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N-Alkynyl Imides (Ynimides): Synthesis and Use as a Variant of Highly Labile Ethynamine

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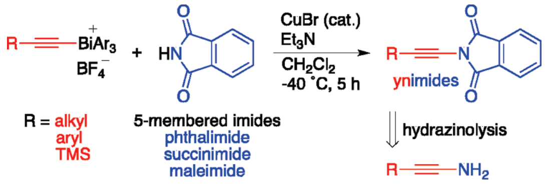
ABSTRACT



This study describes the first reliable synthesis of *N*-alkynyl imides (ynimides). This was accomplished with a copper-catalyzed coupling reaction between alkynyl(triaryl)bismuthonium salts and five-membered imides. We also found that it was possible to utilize *N*-ethynyl phthalimide as a variant of the highly labile ethynamine. 4-Amino-1,2,3-triazole was successfully obtained via the CuAAC reaction of *N*-ethynyl phthalimide with azide followed by hydrazinolysis of the phthaloyl protecting group.

Among the heteroatom-substituted alkynes, those with nitrogen substitutions have become an important building block in modern organic synthesis. The electronic bias imposed by the nitrogen atom controls the stability and reactivity of these alkynes. In general, ynamines that retain the unsubstituted nitrogen atom are the most reactive of this series; for example, ethynamine could not be isolated, because the equilibrium is shifted completely toward the more stable acetonitriles.[1] To overcome this unfavorable equilibrium, a variety of ynamines have been developed.[2] In most cases, the stability of ynamines was increased by introducing electron-withdrawing groups on the nitrogen atom or on the triple bond.[3] At present, special attention has been focused on ynamides that are placed on an electron-withdrawing carbonyl group on the nitrogen atom; these have set the standard for balancing reactivity and stability.[2c,3,4]

In contrast to the well-defined ynamides, to date, there is only one example of the production of an *N*-alkynyl imide (ynimide) (Figure 1).[5] Like ynamides, ynimides are also considered to be stable and easy to handle, due to the two carbonyl groups on the nitrogen atom. Furthermore, imido groups are of great interest, because they are common fragments of many biologically active molecules, and a traditionally reliable hydrazinolysis of the phthaloyl group can lead to a free amino group. Herein, we report the first reliable preparation of ynimides (**3**) in a copper-catalyzed C−N coupling reaction between alkynylbismuthonium salts (**1**) and imides (**2**). Furthermore, we also found that *N*-ethynyl phthalimide (**3b**) can be successfully applied to the production of 4-amino-1-benzyl-1,2,3-triazole (**7**) via a copper-promoted alkyne−azide cycloaddition

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[2] For representative reviews on ynamines, see: (a) Witulski, B.; Alayrac, C. *Sci. Synth.* **2006**, *24*, 1007. (b) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455. (c) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (d) Collard-Motte, J.; Janousek, Z. *Top. Curr. Chem.* **1986**, *130*, 89. (e) Ficini, J. *Tetrahedron* **1976**, *32*, 1449.

[3] For a special issue on the chemistry of electron-defficient ynamines and ynimides, see: *Tetrahedron* 2006, *62*, 3771.

[4] For representative reviews on ynamides, see: (a) Dekorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Louvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (c) Witulski, B.; Alayrac, C. *Sci. Synth.* **2006**, *24*, 1031. (d) Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. *Sci. Synth.* **2005**, *21*, 387. (e) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379.

[5] The formation of 1-phenyl-2-(tetramethylsuccinimido)acetylene (y. 5%) as side product from the reaction of 2-bromo-1-phenylacetylene with *N*-tetramethylsuccinimide-tetrabutylammonium tetramethylsuccinimide complex has been reported, see: Eberson, L.; Lepistö, M.; Finkelstein, M.; Hart, S. A.; Moore, W. M.; Ross, S. D. *Acta Chem. Scand.* **1988**, *B42*, 666.

