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Copper(II)/Copper(I)-Catalyzed Aza-Michael Addition/Click Reaction of in Situ Generated α-Azidohydrazones: Synthesis of Novel Pyrazolone−Triazole Framework

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ABSTRACT

A one-pot Cu(II)-catalyzed aza-Michael addition of trimethylsilyl azide to 1,2-diaza-1,3-dienes and Cu(I)-catalyzed 1,3-dipolar cycloaddition of in situ generated α-azidohydrazones with alkynes is reported. This process combining two consecutive steps with recycling of the catalyst ($Cu(OAc)_2·H_2O$) represents a useful protocol for the smooth synthesis of novel pyrazolone−triazole derivatives.

Nitrogen-containing heterocycles (azaheterocycles) occur in a wide variety of natural and biologically active compounds.[1] From a recent survey of GMP bulk reactions run in a research facility (Pfizer-Groton) it is estimated that over 90% of pharmaceutical have at least one nitrogen atom in their structure and about one reaction out of seven in the pharmaceutical industry involves the formation of a carbon−nitrogen bond.[2] For these reasons, efficient methods for the synthesis of nitrogen-containing molecules merits further investigations. Surprisingly, little attention has been focused on the copper-promoted C−N bond formation-based protocols.[3] Among them, undoubtedly, "click reaction"[4] and in particular Huisgen [3 + 2] cycloaddition[5] has emerged as a "near perfect" (very fast, selective, high-yield, and wide scope) carbon−nitrogen bond forming reaction toward the synthesis of *N*-substituted 1,2,3-triazoles. This process that occurs between organic azides and alkynes is significantly accelerated by Cu(I) catalysis,[6] and it offers easy access to the 1,4-disubstituted isomer. 1,2,3-Triazoles have found numerous applications ranging from chemical and combinatorial synthesis, bioconjugation and biology, to material science, especially polymer and dendrimer synthesis.[7] Despite

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(3) For a review on copper-mediated coupling reactions and their applications in natural products and designed biomolecules synthesis, see: Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131.

(4) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.

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their importance as reported from a myriad of synthetic methods existing for their preparation,[8] relatively few examples are known to give *N*-triazole-based heterobicycles. For example, a series of 4-(1-aryl-triazol-4-yl)-tetrahydropyridines was identified as an orally active new class of metabotropic glutamate receptor 1 (mGluR1) antagonist.[9] Also, a synthesis of a large library of pure fluorescent triazolylcoumarin dyes using azide−alkyne ligation was reported.[10]

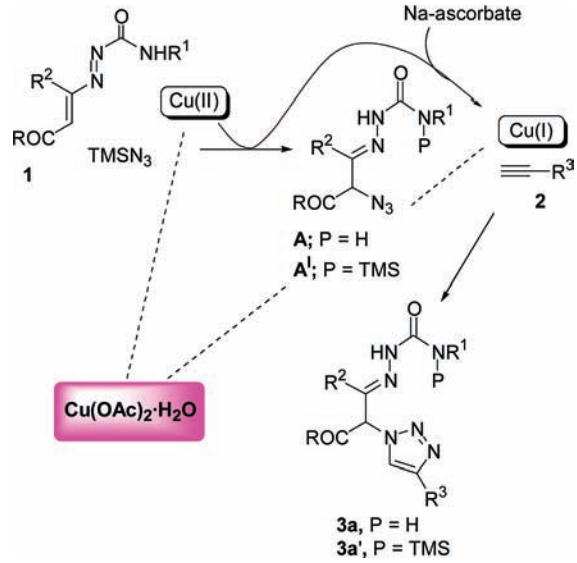
Here, we report an interesting application of the "click reaction" to α-azidohydrazones with the aim to obtain new heterobicyclic scaffolds.

