Solvent-free synthesis of 1,4-disubstituted 1,2,3-triazoles using a low amount of Cu(PPh₃)₂NO₃ complex[†]

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We have developed an environmentally friendly and highly efficient method for copper-catalyzed cycloaddition of organic azides and terminal alkynes under solvent-free conditions. The protocol uses the cheap and easy-to-prepare $Cu(PPh_3)_2NO_3$ complex as the catalyst.

Introduction

1.2.3-Triazoles are basically five-membered nitrogen heterocyclic compounds. They have tremendous applications in various research fields, including biological science,1 synthetic organic chemistry,² medicinal chemistry³ and material chemistry.⁴ Numerous synthetic methods for the preparation of 1,2,3triazole derivatives have been developed. Among them, Cu(I)catalyzed azide-alkyne cycloaddition (CuAAC) reaction is the most efficient way to assemble the 1,2,3-triazole ring because of its 100% atom economy, exclusive regioselectivity, wide substrate scope and mild reaction conditions. CuAAC was discovered by the groups of Sharpless⁵ and Meldal⁶ in 2002. Until now, a number of CuAAC procedures have been developed including the use of (1) Cu(II) salts/reductants,⁵ (2) Cu(I) salts directly,6 (3) Cu(II) salts,7 (4) Cu(I) complexes,8 (5) coppercontaining nanoparticles9 and (6) oxidation of copper metal turning to give Cu(I) species.¹⁰ These CuAAC procedures are efficient methods for the synthesis of 1,4-disubstituted 1,2,3triazoles, and the reaction mechanism is getting mature.5,8a,10,11 However, their corresponding catalytic systems have some drawbacks. They required reductants, a significant amount of expensive and difficult-to-prepare catalyst and organic solvent (such as methanol, acetone, toluene, dioxane, tert-butyl alcohol, dichloromethane and mixed solvents). Pericàs et al. described such reaction in the presence of tris(triazolyl)methanol-CuCl complexes.12 This system has been shown to be broad in scope and highly efficient under mild conditions, but the catalyst was not easy-to-prepare. Lipshutz et al. reported the efficient Cu/C-promoted click chemistry between organic azides and terminal alkynes,13 but solvents are required. Recently, the groups of Kiser¹⁴ and Fokin¹⁵ developed the transitionmetal-free methods for promoting the Huisgen cycloaddition reaction. The transition-metal-free systems are efficient and economic, but they also present some imperfections. Solvents

and other additives were also required and substrate scope was limited. In this paper, we report an environmentally friendly, efficient solvent-free system that allows the 1,3-dipolar Huisgen cycloaddition reaction of terminal alkynes with organic azides based on low catalyst loadings of $Cu(PPh_3)_2NO_3$ complex¹⁶ at room temperature.

Results and discussion

We initialized the copper-catalyzed optimum cycloaddition conditions using benzyl azide with phenylacetylene as the model substrates, as shown in Table 1. In this preliminary experiment, the Huisgen cycloaddition reaction was carried out in various solvents, with Cu(PPh₃)₂NO₃ complex (0.5 mol%) as a catalyst, in air at room temperature for 40 min. The reaction proceeded perfectly in toluene or water (Table 1, entries 1 and 2), but the yields decreased when the reaction was carried out in other solvents (Table 1, entries 3–7). It was very surprising that the reaction proceeded in excellent yields (96%) under solvent-free conditions (Table 1, entry 8). Considering

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

Ph —	\equiv + BnN ₃ ·	cat. (0.5 mo rt, solvent or	I%) neat N	'=\ `_N
	1a 2a		3a	N ^{Bn}
Entry	Catalyst	Solvent	Time/min	Yield (%) ^b
1	$Cu(PPh_3)_2NO_3$	Toluene	40	96
2	$Cu(PPh_3)_2NO_3$	H_2O	40	92
3	$Cu(PPh_3)_2NO_3$	DMSO	40	64
4	$Cu(PPh_3)_2NO_3$	CH_2Cl_2	40	14
5	$Cu(PPh_3)_2NO_3$	C_2H_5OH	40	32
6	$Cu(PPh_3)_2NO_3$	CH ₃ COCH ₃	40	21
7	$Cu(PPh_3)_2NO_3$	THF	40	19
8	$Cu(PPh_3)_2NO_3$	Neat	40	96
9	$Cu(PPh_3)_2NO_3$	Neat	35	96 ^c
10	$Cu(PPh_3)_2NO_3$	Neat	25	97 ^a
11	$Cu(PPh_3)_2NO_3$	Neat	15	92 ^e
12	CuI	Neat	60	Trace
13	CuBr	Neat	60	61
14	CuCl	Neat	60	42
15	Cu_2O	Neat	60	30
16	Cu(PPh ₃) ₃ Br	Neat	40	90
17	Cu(PPh ₃) ₃ Cl	Neat	40	91