10.1021/ol2014973

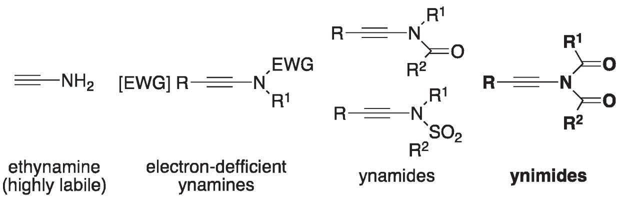


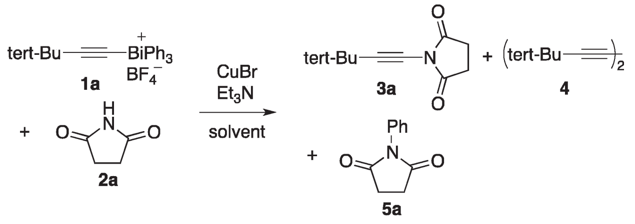
Figure 1. Ethynamine and its electron-deficient variants.

(CuAAC) followed by hydrazinolysis of the phthaloyl protecting group.

In modern organic synthesis, transition-metal-catalyzed coupling reactions are one of the most general procedures for unsaturated carbon–nitrogen bond formation. Among the transition metals, copper salts appear to be the most effective in coupling with poorly nucleophilic nitrogen sources such as amides and imides.[6] As a carbon source, we focused on the low toxicity of organobismuth compounds[7] for use in copper-mediated C–N bond formation with imides. These coupling reactions were developed by Barton and Finet,[8] and moreover, imide arylation and cyclopropanation were successfully achieved by Chan[9] and Gagnon,[10] respectively. They combined the corresponding trivalent organobismuth compounds with a stoichiometric amount of copper salt. However, for the purpose of alkynylation, trivalent alkynylbismuth compounds were considered troublesome because of their low stability. Only alkynyl(diaryl)-bismuth compounds are purely isolable, but they are difficult to handle due to their marked tendency to hydrolyze.[11] In contrast to trivalent alkynylbismuth compounds, alkynyl(triphenyl)bismuthonium salts[12] are relatively stable and easy to handle in practical use. However, employing alkynylbismuthonium salts as an alkynyl donor for the coupling reaction was also considered to be very challenging because (1) only four alkynylbismuthonium salts have been synthesized,[12] (2) therefore, very little is known about their reactivities, (3) no information is available on copper salt reactions with polyvalent bismuth compounds that bear different hybridized carbon ligands, and (4) alkynylbismuthonium salts would be expected to be formally tetraphilic (acetylenic α- and β-carbon, arylic ipso-carbon, and Bi atom) toward the attack of nucleophiles.

We initiated this study by examining the reaction between alkynyl(triphenyl)bismuthonium salt (**1a**) and succinimide (**2a**) in the presence of 30 mol % of CuBr and a stoichiometric amount of Et_3N in CH_2Cl_2. This resulted in the formation of ynimide (**3a**), diyne (**4**), and *N*-aryl imide (**5a**) (Table 1). Apparently, CuBr caused the cleavage of both $C_{alkynyl}$–Bi and C_{Ar}–Bi bonds, regardless of their geometric positions.[13] Lowering the reaction temperature enhanced the selectivity of $C_{alkynyl}$–Bi bond cleavage and reduced the yield of the undesired **5a**. Even at −40 °C, the reaction proceeded to give **3a** (48% yield) as a major product, probably due to the high leaving ability of the bismuthonio groups. We found that the distribution of coupling products was also dramatically affected by the solvent used in the reaction. Toluene, a nonpolar solvent, favored the formation of *N*-aryl imide (**5a**). On the other hand, with increasingly polar solvents, the cleavage of the $C_{alkynyl}$–Bi bond was enhanced, and in DMF, the predominant product was the homocoupled dimer (**4**). Control reactions carried out without Et_3N or without CuBr delivered no coupled products; this indicated that the base and the copper catalyst were necessary for the coupling reaction. In addition, no ynimide (**3a**) was obtained by substituting Et_3N with pyridine. Other copper salts, including $Cu(OAc)_2$, CuCl, or CuI, provided lower yields of **3a**.