The previous experience of some of us in the use of 2-chlorohydrazones for the synthesis of 2-oxohydrazones via α-azidohydrazone intermediates[11] has prompted us to investigate alternative synthetic applications of these and related substrates. Thus, based on this study and continuing our investigations on the utility of the 1,2-diaza-1,3-dienes (DDs)[12] in organic synthesis, we postulated that α-azidohydrazones could be directly employed in copper-mediated azide−alkyne 1,3-dipolar cycloaddition (CuAAC) to give α-triazolehydrazones, which could be a useful precursor for the construction of linked small heterocycles. We reasoned that in the presence of an opportune reagent of azidation reaction, DD compound **1** would be transformed into the corresponding azido derivative **A** (and $\mathbf{A^I}$) which, in turn, could be converted *in situ* into 1,4-disubstituted-1,2,3-triazoles **3**. Thus, the process would provide a one-pot conversion of the azo-ene systems of DDs into α-triazolehydrazone, where the copper(II) acetate monohydrate would fulfill a dual role, acting as a catalyst in both steps. The essential element of this procedure is the generation of a Cu(I) species required for the azide−alkyne cycloaddition by adding a reducing agent (sodium ascorbate) after complete Cu(II)-catalyzed azido addition (Scheme 1).

Given this designed strategy, we chose the DD **1a** as the standard substrate in our efforts to find an effective condition for a sequential one-pot procedure.

In orienting experiments, we showed that the presence of the copper(II)/sodium ascorbate[13] system [$Cu(OAc)_2$·H_2O/Na ascorbate (1:2)/THF-H_2O (1:1) (yield = 47%), $CuSO_4$·$5H_2O$/Na ascorbate (1:2)/THF-H_2O (1:1) (yield = 43%), and $CuSO_4$·$5H_2O$/Na ascorbate (1:2)/*t*-Bu-H_2O (1:1) (yield = 52%)] proved to be essential for the Huisgen 1,3-dipolar cycloaddition. No

Scheme 1. One-Pot Copper-Catalyzed Azidation (Aza-Michael)/Huisgen 1,3-Dipolar Cycloaddition Reaction



reaction was observed in the absence of Cu(I) or when Cu(I) salts (CuCl in THF or toluene at rt or reflux) were employed. In addition, the use of acqueous solvent systems such as polar solvents (for example THF, CH_3CN, MeOH, DMF) led to the formation of undesirable 2-oxohydrazone byproduct[11] with consequent lower yields. Among all of the solvents examined, dichloromethane was the only one where the reaction proceeded without appreciable amount of byproducts.

On the other hand, we also found that the copper(II)-catalyzed aza-Michael additions proceeded smoothly to completion (15 min at rt as analyzed by TLC) in CH_2Cl_2 and almost quantitative yields to give hydrazonic 1,4-adducts **A** (and $\mathbf{A^I}$). Various copper(II) Lewis acids such as $CuSO_4$·$5H_2O$, $Cu(OAc)_2$·H_2O, $CuCl_2$, $Cu(TfO)_2$, $Cu(NO_3)_2$, and CuO exhibited remarkable catalytic activity. Our choice of $Cu(OAc)_2$·H_2O[14] was based on the higher stability, greater affinity for soft ligands (e.g., alkynes), together with lower cost with respect to other tested catalysts.

Therefore, 1,4-addition of trimethylsilyl azide ($TMSN_3$)[15,16] to DD **1a** was carried out in the presence of catalytic amount of $Cu(OAc)_2$·H_2O in CH_2Cl_2[17,18] at room temperature (Table 1, entry 1). After the disappearance of the starting DD, the check of the crude mixtures by the TLC analysis revealed the presence of two products as major components, easily identified as the desilylated (**A**) and the

