sterically hindered alkynes (Entries 1, 2, 3 in Table 1) react readily with **2** *via* Huisgen reactions. We noticed that there is big difference in the reaction yield when the substituent on the alkynes is changed from COOMe to COOEt. This might be explained that the ethyl group is larger than the methyl group and therefore more sterically demanding, leading to less product formation. It is important to point out further that the bulky aromatic alkynes (Entries 4, 5 in Table 1) are not ready to participate in this reaction.

Table 1: 1,3-Dipolar cycloaddition reaction between methyl 5-azido-1,2,4-triazole-3-carboxylate (**2**) and alkynes by direct heating.



Entry	R_1	R_2	Time (h)	Yield (%) [a]
1	$CH_3OC(=O)-$	H	55	74.6 [a]
2	$CH_3CH_2OC(=O)-$	H	76	22.5 [a]
3	$CH_3CH_2OC(=O)-$	$CH_3CH_2OC(=O)-$	20	30.5 [a]
4	$CH_3-C_6H_4-$	H	72	1.8 [a]
5	$CH_3O-C_6H_4-$	H	52	5.1 [b]

[a]: Yield of isolated regioisomer (**1**). [b]: Yield of the isolated mixture of regioisomers (**1**) and (**1**')

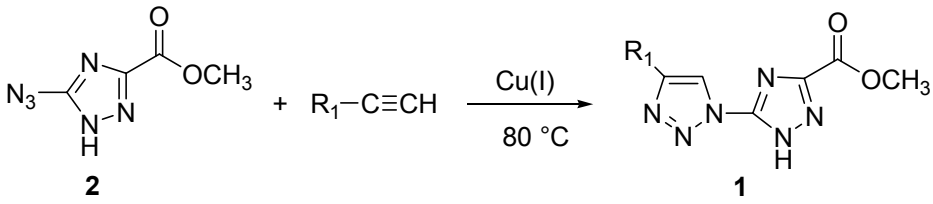
Sharpless *et al.* recently reported on the copper(I)-catalyzed synthesis of 1,2,3-triazole from azides and terminal alkynes.[10] The copper(I)-catalyzed Huisgen reaction can be carried out under mild conditions

and give regioselective 1,4-disubstituted 1,2,3-triazole products, and thus has found a wide range of applications in medicinal science.[11] During our efforts to optimize the synthesis of bitriazolyl units *via* Huisgen reaction using azidotriazole and alkynes, we observed that the copper(I)-catalyzed route efficiently and regiospecifically unites the azidotriazole (**2**) and terminal acetylenes, giving only 1,4-disubstituted 1,2,3-triazoles isomers in good yields in a mixed THF/H_2O solvent system.