^{*a*} The reaction was carried out using **1a** (1 mmol) and **2a** (1 mmol) in the presence of catalyst (0.005 mmol) in the solvent (2 ml) at room temperature in air. ^{*b*} Isolated yields after column chromatography or reduced pressure distillation. ^{*c*} Cu(PPh₃)₂NO₃ (1 mol%). ^{*d*} Cu(PPh₃)₂NO₃ (2.5 mol%). ^{*e*} The reaction temperature is 45 °C.

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Table 2 Substrate scope of terminal alkynes^a

$R^{1} \xrightarrow{\qquad} + Bn \xrightarrow{\qquad} N_{3} \xrightarrow{\qquad} Cu(PPh_{3})_{2}NO_{3} (0.5 \text{ mol}\%) \xrightarrow{\qquad} N_{N} \xrightarrow{\qquad} N$						
1	2a		3	;		
Entry	\mathbf{R}^1	Time	Product	Yield $(\%)^b$		
1	Phenyl (1a)	40 min	3a	96		
2	$4 - FC_{6}H_{4}$ (1b)	5 h	3b	80		
3	$4 - NO_2C_6H_4$ (1c)	10 h	3c	81		
4	$4 - n - C_5 H_{11} O C_6 H_4$ (1d)	15 h	3d	81		
5	Pyridine-2-yl (1e)	4 h	3e	86		
6	Thiophen-3-yl (1f)	40 min	3f	99		
7	Ferrocenyl (1g)	10 h	3g	70		
8	$n-C_4H_9$ (1 h)	20 h	3h	94		
9	$t-C_{4}H_{9}(1i)$	15 h	3i	95		
10	$n-C_8H_{17}(1j)$	1 h	3j	98		
11	$HOC(CH_2)_2$ (1k)	7 h	3k	95		

^{*a*} The reaction was carried out using 1 (1 mmol) and 2a (1 mmol) in the presence of Cu(PPh₃)₂NO₃ (0.005 mmol) at room temperature in air. ^{*b*} Isolated yields after column chromatography or reduced pressure distillation.

to develop an economic and environmentally friendly reaction, these solvent-free conditions are clearly the most favorable. We then investigated the activity of copper catalysts (including Cu(I) salts and Cu(I) complexes) in the Huisgen cycloaddition. The results show that Cu(I) salts displayed poor activity under these conditions (entries 12–15), in contrast to those with Cu(I) complexes. Cu(PPh₃)₂NO₃ complex provided the best result among Cu(I) complexes: the cycloaddition reached completion within 40 min (entry 8). Reaction time decreased gradually with increasing the catalyst loadings or reaction temperature (entries 9–11).

Encouraged by the efficiency of the reaction protocol described above, the scope of the reaction was examined with $Cu(PPh_3)_2NO_3$ (0.5 mol%) under solvent-free conditions at room temperature. Firstly, various terminal alkynes were investigated to be reacted with benzyl azide. As shown in Table 2, electron-rich and electron-poor alkynes were suitable cycloaddition partners (entries 2-4). The reaction of the heteroatomcontaining alkynes 1e, 1f also proceeded efficiently (entries 5, 6). Several aliphatic alkynes were suitable substrates to produce 1,4-disubstituted 1,2,3-triazoles in excellent yields (94-98%), as shown in entries 8-11. When ferrocenylacetylene was used, the yield was somewhat lower (entry 7). In addition, the crude products of 1,4-disubstituted 1,2,3-triazoles could be purified by reduced pressure distillation (except 3c and 3g). Reduced pressure distillation is simpler and more environmentally friendly than column chromatography. It was shown that the solventfree Cu(PPh₃)₂NO₃-catalyzed Huisgen cycloaddition reaction tolerates a variety of terminal alkynes. Notably, no direct correlation could be drawn between the electronic nature of the terminal alkynes and the outcome of the reaction. The longer chain aliphatic terminal alkynes can accelerate the process.