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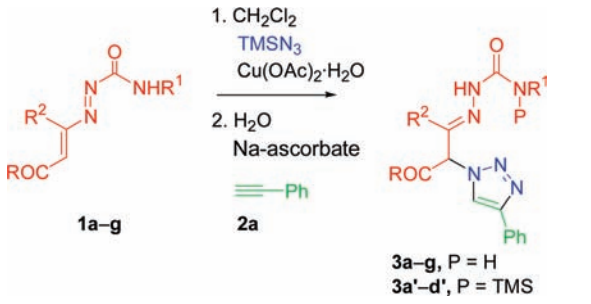
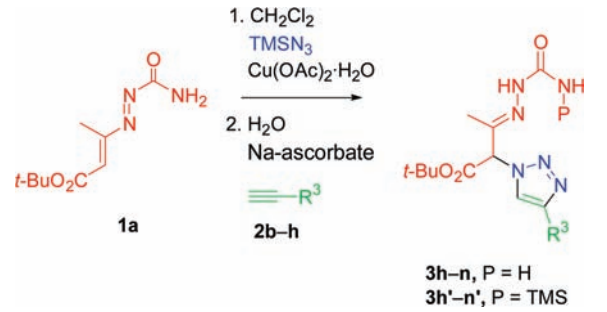
Table 1. One-pot Synthesis of the α-Triazolehydrazones **3a**−**g** and **3a′**−**d′** from DDs **1a**−**g**, $TMSN_3$, and Phenylacetylene **2a**.



1,2-diaza-1,3-diene **1**				α-triazolehydrazone **3**		
1	R	R^1	R^2	**3**[a]	*t* (h)	yield (%)[b]
1a	*t*-BuO	H	Me	**3a/3a′** (53/47)	1.5	60[c]
1b	EtO	H	Me	**3b/3b′** (49/51)	2	54[c]
1c	Me_2N	H	Me	**3c/3c′** (50/50)	2.5	43[c]
1d	MeO	H	Et	**3d/3d′** (46/54)	2	47[c]
1e	$MeO(CH_2)_2O$	Ph	Me	**3e** (100)	4	45[d]
1f	EtO	Ph	Me	**3f** (100)	2	48[d]
1g	MeO	*m*-F−C_6H_4	Me	**3g** (100)	4	59[d]

[a] Ratio was determined by ^1H NMR spectroscopy on the mixture of the purified products. [b] Yield of the isolated purified compounds **3a**−**g** and **3a′**−**d′** based on the phenylacetylene **2a**. [c] Conditions: DD (1 mmol), CH_2Cl_2 (5 mL), $Cu(OAc)_2{\cdot}H_2O$ (0.2 mmol), $TMSN_3$ (1.1 mmol), phenylacetylene (1.0 mmol), sodium ascorbate (0.4 mmol), H_2O (5 drops). [d] Phenylacetylene **2a** (0.5 mmol) was used.

Table 2. One-Pot Synthesis of the α-Triazolehydrazones **3h**−**n** and **3h′**−**n′** from DD **1a**, $TMSN_3$, and Alkynes **2b**−**h**.



alkyne **1**		α-triazolehydrazone **3**		
2	R^3	**3**[a]	*t* (h)	yield (%)[b,c]
2b	*n*-Bu	**3h/3h′** (62/38)	2	65
2c	CH_2OH	**3i/3i′** (71/29)	5	41
2d	$SiMe_3$	**3j/3j′** (68/32)	5	54
2e	*p*-Me-C_6H_5	**3k/3k′** (59/41)	1.5	52
2f	*p*-OMe-C_6H_5	**3l/3l′** (81/19)	3	58
2g	CO_2Et	**3m/3m′** (65/35)	4	40
2h	COMe	**3n/3n′** (78/22)	0.6	51

[a] Ratio was determined by ^1H NMR spectroscopy on the mixture of the purified products. [b] Yield of the isolated purified compounds **3h**−**n** and **3h′**−**n′** based on the alkynes **2b**−**h**. [c] Conditions: DD (1 mmol), CH_2Cl_2 (5 mL), $Cu(OAc)_2{\cdot}H_2O$ (0.2 mmol), $TMSN_3$ (1.1 mmol), alkyne (1.0 mmol), sodium ascorbate (0.4 mmol), H_2O (5 drops).

silylated (**A**$^{\mathbf{I}}$) azidohydrazonic 1,4-adducts, respectively. Similar behavior was observed by our group during the Mukaiyama−Michael addition of enolsilyl derivatives to DDs.[19] After complete conversion of DD **1a**, phenylacetylene, sodium ascorbate reducing agent, and five drops of water were added directly to the reaction mixture without any workup procedure. Also in this step, both α-triazolehydrazones **3a** and **3a′** were observed from the TLC analysis.