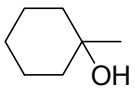
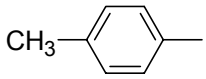
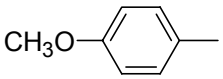
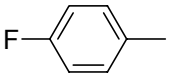
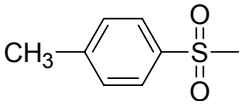
Azidotriazole (**2**) readily engaged in a copper(I)-catalyzed Huisgen reaction with a variety of terminal acetylenes (Table 2). Triazole products (**1**) were obtained by stirring **2** and the corresponding alkynes in the presence of $CuSO_4{\cdot}5H_2O$ and ascorbic acid or sodium ascorbate at 80 °C for 1-5 h in the mixed THF/H_2O solvent system, followed by a chromatographic purification step. Only the 1,4-disubstituted 1,2,3-triazoles were obtained, while no 1,5-disubstituted triazole isomer was obtained upon performing either TLC or column separation. This regioselectivity is in agreement with previous findings and the proposed reaction mechanism, where the formed copper(I) acetylide undergoes stepwise addition with the azide.[10] It has also been reported that a number of copper(I) sources can catalyze this reaction. However, among the various catalysts (CuCl, CuBr, and $CuBr_2$, $Cu(OAc)_2$, $CuSO_4$ in the presence of a reductant) we tested, the best results were obtained with the catalyst prepared *in situ* by reducing $CuSO_4{\cdot}5H_2O$ in the presence of ascorbic acid or sodium ascorbate. Although both ascorbic acid and sodium ascorbate were reported to be excellent reductant in the copper(I)-catalyzed Huisgen cycloaddition procedure,[10] we noted that sodium ascorbate led to better and more reproducible yields (Conditions B and C in Entries 5, 6, Table 2). Further, higher loading of the copper(I) catalyst could also improve the reaction yield and reduce the reaction time to some extent (Conditions A and B in Entries 5, 6, Table 2). Meanwhile, a judicious choice of solvent is crucial to the outcome of the reaction. In comparison with THF alone, the use of THF/H_2O co-solvent significantly reduces the reaction time and improves the reaction yield (data not shown). The best results were obtained with a THF/H_2O 1/2 co-solvent system. The beneficial effect of co-solvent system might be attributable to the enhanced hydrophobic interactions occurring between the substrates during the activation process, which favors the reaction.[12] We also ran the reaction at room temperature, but the reaction obtained under these conditions was not complete, even when the reaction time was extended. It is necessary to maintain the temperature at around 80 °C in order to obtain good product yields in short reaction time. With the various alkyne substituents tested, no significant effects on the outcome of the reaction were observed, whether these substituents were alkyl (Entries 3, 4 in Table 2), aromatic (Entries 5, 6, 7 in Table 2) or electron-withdrawing groups or not (Entries 1, 2, 8 in Table 2).

It is worth noting that the aromatic protons in the triazole rings of **1a-b** and **1e-h** are strongly deshielded when compared with those of normal triazoles. This may be explained that the protons in the triazole rings of **1a-b** are in the deshielding regions of the oxygen atoms, while those of **1e-h** the adjacent benzene rings. We also observed important solvent effect for the aromatic proton in the triazole ring of **1b**, with its

Table 2: Copper(I)-catalyzed Huisgen reaction using methyl 5-azido-1,2,4-triazole-3-carboxylate (**2**) and terminal alkynes.



2 **1**

Entry	R_1	Product	Condition [a]	Time (h)	Yield (%)
1	$CH_3OC(=O)-$	**1a**	A	4.0	81.2
2	$CH_3CH_2OC(=O)-$	**1b**	A	1.5	85.3
3	$CH_3C(=O)OCH_2-$	**1c**	A	1.0	92.4
4		**1d**	A	2.0	77.7
5		**1e**	A B C	5.0 6.0 6.0	84.5 69.3 61.4
6		**1f**	A B C	2.5 5.5 5.0	82.5 75.2 53.9
7		**1g**	A	4.0	70.0
8		**1h**	A	1.5	76.1

a: Condition: (A): THF/H_2O 1/2, $CuSO_4 \cdot 5H_2O$ (0.16 eq.)/sodium ascorbate. (B): THF/H_2O 1/2, $CuSO_4 \cdot 5H_2O$ (0.08 eq.)/sodium ascorbate; (C): THF/H_2O 1/2, $CuSO_4 \cdot 5H_2O$ (0.08 eq.)/ascorbic acid。

chemical shift being 8.98 ppm in $CDCl_3$ and 9.30 ppm in DMSO-d_6. This might be due to the conformational change induced by a change of solvent. Unfortunately, we were not able to further

confirm the solvent effect with other compounds or other solvents because all the compounds **1a-h** are soluble only in DMSO-d_6 with exception that **1b** is well soluble in $CDCl_3$.

In conclusion, the results of the present study show that the copper(I)-catalyzed Huisgen reaction is an efficient and regiospecific method of synthesizing bitriazolyl units starting with the azidotriazole (**2**) and terminal alkynes in a mixed solvent THF/H_2O synthesis. Since the bitriazolyl units (**1**) synthesized here have different functional groups, they should provide useful scaffolds for further synthesis or for setting up libraries of biologically active compounds and functional molecular materials.