Table 1. Selected Screening Results for Copper-Catalyzed Reaction of Alkynyl(triphenyl)bismuthonium Salt (**1a**) with Succinimide (**2a**)[a]



entry	solvent (ε^b)	temp	yield,[c] %			ratio[c]
			3a	**4**	**5a**	(**3a**+**4**):**5a**
1	CH_2Cl_2 (8.9)	rt	34	5	59	40:60
2	CH_2Cl_2	0 °C	48	0	37	56:44
3	CH_2Cl_2	−20 °C	50	22	27	73:27
4	CH_2Cl_2	−40 °C	48	18	25	71:29
5	toluene (2.4)	−20 °C	3	1	87	4:96
6	Et_2O (4.3)	−20 °C	0	12	83	13:87
7	THF (7.5)	−20 °C	34	6	48	45:55
8	DMF (38)	−20 °C	0	79	0	100:0

[a] **1a** (0.1 mmol), **2a** (1.0 equiv), CuBr (30 mol %), and Et_3N (1.0 equiv) for 5 h. [b] Dielectric constant. [c] Determined by ^1H NMR.

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(6) For representative reviews on copper-mediated C–N bond formation, see: (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(7) Ge, R.; Sun, H. *Acc. Chem. Res.* **2007**, *40*, 267 and references therein.

(8) For reviews on C–N bond-forming reactions using organobismuth compounds, see: (a) Finet, J.-P.; Pedonov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597. (b) Finet, J.-P. *Chem. Rev.* **1989**, *89*, 1487. (c) Abramovitch, R. A.; Barton, D. H. R.; Finet, J.-P. *Tetrahedron* **1988**, *44*, 3039. (d) Barton, D. H. R.; Finet, J.-P. *Pure Appl. Chem.* **1987**, *59*, 937.

(9) Chan, D. M. T. *Tetrahedron Lett.* **1996**, *37*, 9013.

(10) Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabé, F. *J. Am. Chem. Soc.* **2007**, *129*, 44.

(11) (a) Rudolph, K.; Wieber, M. *Z. Naturforsch.* **1991**, *46b*, 1319. (b) Hartmann, H.; Habenicht, G.; Reiss, W. *Z. Anorg. Allg. Chem.* **1962**, *317*, 54.

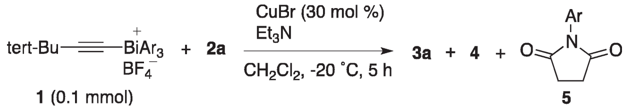
(12) Matano, Y. *Chem. Commun.* **2000**, 2233.

(13) The bismuth center of alkynyl(triphenyl)bismuthonium tetrafluoroborate (**1a**) adopts a pseudotrigonal bipyramidal (TBPY) geometry with three phenyl ipso carbons at the equatorial sites and an acetylenic carbon and fluorine atom at the apical sites. The TBPY geometry is most probably maintained in solution, see ref 12.

Next, the *para*-substituted alkynyl(triaryl)bismuthonium salts (**1a**−**1d**) were subjected to the coupling reaction (Table 2). A Hammett plot was generated as follows: the logarithm of the ratio of the product derived from $C_{alkynyl}$−Bi bond cleavage (**3a** + **4**) to *N*-aryl succinimide (**5**) was plotted against the corresponding Hammett σ parameter for each substituents (see Supporting Information). The slope of the plot indicated that the C_{alkyl}−Bi bond cleavage was most favorable for aryl groups with electron-donating substituents.

A remaining problematic byproduct was the homocoupled diyne (**4**). This homocoupled dimer was probably derived from the bis-alkynyl-$Cu^{(III)}$ intermediate. Stahl previously investigated the copper-catalyzed aerobic oxidative coupling of terminal alkkynes and amides that led to the formation of ynamides.[14] On the basis of Stahl's work, the slow addition of an alkynyl source to the reaction mixture could be expected to overcome the formation of **4**. For the practical simplicity, we chose to use excess equivalents of imide. We found that 3.0 equiv of **2a** was necessary to obtain a meaningful yield of ynimide (**3a**); however, this also slightly increased the yield of *N*-aryl succinimide (**5**) (Table 2).