In an attempt to optimize the efficiency of this reaction, we have changed the ratio of the alkyne employed. It was observed that upon increasing the amount of phenylacetylene no significant improvement of the yield was observed. Moreover, the best results were obtained using 20% mol of $Cu(OAc)_2{\cdot}H_2O$ and 40% of sodium ascorbate; only in this case did the TLC analysis of crude reaction mixture reveal that starting DD **1a** and successively α-azidohydrazone intermediates (**A** and **A**$^{\mathbf{I}}$) were completely consumed.

Encouraged by these results, we examined the feasibility of a one-pot copper(II) acetate-catalyzed aza-Michael addition/click reaction with various DDs[20] under these optimized conditions. It was found that this procedure works well for a wide range of different DDs **1a**−**g**[21] (Table 1, entries 1−7). So α-triazolehydrazones **3a**−**g** and **3a′**−**d′** were obtained in moderate to good yields (43−60%).

Motivated by the importance of the final target to develop new general method toward widely functionalized pyrazolone−triazole framework, we next examined the extension of this procedure to other alkynes. The reaction proceeded effectively with aliphatic and aromatic terminal acetylenes to give the corresponding α-triazolehydrazones **3h**−**n** and **3h′**−**n′** (Table 2).

Thus, a variety of 1,4-disubstituted-1,2,3-triazoles, containing alkylic residue (enty 1), primary aliphatic alcohol (entry 2), silyl group (entry 3) as well as electron-donating aryl groups (entries 4 and 5), electron-withdrawing groups (carboxy and carbonyl; entries 6 and 7) at the C-4 position of the triazole ring were obtained.

Moreover, as expected, disubstituted acetylene, such as diphenylacetylenes and dimethyl acetylene dicarboxylate, did not react under these reaction conditions.

(17) **Attention:** The main concern about this one-pot procedure may appear a serious safety issue. In fact it is well documented in the literature that ionic azides react with dichloromethane to form explosive azidochloromethane and/or diazidomethane. See: (a) Conrow, R. E.; Dean, W. D. *Org. Process Res. Dev.* **2008**, *12*, 1285–1286. (b) Hassner, A.; Stern, M.; Gottlieb, H. E. *J. Org. Chem.* **1990**, *55*, 2304–2306. Luckily, under our reaction conditions (short reaction times, stoichiometric amount of $TMSN_3$), the possible competitive nucleophilic substitution on CH_2Cl_2 is effectively suppressed since the Michael addition is the favorite and exclusive pathway.

(18) **Caution:** organic azides are potentially explosive compounds (when dry) and should be handled with great care. During our studies we used $TMSN_3$ and we encountered no problem.

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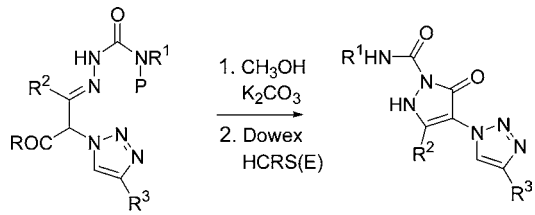
(20) For representative examples of one-pot synthesis of 1,2,3-triazoles, see: (a) Li, J.; Wang, D.; Zhang, Y.; Li, J.; Chen, B. *Org. Lett.* **2009**, *11*, 3024–3027. (b) Jaroslaw, K.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171–3174. (c) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081–3084. (d) Beckmann, H. S. G.; Wittmann, V. *Org. Lett.* **2007**, *9*, 1–4. (e) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223–4225.

(21) DDs **1a**−**g** were synthesized from the corresponding chlorohydrazones by treatment with base (see Supporting Information).

Table 3. Synthesis of 1-(3-Oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-1,2,3-triazoles **4a**−**k** from α-Triazolehydrazones **3a**−**n** and **3a′**−**d′**, **h′**−**n′**.