The substrate scope of organic azides was further investigated (Table 3). The results indicated that benzyl, alkyl, and aryl azides were successfully employed. The electronic properties of organic azides did not affect the yields. The steric hindrance and physical

Table 3 Substrate scope of organic azides^a

Ph —	Ξ + _R ² —N ₃ <u>Cu(</u> PF	² <u>h₃)₂NO₃ (0</u> solvent-fr	. <u>5 mol %)</u> ree	$\sim N \sim N^2 N^2 R^2$
Entry	R ²	Time	Product	• Yield (%) ^b
1	$4-NO_{2}C_{6}H_{4}CH_{2}$ (2a)	2 h	4 a	98
2	$n-C_5H_{11}$ (2b)	3 h	4b	94
3	$n-C_8H_{17}$ (2c)	40 min	4c	99
4	$n-C_{12}H_{25}$ (2d)	3 h	4d	90
5	Phenyl (2e)	20 min	4 e	98
6	$2-ClC_{6}H_{4}(2f)$	16 h	4 f	98
7	$3-ClC_{6}H_{4}(2g)$	30 min	4g	98
8	$4-ClC_6H_4$ (2h)	4 h	4h	57
9	$2 - NO_2C_6H_4$ (2i)	24 h	4 i	45
10	$3-NO_2C_6H_4(2j)$	5 h	4i	81
11	$2-BrC_{6}H_{4}(2k)$	5 h	4k	97
12	$2-IC_6H_4$ (21)	24 h	41	81
13	$2-CH_{3}OC_{6}H_{4}$ (2m)	24 h	4m	99
14	$4-CH_{3}OC_{6}H_{4}$ (2n)	2 h	4n	99
15	$2-CH_{3}C_{6}H_{4}(20)$	24 h	40	85
16	$3,4-CH_{3}C_{6}H_{3}(\mathbf{2p})$	1 h	4p	98

^{*a*} The reaction was carried out using **1a** (1 mmol) and **2** (1 mmol) in the presence of $Cu(PPh_3)_2NO_3$ (0.005 mmol) at room temperature in air. ^{*b*} Isolated yields after column chromatography or reduced pressure distillation.

state of organic azides are critical. Longer reaction times were required for organic azides containing substituents at the 2-position (entries 6, 9, 11, 12, 13, 15), and solid organic azides gave poorer results because they easily precipitated from alkyne (entries 8, 9, 10).

Encouraged by the high activity of this catalytic system, we further examined the possibility of decreasing the amount of metal used in this transformation (Table 4). Several 1,4-disubstituted 1,2,3-triazoles were synthesized at low catalyst loadings at reasonable reaction times. A variety of functional groups were suitable substrates for the conditions. The synthesis of **3a** showed the best results (entry 1): When the loading of catalyst was reduced to 50 ppm, **3a** was obtained in 81% yield at the reaction time of 24 h.

Taking into account the interest of avoiding storage and manipulation of organic azides, a one-pot process was explored through the reactions of alkyne, sodium azide and bromides (Table 5). When the bromides with benzyl were used, this tandem process performed nicely without other additive in water for 14 h at room temperature. Unfortunately, due to the inability of phenyl bromide to undergo SN2 reactions, only trace product was obtained when the bromide was employed. 1-Bromooctane also led a poor result, probably because of the insolubility of 1-bromooctane in water. Then, we attempted to add some quaternary ammonium salts as phase transfer catalyst to promote the heterogeneous reaction. The results showed that quaternary ammonium salts produced the desired product in 21-82% yield. The cetyl trimethyl ammonium bromide provided the best result at 60 °C (entry 6). When 1-bromopentane and 1-bromododecane were employed, the corresponding yields of 1,4-disubstituted 1,2,3-triazoles obtained were in 78% and 83%, respectively.

