

Quick and highly efficient copper-catalyzed cycloaddition of organic azides with terminal alkynes†

Dong Wang,^{a,b} Mingming Zhao,^{a,b} Xiang Liu,^{a,b} Yongxin Chen,^{a,b} Na Li^{a,b} and Baohua Chen^{*a,b}

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Good to excellent yields of 1,4-disubstituted 1,2,3-triazoles were obtained within 2–25 min when the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction was carried out under solvent-free conditions, with [Cu(phen)(PPh₃)₂][NO₃] (1 mol%) as the catalyst.

In 2001, Sharpless and co-workers defined the concept of “click chemistry” and the criteria for a transformation to be considered as a “click” reaction.¹ The copper-catalyzed 1,3-dipolar cycloaddition of alkynes and azides yielding 1,2,3-triazoles is undoubtedly the premier example of a “click” reaction to date. A number of CuAAC procedures have been developed² since it was discovered by the groups of Sharpless³ and Meldal⁴ in 2002, and the reaction mechanism is getting mature.^{3a,5} Due to its exclusive regioselectivity, 100% atom economy, wide substrate scope, mild conditions and high yields, CuAAC has found a myriad of applications in chemical synthesis, biology and material science.^{6,1b} Less attention has been focused on decreasing the amount of copper used,⁷ the development of “green” catalytic systems^{5a,8} and reducing reaction time.^{5a,8b,8c,9} These points are extremely important for future industrial applications. We recently reported that a low amount of Cu(PPh₃)₂NO₃ complex can efficiently promote the CuAAC reaction under solvent-free conditions.^{8a} But the Cu(PPh₃)₂NO₃-catalyzed reaction proceeded relatively slowly, as did most of the CuAAC catalytic systems. Substantially increasing the reaction temperature¹⁰ and using a microwave-assisted method¹¹ could reduce this time, but these processes are not favored for molecules containing polyfunctional groups. In this paper, we report a quick, environmentally friendly, efficient solvent-free system for the 1,3-dipolar Huisgen cycloaddition reaction of terminal alkynes with organic azides based on low catalyst loadings of [Cu(phen)(PPh₃)₂][NO₃] complex.¹²

We used benzyl azide and phenylacetylene as the model substrates to initialize the copper-catalyzed optimum cycloaddition condition, as shown in Table 1. In this preliminary experiment, the Huisgen cycloaddition reaction was carried out without a solvent, catalyzed by PPh₃-containing copper(I) complexes (1 mol%), at

room temperature (25–28 °C) for 5 min. The results showed that the [Cu(phen)(PPh₃)₂][NO₃] complex provided the best result: the cycloaddition reached completion within 5 min. The use of amines as additives can promote the CuAAC reaction (entries 6–10), and the effects of phen and TBTA were especially remarkable (entries 9 and 10).

The reaction time gradually decreased when the catalyst loading or reaction temperature increased (entries 11 and 12). Replacing [Cu(phen)(PPh₃)₂][NO₃] complex by copper(I) salts (such as Cu₂O, CuCl, CuBr and CuI) almost completely shut down the catalysis, confirming the role of [Cu(phen)(PPh₃)₂][NO₃] complex as the catalyst. The reaction proceeded perfectly in toluene or water (entries 17 and 18), but the yields decreased seriously when the reaction was carried out in DMSO or THF (entries 19 and 20). In addition, triazole **3a** was isolated in excellent yields and high purity after simple filtration or evaporation. According to the “click laws”, no precautions to exclude oxygen or moisture were taken in any of these reactions.

Encouraged by the efficiency of the reaction protocol described above, the scope of the reaction was examined. Firstly, the optimized conditions were applied to the cycloaddition of other terminal alkynes with benzyl azide. As shown in Table 2, for liquid aromatic terminal alkynes (including electron-rich, electron-poor and heteroatom-containing aromatic alkynes), experiments were carried out smoothly to completion in short reaction times (3–5 min) at room temperature, and the corresponding triazoles were obtained in excellent yields (entries 2, 3, 4, 6 and 7). When the solid alkyne **1e** was used, the yield and reaction rate were somewhat lower, and increasing the reaction temperature can improve the yield (entry 5). We successfully extended the procedure to ferrocenyl acetylene, with the yield of the obtained product being 89% (entry 8). Besides aromatic terminal acetylenes, the reactivity of aliphatic compounds toward azides was also tested. Although, compared to the aromatic acetylenes, the aliphatic acetylenes required much more time (12–25 min); the click products were obtained in good to excellent yields at 40 °C (entries 9–12). It was shown that the quick solvent-free [Cu(phen)(PPh₃)₂][NO₃]-catalyzed Huisgen cycloaddition reaction tolerates a variety of terminal alkynes.