3a–n, P = H
3a'–d', h'–n', P = TMS

4a–k

α-triazolehydrazone **3**					pyrazolone-triazole **4**		
3[a]	R	R^1	R^2	R^3	**4**	*t* (h)	yield (%)[b,c,d]
3a/3a′ (53/47)	*t*-BuO	H	Me	Ph	**4a**	0.1	99
3b/3b′ (49/51)	EtO	H	Me	Ph	**4a**	0.1	95
3c/3c′ (50/50)	Me_2N	H	Me	Ph	**4a**	2	98
3d/3d′ (46/54)	MeO	H	Et	Ph	**4b**	0.1	93
3e (100)	$MeO(CH_2)_2O$	Ph	Me	Ph	**4c**	0.1	97
3f(100)	EtO	Ph	Me	Ph	**4c**	0.2	99
3g (100)	MeO	*m*-F−C_6H_4	Me	Ph	**4d**	0.2	94
3h/3h′ (62/38)	*t*-BuO	H	Me	*n*-Bu	**4e**	0.3	87
3i/3i′ (71/29)	*t*-BuO	H	Me	CH_2OH	**4f**	0.5	98
3j/3j′ (68/32)	*t*-BuO	H	Me	$SiMe_3$	**4g**	0.3	78
3k/3k′ (59/41)	*t*-BuO	H	Me	*p*-Me−C_6H_5	**4h**	0.3	94
3l/3l′ (81/19)	*t*-BuO	H	Me	*p*-OMe−C_6H_5	**4i**	0.8	96
3m/3m′ (65/35)	*t*-BuO	H	Me	CO_2Et	**4j**	0.3	95
3n/3n′ (78/22)	*t*-BuO	H	Me	COMe	**4k**	0.3	97

[a] Ratio was determined by ^{1}H NMR spectroscopy on the mixture of the purified products. [b] Yield of the isolated purified compounds **4a**−**k** based on α-triazolehydrazones **3a**−**n** and **3a′**−**d′**,**h′**−**n′**. [c] Conditions: α-triazolehydrazones (1 mmol), CH_3OH (5 mL), K_2CO_3 (1 mmol). [d] 1-(3-Oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-1,2,3-triazoles were obtained after treatment with cation-exchange resin [Dowex HCRS(E)].

These studies revealed that a single inexpensive copper catalyst ($Cu(OAc)_2 \cdot H_2O$) sequentially enabled two sustainable catalytic transformations, aza-Michael addition and "click reactions", to furnish α-triazolehydrazone derivatives. Thus, the process *internally recycles* an upstream reaction *catalyst* to provide a new *catalyst* for a downstream reaction.[22]

Therefore, with the identification of such a system, we disclosed an attractive synthetic approach that could serve as the basis for the future developments toward planning reaction cascade, particularly useful when active, unstable intermediates as well as organic azides are involved.

Finally, the whole utility of this procedure was demonstrated in the synthesis of different novel pyrazolone−triazole frameworks. Thus, a subsequent cyclization process to give the pyrazol-5-one ring was carried out under basic conditions (potassium carbonate). The reaction proceeds by means of the intramolecular nucleophilic attack of the nitrogen atom of the hydrazino moiety (C═N−*N*H) on the ester/amide function in the γ position with loss of an alcohol/amine molecule to give the pyrazole ring closure. By this procedure, 1-(3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)-1,2,3-triazoles **4a**−**k** from 1,4-disubstituted-1,2,3-triazoles **3a**−**n** and **3a′**−**d′**,**h′**−**n′** were easily achieved (Table 3). It is noteworthy that the overall process (**1**→**4**) involved the formation of four C−N bonds and two heterocyclic scaffolds in a selective and efficient manner.

In conclusion, we developed an efficient pyrazolone−triazoles synthesis relying on click reactions with in situ generated α-azidohydrazones. Thus, we described the use of DDs for the title heterobicyclic scaffold through a reaction sequence comprising "aza-Michael addition/1,3-dipolar cycloaddition/azaheterocyclization". The copper-"assisted-tandem catalysis" involves internal recycling catalyst avoiding isolation and handling of potentially unstable organic azide intermediates. Further investigations are still in progress in our laboratory to improve utility and application of this synthetic methodology.

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Supporting Information Available: Experimental procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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