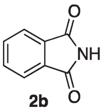
Table 2. Substituent Effects for Copper-Catalyzed Reaction of Alkynyl(triaryl)bismuthonium Salt (**1**) with Succinimide (**2a**)

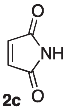


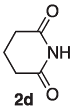
	equiv		yields[a], %			
Ar (**1**)	**2a**	Et_3N	**3a**	**4**	**5**	ratio[a] (**3a**+**4**):**5**
p-$MeOC_6H_4$ (**1b**)	1	1	54	32	9 (**5b**)	91:9
p-$MeOC_6H_4$ (**1b**)	2	2	69	7	14 (**5b**)	84:16
p-$MeOC_6H_4$ (**1b**)	3	3	70	10	20 (**5b**)	80:20
p-MeC_6H_4 (**1c**)	1	1	72	13	17 (**5c**)	82:18
p-MeC_6H_4 (**1c**)	2	2	70	10	20 (**5c**)	80:20
p-MeC_6H_4 (**1c**)	3	3	80	2	18 (**5c**)	82:18
Ph (**1a**)	1	1	50	22	27 (**5a**)	73:27
p-ClC_6H_4 (**1d**)	1	1	13	21	66 (**5d**)	34:66

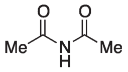
[a] Determined by ^{1}H NMR.

Table 3. Copper-Catalyzed C−N Coupling Reaction Using Alkynyl(triaryl)bismuthonium Salts (**1**)[a]

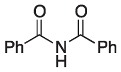

2b


2c


2d



2e



2f

entry	**1** ($R-\!\equiv\!-\overset{+}{Bi}Ar_3\ BF_4^-$)		**2**	yields, %	
	R	Ar		**3**[b]	**5**[c]
1	H (**1e**)	*p*-MeC_6H_4	**2b**	2(**3b**)	88 (**5d**)
2	Bu (**1f**)	*p*-MeC_6H_4	**2a**	57 (**3c**)	14 (**5c**)
3	Bu (**1f**)	*p*-MeC_6H_4	**2b**	52 (**3d**)	33 (**5d**)
4	*i*-Pr (**1g**)	*p*-MeC_6H_4	**2a**	71 (**3e**)	16 (**5c**)
5	*i*-Pr (**1g**)	*p*-MeC_6H_4	**2b**	60 (**3f**)	27 (**5d**)
6	*c*-C_6H_{11} (**1h**)	*p*-MeC_6H_4	**2a**	74 (**3g**)	16 (**5c**)
7	*c*-C_6H_{11} (**1h**)	*p*-MeC_6H_4	**2b**	61 (**3h**)	34 (**5d**)
8	*tert*-Bu (**1c**)	*p*-MeC_6H_4	**2a**	76 (**3a**)	18 (**5c**)
9	*tert*-Bu (**1c**)	*p*-MeC_6H_4	**2b**	75 (**3i**)	23 (**5d**)
10	*tert*-Bu (**1c**)	*p*-MeC_6H_4	**2c**	52 (**3j**)	21 (**5e**)
11	*tert*-Bu (**1c**)	*p*-MeC_6H_4	**2d**	0 (**3k**)	38 (**5f**)
12	*tert*-Bu (**1c**)	*p*-MeC_6H_4	**2e**	0 (**3l**)	57 (**5g**)
13	*tert*-Bu (**1c**)	*p*-MeC_6H_4	**2f**	0 (**3m**)[d]	99 (**5h**)
14	Ph (**1i**)	*p*-MeC_6H_4	**2a**	51 (**3n**)	18 (**5c**)
15	Ph (**1i**)	*p*-MeC_6H_4	**2b**	25 (**3o**)	43 (**5d**)
16	TMS (**1j**)	*p*-MeC_6H_4	**2a**	57 (**3p**)	14 (**5c**)
17	TMS (**1j**)	*p*-MeC_6H_4	**2b**	52 (**3q**)	33 (**5d**)
18	TMS (**1k**)	*p*-$MeOC_6H_4$	**2b**	53 (**3q**)	20 (**5d**)
19	TMS (**1k**)[e]	*p*-$MeOC_6H_4$	**2b**	53 (**3q**)	nd (**5d**)

[a] **1** (0.1 mmol), **2** (3.0 equiv), CuBr (30 mol %), and Et_3N (3.0 equiv) at −40 °C for 5 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] 6% of 1-(3,3-dimethyl-2-oxobutyl)piperidine-2,6-dione was isolated. [e] 10 mmol of **1k** was employed.