EXPERIMENTAL

General: The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 150 MHz, respectively, on Varian Mercury-VX300 and Varian Inova-600 spectrometers. The chemical shifts were recorded in parts per million (ppm) with TMS as the internal reference. FAB and ESI MS were determined using ZAB-HF-3F or Finnigan LCQ Advantage mass spectrometer. UV spectral analysis was performed with a Perkin Elmer Lambda 35 UV/VIS spectrophotometer. All the compounds were purified by performing flash chromatography on silica gel (200-300 mesh). Element analysis (EA) was measured on a Vario ELIII Chnso elemental analyzer.

Preparation of methyl 5-azido-1,2,4-triazole-3-carboxylate (2). 5-Amino-1,2,4-triazole-3-carboxylate (30.0 g, 0.21 mol) was suspended in a mixture of water (120 mL) and conc.H_2SO_4 (3 mL). Then an aqueous solution of $NaNO_2$ (16.4 g, 0.23 mol) was added portionwise to the suspension at -3 °C. After allowing 20 min. for the reaction, NaN_3 (16.7 g, 0.25 mol, freshly prepared solution in water) was added dropwise. The mixture was extracted with ethyl acetate after stirring it for about 3 h at 25 °C. The pure product was obtained after being evaporated under reduced pressure, yielding **2** (18.8 g, 53.1%) as white solid, which can be further purified by crystallization in ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): 158.8, 155.6, 150.0, 53.7. IR (KBr, cm^{-1}): 2145. FAB-MS: *m/z* 169.0 $[M+H]^+$. UV: (MeOH) λ_{max} 231.4 nm (ε 5132). Anal. Calcd for $C_4H_4N_6O_2$: C, 28.58; H, 2.40; N, 49.99. Found: C, 28.51; H, 2.45; N, 50.10.

General procedure for preparing 1 *via* Huisgen reaction by simply heating. Heating mixture of azide (**2**, 0.4 mmol) and alkynes (0.48 mmol) in toluene (10 mL) at 120 °C for 20-75 h afforded the corresponding products. The product was purified by column chromatography with CH_2Cl_2/MeOH 30/1 and dried *in vacuo* to afford **1**.

General procedure for preparing 1 *via* copper(I)-catalyzed Huisgen reaction. The azide (**2**, 0.4 mmol) and alkynes (0.48 mmol) were dissolved in a mixed solvent system (THF/H_2O = 1/2, 9 mL). Sodium

ascorbate (0.2 mmol, freshly prepared solution in water) was added, followed by $CuSO_4 \cdot 5H_2O$ (0.064 mmol, freshly prepared solution in water). The yellowish mixture was stirred at 80 °C, at which point TLC analysis indicated complete consumption of **2**. The solvent in the reaction mixture was evaporated and the residue was purified by column chromatography with CH_2Cl_2/MeOH 30/1. The product was dried *in vacuo* to afford **1**.

1a: White solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.30 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H,). ^{13}C NMR (150 MHz, DMSO-d_6): δ 163.0, 159.8, 156.8, 150.4, 142.1, 131.1, 56.0, 55.0. ESI-MS: *m/z* 251.0 $[M-H]^-$. UV: (MeOH) λ_{max} 244.6 nm (ε 5771). Anal. Calcd for $C_8H_8N_6O_4$: C, 38.10; H, 3.20; N, 33.32. Found: C, 37.89; H, 3.32; N, 33.13.

1b: White solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.30 (s, 1H), 4.34 (q, 2H, J= 7.0 Hz), 3.95 (s, 3H), 1.32 (t, 3H, J= 7.0 Hz). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (s, 1H), 4.48 (q, 2H, J= 7.0 Hz), 4.10 (s, 3H), 1.45 (t, 3H, J= 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.1 157.1, 154.5, 147.8, 140.5, 126.7, 61.9, 53.8, 14.2. ESI-MS: *m/z* 265.0 $[M-H]^-$. UV: (MeOH) λ_{max} 237.6 nm (ε 5867). Anal. Calcd for $C_9H_{10}N_6O_4$: C, 40.61; H, 3.79; N, 31.57. Found: C, 40.79; H, 3.73; N, 31.89.