The substrate scope of organic azides was further investigated (Table 3). The results indicated that benzyl, alkyl, and aryl azides reacted quickly with phenylacetylene and the corresponding triazoles were obtained in high yields at room temperature or 40 °C within 2–25 min. The steric hindrance is a principal factor

^aState Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000, P.R. of China. E-mail: chbh@lzu.edu.cn

^bKey Laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Lanzhou, 730000, P. R. of China

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Table 1 Screening of catalysts for Huisgen [3+2] cycloaddition reaction^a

Entry	Catalyst	Solvent	Additive (1 mol%)	Time (min)	Yield (%) ^b
1	Cu(PPh ₃) ₂ NO ₃	Neat	None	5	53
2	Cu(PPh ₃) ₃ Br	Neat	None	5	45
3	Cu(PPh ₃) ₃ Cl	Neat	None	5	50
4	[Cu(phen)(PPh ₃) ₂]NO ₃	Neat	None	5	97
5	Cu(PPh ₃) ₂ NO ₃	Neat	phen	5	93
6	Cu(PPh ₃) ₂ NO ₃	Neat	TBTA ^c	5	89
7	Cu(PPh ₃) ₂ NO ₃	Neat	<i>i</i> -Pr ₂ EtN	5	62
8	Cu(PPh ₃) ₂ NO ₃	Neat	Et ₃ N	5	65
9	Cu(PPh ₃) ₂ NO ₃	Neat	2,6-Lutidine	5	71
10	Cu(PPh ₃) ₂ NO ₃	Neat	2,2'-Bipyridine	5	79
11	[Cu(phen)(PPh ₃) ₂]NO ₃	Neat	None	2	96 ^d
12	[Cu(phen)(PPh ₃) ₂]NO ₃	Neat	None	3	97 ^e
13	Cu ₂ O	Neat	None	5	Trace
14	CuCl	Neat	None	5	Trace
15	CuBr	Neat	None	5	Trace
16	CuI	Neat	None	5	Trace
17	[Cu(phen)(PPh ₃) ₂]NO ₃	Toluene	None	5	89
18	[Cu(phen)(PPh ₃) ₂]NO ₃	H ₂ O	None	5	83
19	[Cu(phen)(PPh ₃) ₂]NO ₃	DMSO	None	5	7
20	[Cu(phen)(PPh ₃) ₂]NO ₃	THF	None	5	Trace

^a The reaction was carried out using **1a** (0.5 mmol) and **2a** (0.5 mmol) in the presence of a catalyst (0.005 mmol) in air. ^b Isolated yields after column chromatography or reduced pressure distillation. ^c TBTA = *tris*-(benzyltriazolylmethyl)amine. ^d The reaction temperature is 40 °C. ^e [Cu(phen)(PPh₃)₂]NO₃ complex (2 mol%).

Table 2 Substrate scope of terminal alkynes^a

Entry	R ¹	T (°C)	Time (min)	Yield (%) ^b
1	Phenyl (1a)	RT	5	97 (3a)
2	4-CH ₃ OC ₆ H ₄ (1b)	RT	3	93 (3b)
3	4- <i>n</i> -C ₅ H ₁₁ OC ₆ H ₄ (1c)	RT	3	97 (3c)
4	4-FC ₆ H ₄ (1d)	RT	4	98 (3d)
5	4-NO ₂ C ₆ H ₄ (1e)	RT	20	70 (3e)
		40	20	82 (3e)
6	Pyridine-2-yl (1f)	RT	3	95 (3f)
7	Thiophen-3-yl (1g)	RT	3	93 (3g)
8	Ferrocenyl (1h)	40	25	89 (3h)
9	<i>n</i> -C ₄ H ₉ (1i)	RT	25	45 (3i)
		40	25	81 (3i)
10	<i>t</i> -C ₄ H ₉ (1j)	40	25	80 (3j)
11	<i>n</i> -C ₈ H ₁₇ (1k)	40	20	95 (3k)
12	HOC(CH ₃) ₂ (1l)	40	12	90 (3l)

^a The reaction was carried out using **1** (0.5 mmol) and **2a** (0.5 mmol) in the presence of [Cu(phen)(PPh₃)₂]NO₃ (0.005 mmol) in air. ^b Isolated yields after column chromatography or reduced pressure distillation.

influencing the reaction rate. Longer reaction times were required for organic azides containing substituents at the 2-position (entries 3, 6 and 7).