The above findings suggested that the copper-catalyzed reaction between alkynyl(triaryl)bismuthonium salts (**1**) and several equivalents of imides (**2**) would lead to the preferable formation of ynimides (**3**) when **1** contained an electron-donating substituent on the aryl group and the reaction conditions included a slightly polar solvent and a low temperature. Subsequently, we investigated cross-coupling reactions between various alkynylbismuthonium salts (**1**) and a variety of imides (**2**) (Table 3). We found that aliphatic alkynyl groups coupled with five-membered imides (**2a**, **2b**, and **2c**) gave moderate to good isolated yields. Among these, the hindered alkynyl groups appeared to be the most effective coupling partners. The reaction was also compatible with a silyl-substituted group (entries 18 and 19 used trimethylsilyl, **1k**). Compared to alkynyl sources, the 2-phenylethynylbismuthonium salt gave a lower yield of **3** (entries 14 and 15). Although our coupling conditions were not applicable to the *N*-ethynylation of imide (entry 1), we could obtain *N*-ethynyl phthalimide (**3b**) via the protiodesilylation of **3q** (Scheme 2). Most ynamines that do not have a substituent readily undergo hydrolysis or polymerization; in contrast, **3b** was stable in aqueous workups, silica gels, heating, etc. and could be stored at room temperature for several months. The six-membered and acyclic imides (**2d**, **2e**, and **2f**) exhibited a lower acidity[15] than that of five-membered **2a**, **2b**, and **2c** compounds and were not suitable for our *N*-alkynylation conditions (entries 11−13).

To date, it is unclear what mechanisms underline the copper-catalyzed coupling reaction between alkynyl(triaryl)bismuthonium salt (**1**) and imide nucleophiles (**2**). As shown in Scheme 1, we offer a general proposal for the

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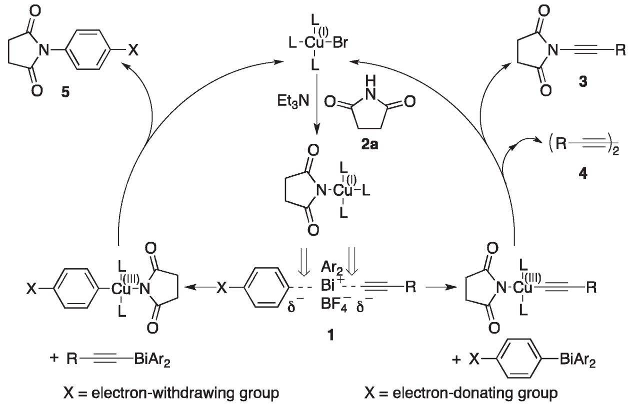
(14) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.

(15) Breugst, M.; Tokuyasu, T.; Meyr, H. *J. Org. Chem.* **2010**, *75*, 5250.

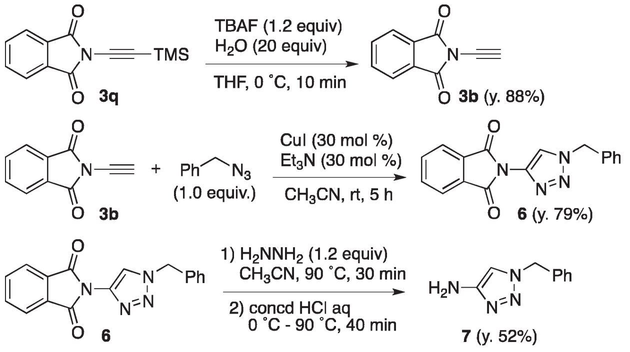
Scheme 1. Plausible Reaction Mechanism for the Copper-Catalyzed Coupling Reaction of Alkynyl(triaryl)bismuthonium Salts (**1**) and Imides (**2a**)