	$R^1 \longrightarrow R^2 \longrightarrow N_3 \longrightarrow Cu(PPh_3)_2NO_3 \longrightarrow R^1 \longrightarrow N_2 \longrightarrow N_3$					
	1 2					
Entry	Product	Cu(PPh ₃) ₂ NO ₃ /ppm	Time/h	Yield (%) ^b		
1	Ph N∵N√Ph 3a	1000 100 50	1 11 24	92 91 81		
2	^{Ph} ∕→ N _{°N} N- _{Ph} 4e	200	24	80		
3	Ap	200	48	62		
4		200	72	35		
5	NNN CI 4g	200	40	68		
6	N N N N N N Ph 3e	200	48	81		
7	s Nin North 3f	200	48	80		

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

^{*a*} The reaction was carried out using 1 and 2 in the presence of $Cu(PPh_3)_2NO_3$ (50–1000 ppm) at room temperature in air. The reaction scale is about 5 mmol. ^{*b*} Isolated yields after column chromatography or reduced pressure distillation.

Table 5 On	e-pot azide	formation	plus	CuAAC	reaction	mediated	by	Cu(PPh ₃) ₂ N	IO_3^a
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$R^{2}-Br + NaN_{3} + Ph \longrightarrow \frac{Cu(PPh_{3})_{2}NO_{3}(0.5 \text{ mol}\%)}{H_{2}O, 14h, PTC(10 \text{ mol}\%)} \xrightarrow{Ph}_{N \times N} N \times R^{2}$						
Entry	\mathbb{R}^2	PTC ^b	T/°C	Yield (%) ^c		
1	$C_6H_4CH_2$	None	RT	97		
2	$4-NO_2C_6H_4CH_2$	None	RT	96		
3	Ph	None	RT	Trace		
4	$n-C_8H_{17}$	None	RT	Trace		
5	$n-C_8H_{17}$	Cetyl trimethyl ammonium bromide	RT	30 57 ^d		
6	$n-C_8H_{17}$	Cetyl trimethyl ammonium bromide	60	82		
7	$n-C_8H_{17}$	Tetrabutyl ammonium bromide	60	41		
8	$n-C_8H_{17}$	Tetrabutyl ammonium iodide	60	35		
9	$n-C_8H_{17}$	Tetraethyl ammonium Bromide	60	42		
10	$n-C_8H_{17}$	Benzyl triethyl ammonium chloride	60	21		
11	$n-C_5H_{11}$	Cetyl trimethyl ammonium bromide	60	78		
12	$n-C_{12}H_{25}$	Cetyl trimethyl ammonium bromide	60	83		

^{*a*} The reaction was carried out using bromide (1 mmol), sodium azide (1 mmol), phenylacetylene (1 mmol) and PTC (0.1 mmol) in the presence of Cu(PPh₃)₂NO₃ (0.005 mmol) in water. ^{*b*} PTC (phase transfer catalyst). ^{*c*} Isolated yields after column chromatography. ^{*d*} PTC (25 mol%).

Conclusion

In summary, an environmentally friendly, economical and efficient method was successfully developed for synthesizing 1,4-disubstituted 1,2,3-triazoles based on low catalyst loadings of Cu(PPh₃)₂NO₃ complex under solvent-free conditions at room temperature. This system is broad in scope and highly efficient even at very low catalyst loadings (down to 50 ppm). In addition, the catalyst could be applied to the one-pot synthesis of triazoles from aliphatic bromides, alkyne and sodium azide. The catalyst Cu(PPh₃)₂NO₃ is cheap and easy-to-prepare. Thus, the procedure reported in this work is in accordance with the principles of click chemistry and green chemistry.

Experimental

All reagents were commercially available without further purification. Flash column chromatography was performed on silica gel (200–300 mesh) and thin layer chromatography (TLC) analyses were performed on commercial silica gel plates (60 F254).

General procedures for copper-catalyzed cycloaddition of organic azides with alkynes to triazoles

Alkyne (1 mmol), azide (1 mmol) and $Cu(PPh_3)_2NO_3$ (0.005 mmol, 3.28 mg) were added to a flask with a stir bar, and the mixture was stirred at room temperature (~25 °C) without exclusion of air under solvent-free conditions. When the starting materials became solid, the reaction time was recorded and the product was purified. Two methods were used to purify the product. For the first method, the mixture was diluted with ethyl acetate and filtered. The filtrate was removed under reduced pressure to get the crude product, which was further purified by silica gel chromatography (petroleum ether/ethyl acetate as eluent) to yield corresponding triazole. For another purification method, the mixture was diluted with ethyl acetate and filtered. The filtrate was removed under reduced pressure to get the pure product. The second method was only applied to the triazoles whose starting materials are liquid.

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