By decreasing the amount of catalyst, we were able to achieve the click reaction with 100–250 ppm [Cu(phen)(PPh₃)₂]NO₃, but a significant drop in the yield and reaction rate were detected on lowering the catalyst content (Table 4). In the presence of 100 ppm [Cu(phen)(PPh₃)₂]NO₃, the click reaction of benzyl azide and phenylacetylene gives yields of 65% in 14 h at room temperature. At

Table 3 Substrate scope of organic azides^a

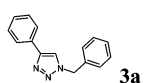
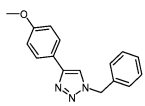
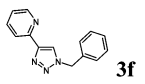
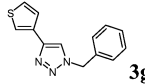
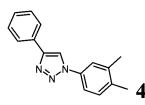
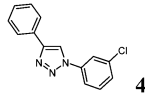
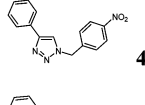
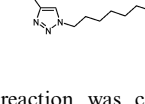
Entry	R ²	T (°C)	Time (min)	Yield (%) ^b
1	Phenyl (2a)	RT	3	96 (4a)
2	4-CH ₃ OC ₆ H ₄ (2b)	RT	6	97 (4b)
		40	2	97 (4b)
3	2-CH ₃ OC ₆ H ₄ (2c)	RT	25	80 (4c)
		40	15	81 (4c)
4	3,4-DiCH ₃ C ₆ H ₃ (2d)	RT	5	97 (4d)
5	3-ClC ₆ H ₄ (2e)	RT	5	98 (4e)
6	2-ClC ₆ H ₄ (2f)	40	25	96 (4f)
7	2-IC ₆ H ₄ (2g)	40	25	76 (4g)
8	4-NO ₂ C ₆ H ₄ CH ₂ (2h)	RT	3	91 (4h)
9	<i>n</i> -C ₅ H ₁₁ (2i)	RT	25	97 (4i)
		40	12	93 (4i)
10	<i>n</i> -C ₈ H ₁₇ (2j)	RT	8	94 (4j)
		40	4	93 (4j)
11	<i>n</i> -C ₁₂ H ₂₅ (2k)	RT	16	89 (4k)
		40	5	95 (4k)

^a The reaction was carried out using **1a** (0.5 mmol) and **2** (0.5 mmol) in the presence of [Cu(phen)(PPh₃)₂]NO₃ (0.005 mmol) in air. ^b Isolated yields after column chromatography or reduced pressure distillation.

40 °C the reaction takes place faster, and we obtained the triazole product with 85% yield after 14 h. A variety of functional groups were suitable substrates for the low catalyst loading condition, and the corresponding triazoles were synthesized with 52–85% yields.

In conclusion, we have developed a quick, environmentally friendly and economical catalytic system, [Cu(phen)(PPh₃)₂]NO₃ complex without solvent, for the [3+2] cycloaddition of azides

Table 4 [Cu(phen)(PPh₃)₂]₂NO₃-catalyzed synthesis of triazoles at low catalyst loadings^a

$\text{R}^1\text{-C}\equiv\text{C} + \text{R}^2\text{-N}_3 \xrightarrow[\text{rt, solvent-free}]{[\text{Cu}(\text{phen})(\text{PPh}_3)_2]\text{NO}_3 (100\text{-}250 \text{ ppm})}$		$\text{R}^1\text{-C}_5\text{H}_3\text{N}_3\text{-R}^2$		
Entry	Product	[Cu(phen)(PPh ₃) ₂]-NO ₃ (ppm)	Time (h)	Yield (%) ^b
1		100	14	65
		100	14	85 ^c
2		150	15	73
3		150	52	67
4		150	24	81
5		150	15	73
6		250	48	71
7		250	48	53
8		150	24	52

^a The reaction was carried out using **1** and **2** in the presence of [Cu(phen)(PPh₃)₂]₂NO₃ (100–250 ppm) at room temperature in air.

^b Isolated yields after column chromatography or reduced pressure distillation. ^c The reaction temperature is 40 °C.

and alkynes under click conditions. A series of 1,4-disubstituted-1,2,3-(NH)-triazoles were prepared readily in good to excellent yields within 2–25 min. This system is broad in scope and highly efficient even at very low catalyst loadings (down to 100 ppm). Low catalyst loading, short reaction time and solvent-free conditions make [Cu(phen)(PPh₃)₂]₂NO₃ an outstanding catalyst for CuAAC. Thus, the procedure reported in this work obeys the principles of click chemistry and green chemistry.

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