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An efficient approach to homocoupling of terminal alkynes: Solvent-free synthesis of 1,3-diynes using catalytic Cu(II) and base†

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We report an environmentally friendly, efficient method for transforming terminal acetylenes into 1,3-diynes based on catalytic amounts of a Cu(II) salt and base under solvent-free conditions. The developed process conforms to the principles of 'green' chemistry and addresses the shortage of such methods for the synthesis of 1,3-diynes. The reaction is quite general and results in good yields. Interestingly, the system also allows the synthesis of unsymmetric 1,3-diynes by cross-coupling of two different terminal alkynes. Finally, the catalyst can also be recycled.

Introduction

One of the challenges facing chemists this century is to develop new transformations that are not only efficient, selective, and high-yielding but that are also environmentally benign.[1] During the last decade, the topic of 'green' chemistry has received increasing attention.[1,2] 'Green' chemistry aims at the total elimination (or at least the minimization) of waste, and the implementation of sustainable processes.[1a] The utilization of nontoxic chemicals, renewable materials and solvent-free conditions are the key issues in a green synthetic strategy. In the present work, we describe a green approach towards the synthesis of conjugate 1,3-diyne.

Conjugate 1,3-diyne derivatives are very important materials in the fields of biology and materials science, because they can be converted into various structural entities, especially substituted heterocyclic compounds.[3] Traditional methods for the synthesis of 1,3-diynes include Glaser oxidative dimerization of terminal alkynes,[4a] various improved Glaser oxidative homocoupling reactions of terminal alkynes,[4b–e] and Sonogashira coupling.[4f] The catalyst system used commonly is the Pd,[5] which involves Cu(I) salts as co-catalyst. Although Pd catalysts play a crucial role because of their mild, efficient and selective properties, they are expensive and often require phosphine or amine reagents.[5e,5g,6] To address this, several groups have reported homocoupling reactions of terminal alkynes using a Pd-free catalytic system.[7] For example, D. F. Li *et al.* described the reaction in the presence of CuI/I₂,[8] and H. F. Jiang *et al.* reported the Cu(II)-promoted oxidative homocoupling reaction of terminal alkynes

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in supercritical carbon dioxide.[9] These Pd-free catalytic systems are efficient and economic, but their imperfections include the requirements of stoichiometric amounts of amine reagents, high pressure, high temperature, utilization of a co-catalyst and an oxygen atmosphere.[5h,7b,7c,10] Moreover, it should be pointed out that the classical syntheses of conjugate 1,3-diynes (including the Pd-catalyzed and the Pd-free systems) generally involve organic solvents such as methanol, acetone, pyridine, methyl cellosolve (2-methoxyethanol) and toluene. Use of organic solvents is environmentally unfriendly, and so it is highly desirable to develop more environmentally friendly and economic methodologies for synthesizing conjugate 1,3-diynes. To achieve this, we report an environmentally friendly, economic, efficient and simple solvent-free system that allows the homocoupling reactions of terminal alkynes based on catalytic amounts of CuCl₂ and triethylamine at 60 °C in air. The method is also useful for the synthesis of unsymmetric 1,3-diynes by cross-coupling of two different terminal alkynes. The results are summarized below.
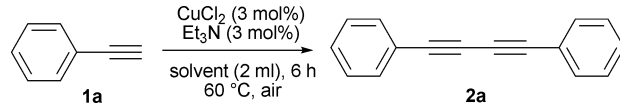
Results and discussion

In order to identify the optimal reaction conditions, phenylacetylene was chosen as a test substrate. In this preliminary experiment, the homocoupling of phenylacetylene was carried out in various solvents, with CuCl₂ (3 mol%) as a catalyst and Et₃N (3 mol%) as a base, in air at 60 °C for 6 h (Table 1). It was found that the reaction proceeded perfectly in toluene or benzene (Table 1, entries 1 and 2), but that the yields decreased when the reaction was carried out in other solvents (Table 1, entries 3–11). However, the reaction surprisingly proceeded in excellent yields (>96%) under solvent-free conditions (Table 1, entry 12). The pure product was purified by column chromatography or reduced-pressure distillation. Considering our goal of an economic and environmentally friendly reaction, these solvent-free conditions are clearly the most favorable.

Then we examined the influence of the catalysts on the yields. The reaction did not occur without a catalyst (Table 2, entry 1), and CuCl₂ was more efficient than other Cu(0), Cu(I) and Cu(II) catalysts (Table 2, entries 2–12). It was noted that Cu(OH)ₓ/TiO₂ produced the desired product in 65% yield in the absence of base at 100 °C under an oxygen atmosphere (entry 2).

