Communications

One-Pot Synthesis of 1,2,3-Triazoles from Michael Reaction

Ihl Young Choi Lee,* Ok Jong Yu,† Hee-Jeong Lim, and Hyo Won Lee†

*Korea Research Institute of Chemical Technology, Daejeon 305-343, Korea. *E-mail: iychoi@krict.re.kr*
†Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea
Received January 5, 2008

Key Words: Triazole, Click chemistry, α,β-Unsaturated ketone, Cycloaddition

1,2,3-Triazoles, which can be readily prepared from click chemistry, are important building components that could be exploited in many applications in organic, organometallic, and medicinal chemistry, as well as in materials chemistry. Click chemistry is increasingly being used in medicinal chemistry research. Because it enables a modular approach to pharmacophores, it is finding applications ranging from lead discovery and optimization to the tagging of biological systems such as proteins, nucleotides and whole organisms.[1]

The Huisgen 1,3-dipolar cycloadditions of azides and alkynes produce 1,4-disubstituted 1,2,3-triazoles.[2] The synthesis of 1,4-substituted 1,2,3-triazoles from halides, azides, and acetylenes in the presence of copper (I) salt in one pot is well known,[3] but methods for the synthesis of 1,4-disubstituted 1,2,3-triazoles from enones, azide, and acetylenes have not yet been reported. As for the azides from α,β-unsaturated carbonyl compounds, several groups have reported the β-azidation.[4] Recently Xia *et al.* has reported an efficient Lewis base-catalyzed conjugate addition of an azide ion to cyclic enones in water.[5]

We report herein the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles prepared from the one pot reaction of α,β-unsaturated ketones, sodium azide, and alkynes in the presence of copper(I) salt in an aqueous system. The role of Cu(I) for regioselectivity was reported in the literature.[6] Cu(I) was prepared from the reaction between Cu(0) and Cu(II), as well as another method that was reported in the literature for the generation of Cu(I) employing the reduction of Cu(II) with diisopropylamine.[7] Our method for click chemistry could circumvent the isolation and handling of unstable small organic azides via *in situ* generation from the Michael reaction. The subsequent 1,3-dipolar reaction between organic azides and alkynes yielded 1,2,3-triazoles in one pot.

To circumvent the direct employment of the strongly poisonous and explosive hydrazoic acid, *in-situ* generated hydrazoic acid was readily added to cyclic enones in the presence of a Lewis base such as triethylamine. But, we applied this method to the cyclic enones such as cyclopentenone and cyclohexenone, we found cyclopentenone did not give good yields compared to the results with cyclohexenone. Thus we modified the procedure by employing $TMSN_3$ and other Lewis bases such as DBU and Hunig base to improve the yields. The subsequent click chemistry in one pot worked smoothly with alkyne substrates to give the corresponding 1,4-disubstituted 1,2,3-triazoles in very short times (30 min-1 h). Table 1 shows the results in satisfactory yields.

Most triazoles were isolated in pure form as solids by trituration after workup. When the resulting products were oils, chromatographic purification was carried out.

In the case of acetyl cyclopentene, mixture of a *trans* isomeric triazole and a *cis* isomeric triazole was formed respectively in 35% and 14% yields. The structural identification of these isomers by the conventional NMR spectroscopy was found difficult. The stereochemistry of *cis* and

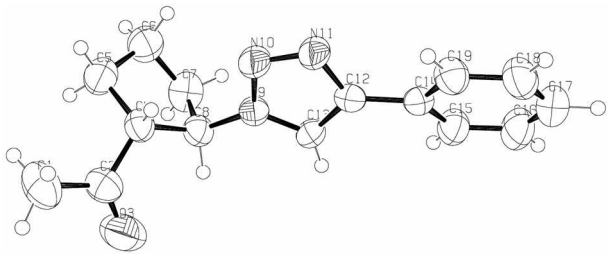
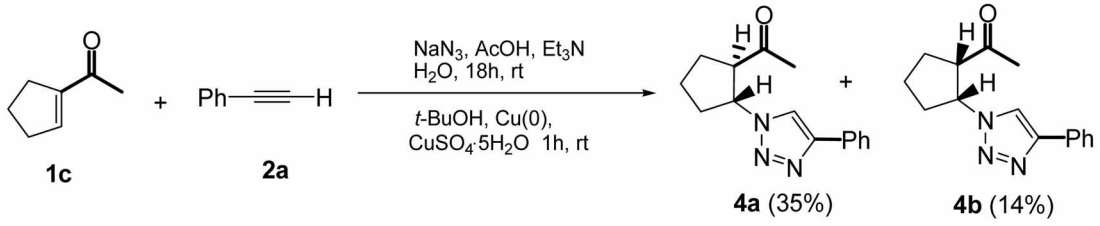
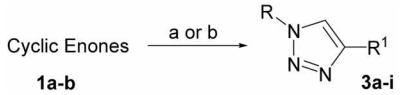


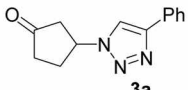
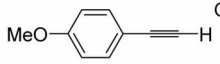
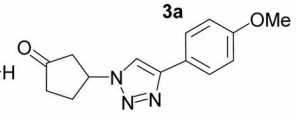
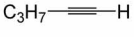
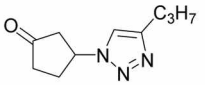
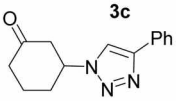
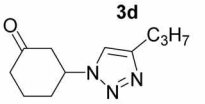
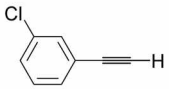
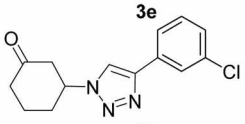
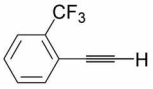
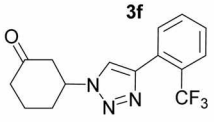
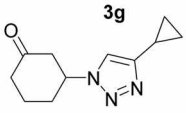
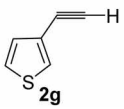
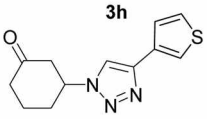
Figure 1. X-ray based ORTEP drawings of **4a**.