formation of the three coupling products formed from the oxidative addition of Cu$^{(I)}$ to **1** and the subsequent reductive elimination.[6b,16] When the alkynylbismuthonium salt (**1c**) was reacted with **2a** in the presence of (4-ClC$_6$H$_4$)$_3$Bi under the standard conditions, *N*-(4-chlorophenyl) succinimide (**5d**) was not observed, and (4-ClC$_6$H$_4$)$_3$Bi was recovered quantitatively. This result suggested that no equilibrium exists between the Cu$^{(I)}$ and Cu$^{(III)}$ species shown in Scheme 1,[17] On the basis of this finding and the slope of the Hammett plot, we proposes that the product-determining step occurs at the oxidative addition of Cu$^{(I)}$ to alkynyl(triaryl)bismuthonium salt (**1**) and not at the reductive elimination of the Cu$^{(III)}$ intermediate. As shown in Scheme 1, the negative charges on the electron-donating groups of the phenyl ring of **1** generate a repulsive force during the oxidative addition process; this favors the cleavage of the C$_{\text{alkynyl}}$−Bi bond and affords the preferable formation of the C$_{\text{alkynyl}}$−Cu$^{(III)}$ intermediate.

Moreover, little *N*-ethynyl phthalimide (**3b**) was obtained directly under the coupling conditions (Table 2, entry 1). This inspired us to attempt the generation of copper acetylide from ynimide. As shown in Scheme 2, *N*-ethynylphthalimide (**3b**) was applied to the copper-mediated alkyne−azide cycloaddition (CuAAC), and this provided a good yield of 4-phthalimido-1-benzyl-1,2,3-triazole (**6**). Notably, ynamides sometimes encounter drawbacks, for example, hydrolysis under the CuAAC reaction conditions.[18] However, **3b** did not generate *N*-acetyl phthalimide generated from its hydrolysis, even in the presence of 100 equiv of H$_2$O. Subsequent hydrazinolysis of the phthaloyl protecting group on **6** afforded 4-amino-1-benzyl-1,2,3-triazole (**7**).[19] Thus *N*-ethynyl phthalimide (**3b**) can be utilized as a variant of the highly labile ethynlamine.

Scheme 2. Copper-Mediated *N*-ethynylphthalimide-Azide Cycloaddition and the Subsequent Hydrazinolysis of Phthaloyl Protecting Group



In conclusion, we have developed a copper-catalyzed coupling reaction between alkynyl(triaryl)bismuthonium salts and imides. The reaction provided the first reliable synthesis of ynimides. This reaction should expand the scope of applications for nitrogen-substituted alkynes in modern organic synthesis.

Supporting Information Available. Synthesis of alkynyl-(triaryl)bismuthonium salts, experimental details, and characterization data for all new compounds.This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Delp, S. A.; Goj, L. A.; Poay, M. J.; Munro-Leighton, C.; Lee, J. P.; Gunnoe, T. B.; Cundari, T. R.; Petersen, J. L. *Organometallics* **2011**, *30*, 55.

(17) Our standard conditions (catalytic amount of CuBr at −40 °C) applied to Ar$_3$Bi did not afforded the corresponding *N*-aryl succinimide at all.

(18) For CuAAC reaction of ynimides, see: (a) Kim, J. Y.; Kim, S. H.; Chang, S. *Tetrahedron Lett.* **2008**, *49*, 1745. (b) Zhang, S.; Hsung, R. P.; Li, H. *Chem. Commun.* **2007**, 2420. (c) Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. P. *Adv. Synth. Catal.* **2006**, *348*, 2437. (d) Zhang, X.; Hsung., R. P.; You, L. *Org. Biomol. Chem.* **2006**, *4*, 2679. (e) IJsselstijn, M.; Cintrat, J.-C. *Tetrahedron* **2006**, *62*, 3837.

(19) For synthesis and characterization for 4-amino-3-benzyl-1,2,3-triazole, see: Albert, A. *J. Chem. Soc. C* **1970**, 230. The chemical shift of ^{1}H NMR (in DMSO-d_6) was not in agreement with that of **7** synthesized in accordance with Scheme 2.