1c: White solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.79 (s, 1H), 5.22 (s, 2H), 3.96 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.2, 158.1, 144.0, 125.1, 57.7, 54.1, 21.5, ESI-MS: *m/z* 264.9 $[M-H]^-$. UV: (MeOH) λ_{max} 235.6 nm (ε 6217). Anal. Calcd for $C_9H_{10}N_6O_4$: C, 40.61; H, 3.79; N, 31.57. Found: C, 40.89; H, 3.98; N, 31.31.

1d: White solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.41 (s, 1H), 5.07 (br s, 1H), 3.93 (s, 3H), 1.89-1.96 (m, 2H), 1.66-1.77 (m, 3H), 1.42-1.50 (m, 3H), 1.21-1.30 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 157.9, 157.2, 121.0, 68.6, 53.7, 38.2, 25.8, 22.3. ESI-MS: *m/z* 291.1 $[M-H]^-$. UV: (MeOH) λ_{max} 236.6 nm (ε 4268). Anal. Calcd for $C_{12}H_{16}N_6O_3$: C, 49.31; H, 5.52; N, 28.75. Found: C, 49.61; H, 5.25; N, 29.06.

1e: White solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.26 (s, 1H), 7.89 (d, 2H, J= 8.1 Hz), 7.28 (d, 2H, J= 8.1 Hz), 3.95 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 156.8, 146.5, 137.5, 129.0, 126.3, 125.1, 119.5, 52.6, 20.4. FAB-MS: *m/z* 285.0 $[M+H]^+$. UV: (MeOH) λ_{max} 247.5 nm (ε 12427). Anal. Calcd for $C_{13}H_{12}N_6O_2$: C, 54.93; H, 4.25; N, 29.56. Found: C, 54.98; H, 4.13; N, 29.87.

1f: White solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.22 (s, 1H), 7.93 (d, 2H, J= 8.7 Hz), 7.03 (d, 2H, J= 8.7 Hz), 3.95 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 160.2, 157.8, 147.7, 127.8, 122.8, 120.1, 115.1, 55.9, 53.7. FAB-MS: *m/z* 301.0 $[M+H]^+$. UV: (MeOH) λ_{max} 255.1 nm (ε 11156). Anal. Calcd for $C_{13}H_{12}N_6O_3$: C, 52.00; H, 4.03; N, 27.99. Found: C, 52.27; H, 4.21; N, 28.34.

1g: White solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.33 (s, 1H), 8.04 (dd, 2H, $^4J_{HF}$ = 5.4, $^3J_{HH}$ =8.7 Hz), 7.31 (dd, 2H, $^3J_{HF}$ = 8.7 Hz, $^3J_{HH}$ = 8.7 Hz), 3.94 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 162.8 ($^1J_{CF}$

= 245.2 Hz), 157.7, 146.8, 128.3 ($^3J_{CF}$ = 8.3 Hz), 126.8, 121.1, 116.6 ($^2J_{CF}$ = 20.4 Hz), 53.7. FAB-MS: *m/z* 289.0 $[M+H]^+$. UV: (MeOH) λ_{max} 242.4 nm (ε 12506). Anal. Calcd for $C_{12}H_9FN_6O_2$: C, 50.00; H, 3.15; N, 29.16. Found: C, 50.34; H, 3.26; N, 29.42.

1h: White solid. ^{1}H NMR (300 MHz, DMSO-*d*): δ 9.59 (s, 1H), 7.92 (d, 2H, *J*= 8.7 Hz), 7.47 (d, 2H, *J* = 8.1 Hz), 3.93 (s, 3H), 2.38 (s, 3H).^{13}C NMR (150 MHz, DMSO-d_6): δ 170.9, 157.4, 149.3, 146.0, 137.5, 131.0, 128.4, 128.1, 53.8, 21.8. ESI-MS: *m/z* 349.1 $[M+H]^+$. UV: (MeOH) λ_{max} 237.4 nm (ε 5758). Anal. Calcd for $C_{13}H_{12}N_6O_4S$: C, 44.82; H, 3.47; N, 24.13. Found: C, 44.54; H, 3.48; N, 23.84.

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