Scheme 1. Click Reaction of 1-Acetylcyclopentene with Phenylacetylene.

Table 1. One-Pot Synthesis of 1,2,3-Triazoles from Cyclic Enones, Azides, and Alkynes



Entry	Enone	Alkyne	Product	Isolated Yield (%)
1	 **1a**	**2a**	 **3a**	58[a]
2		 **2b**	 **3b**	53[a]
3		 **2c**	 **3c**	57[a]
4	 **1b**	**2a**	 **3d**	86[b]
5		 **2c**	 **3e**	79[b]
6		 **2d**	 **3f**	91[b]
7		 **2e**	 **3g**	82[b]
8		 **2f**	 **3h**	85[b]
9		 **2g**	 **3i**	75[b]

[a]$TMSN_3$, AcOH, DBU, CH_2Cl_2, 5 h, rt; alkynes (**2a-c**), CuI, $(i\text{Pr})_2\text{NEt}$, 0.5-1 h, rt. [b]NaN_3, AcOH, Et_3N, H_2O, 12 h, rt; *t*-BuOH, alkynes (**2a**, **2c-g**), Cu(0), $CuSO_4{\cdot}5H_2O$, 0.5-1 h, rt.

trans isomers was identified by X-ray crystallography. The structure of the *trans* isomer is shown in Figure 1.

In summary, we have developed a simple, easy, and safe one-pot procedure for the formation of triazoles from cyclic enones, sodium azide or organic azide, and alkynes in good and moderate yields.

Acknowledgements. This work was supported by the Ministry of Science Technology Grant (KK-0701-C0).

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8. **Typical procedure:** To a solution of 1-cyclohexen-2-one (100 mg, 1.04 mmol) in H_2O (1 mL) was added NaN_3 (271 mg, 4.16 mmol), AcOH (258 μL, 4.16 mmol), and Et_3N (30 μL, 0.21 mmol) at room temperature. After being stirred for 18 h at room temperature, *t*-BuOH (1 mL), phenylacetylene (126 μL, 1.15 mmol), Cu (0) (66 mg, 1.04 mmol), and 1 M $CuSO_4$ (200 μL) were added sequentially to the reaction mixture. The reaction mixture was stirred for 30 min - 1 h to convert the azide to the triazole. The solution was filtered over a pad of Celite 545 with dichloromethane. The filtrate was washed with $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was triturated with hexane:ethyl acetate = 4:1 to provide pure 1,4-disubstituted triazole. **3d:** **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.82 (d, J = 7.2 Hz, 2H), 7.78 (s, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.33 (tt, J = 7.4, 1.0 Hz, 1H), 4.88 (tdd, J = 10.0, 5.1, 4.3 Hz, 1H), 3.04 (dd, J = 14.4, 10.1 Hz, 1H), 2.98 (ddt, J = 14.5, 5.3, 1.4 Hz, 1H), 2.55-2.40 (m, 3H), 2.39-2.31 (m, 1H), 2.15-2.08 (m, 1H), 1.86-1.77 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 206.4, 147.7, 130.4, 128.9, 128.3, 125.7, 118.1, 58.9, 47.3, 40.5, 31.7, 21.7. **MS (*m/z*, relative int):** 241 (M^+, 100), 212 (21), 198 (97), 184, 156, 116. **HRMS**: Calcd for $C_{14}H_{15}N_3O$ 241.1215, found: 241.1222.
9. **Typical procedure:** To a solution of $TMSN_3$ (810 μL, 6.10 mmol) and AcOH (348 μL, 6.10 mmol) in CH_2Cl_2 (5.0 mL) was added at room temperature. After being stirred for 20 min, 1-cyclopenten-2-one (100 mg, 1.22 mmol) was added followed by DBU (36 μL, 0.244 mmol). After being stirred for 5 h at room temperature, phenylacetylene (134 mL, 1.22 mmol), CuI (465 mg, 2.44 mmol) and diisopropylethyl amine (636 μL, 4.88 mmol) were added sequentially to the reaction mixture. The reaction mixture was stirred for 30 min - 1 h to convert the azide to the triazole. The reaction mixture was partitioned between dichloromethane and water. The organic layers were washed with $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Silica gel, hexane: ethyl acetate = 1:1) to provide pure 1,4-disubstituted triazole **3a**: **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.82 (dd, J = 9.5, 1.1 Hz, 3H), 7.43 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H.), 5.24 (qui, J = 5.4 Hz, 1H), 2.91 (br s, 1H), 2.90 (d, J = 2.4 Hz, 1H), 2.71-2.63 (m, 2H), 2.60-2.55 (m, 1H), 2.45-2.38 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 213.2, 148.0, 130.3, 128.9, 128.3, 125.7, 118.5, 57.8, 44.6, 36.5, 30.3. **MS (*m/z*, relative int):** 227 (M^+, 43), 198, 145 (100), 89, 55. **HRMS**: Calcd for $C_{13}H_{13}N_3O$ 227.1059, found: 227.1060.