In the third set of experiments, we performed the reaction with various bases under solvent-free conditions in air (Table 3). As can be seen, the reaction could not be performed without a base (Table 3, entry 1). Organic bases including primary amines, secondary amines and tertiary amines were more effective than inorganic bases, with triethylamine being the best. There was
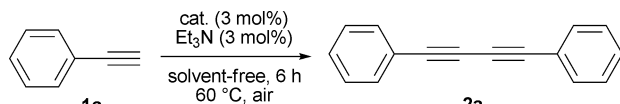
Table 1 Preliminary survey of solvents for the homocoupling reaction of phenylacetylene catalyzed by $CuCl_2$[a]

$$1a \xrightarrow[\text{60 °C, air}]{\substack{CuCl_2 \text{ (3 mol\%)} \\ Et_3N \text{ (3 mol\%)} \\ \text{solvent (2 ml), 6 h}}} 2a$$

Entry	Catalyst	Solvent	Yield (%)[b]
1	$CuCl_2$	Toluene	99
2	$CuCl_2$	Benzene	98
3	$CuCl_2$	Water	3
4	$CuCl_2$	Methanol	14
5	$CuCl_2$	THF	16
6	$CuCl_2$	Acetonitrile	12
7	$CuCl_2$	Ethanol	8
8	$CuCl_2$	DMF	40
9	$CuCl_2$	DMSO	42
10	$CuCl_2$	Dioxane	72
11	$CuCl_2$	Acetone	25
12	$CuCl_2$	None	>96

[a] The reaction was carried out using **1a** (1 mmol) and Et_3N (0.03 mmol) in the presence of $CuCl_2$ (0.03 mmol) in the solvent (2 ml) at 60 °C in air. [b] Isolated yields after column chromatography.
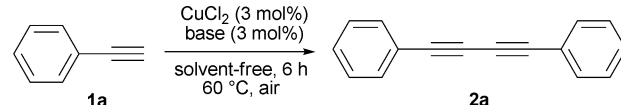
Table 2 Screening of catalysts for the homocoupling reaction of phenylacetylene[a]

$$1a \xrightarrow[\text{60 °C, air}]{\substack{\text{cat. (3 mol\%)} \\ Et_3N \text{ (3 mol\%)} \\ \text{solvent-free, 6 h}}} 2a$$

Entry	Catalyst	Yield (%)[b]
1	None	0
2	$Cu(OH)_x/TiO_2$[c]	65
3	CuCl	16
4	$CuBr_2$	8
5	$Cu(OAc)_2 \cdot H_2O$	7
6	CuI	Trace
7	$Cu(OTf)_2$	7
8	Cu	4
9	$Cu(PPh_3)_3Cl$	2
10	$CuCl_2 \cdot 2H_2O$	49
11	$Cu(PPh_3)_2NO_3$	15
12	$Cu(acac)_2$	Trace

[a] The reaction was carried out using **1a** (1 mmol) and Et_3N (0.03 mmol) in the presence of catalyst (0.03 mmol) at 60 °C in air. [b] Isolated yields after column chromatography. [c] $Cu(OH)_x/TiO_2$ (Cu = 5 mol%).

Table 3 Screening of bases for the homocoupling reaction of phenylacetylene catalyzed by $CuCl_2$[a]

$$1a \xrightarrow[\text{60 °C, air}]{\substack{CuCl_2 \text{ (3 mol\%)} \\ \text{base (3 mol\%)} \\ \text{solvent-free, 6 h}}} 2a$$

Entry	Base	Yield (%)[b]
1	None	0
2	Triethylamine	>96
3	Diethylamine	69
4	Pyridine	12
5	n-butylamine	90
6	K_2CO_3	24
7	KO^tBu	10
8	Piperidine	38
9	Diisopropylamine	35
10	tert-Butylamine	18
11	NaOH	14
12	TMEDA	70[c]
13	$K_3PO_4 \cdot 3H_2O$	7

[a] The reaction was carried out using **1a** (1 mmol) and base (0.03 mmol) in the presence of $CuCl_2$ (0.03 mmol) at 60 °C in air. [b] Isolated yields after column chromatography. [c] TMEDA = tetramethylethylenediamine.

Table 4 Solvent-free synthesis of various conjugate 1,3-diynes by $CuCl_2$[a]

$$1 \xrightarrow[\text{60 °C, air}]{\substack{CuCl_2 \text{ (3 mol\%)} \\ Et_3N \text{ (3 mol\%)} \\ \text{solvent-free}}} 2$$

Entry	R	Time/h	Product	Yield (%)[b]
1	Phenyl (**1a**)	6	**2a**	>96
2	$4\text{-}CH_3OC_6H_4$ (**1b**)	6	**2b**	99
3	$3\text{-}CH_3C_6H_4$ (**1c**)	6	**2c**	>98
4	$4\text{-}FC_6H_4$ (**1d**)	6	**2d**	80
5	Naphthalen-1-yl (**1e**)	6	**2e**	88
6	$2\text{-}ClC_6H_4$ (**1f**)	6	**2f**	85
7	$3\text{-}NH_2C_6H_4$ (**1g**)	4	**2g**	50
8	$4\text{-}n\text{-}C_5H_{11}OC_6H_4$ (**1h**)	6	**2h**	>98
9	Thiophen-3-yl (**1i**)	6	**2i**	90
10	Pyridine-2-yl (**1j**)	4	**2j**	70
11	$BrCH_2$ (**1k**)	6	**2k**	60
12	$n\text{-}C_4H_9$ (**1l**)	6	**2l**	75
13	$HOC(CH_3)_2$ (**1m**)	6	**2m**	40
14	$HOCH_2$ (**1n**)	6	**2n**	45
15	Ferrocenyl (**1o**)	10	**2o**	99[c]

[a] The reaction was carried out using RC≡CH (1 mmol) and Et_3N (0.03 mmol) in the presence of $CuCl_2$ (0.03 mmol) at 60 °C in air. [b] Isolated yields after column chromatography. [c] The reaction was carried out using **1o** (1 mmol) and Et_3N (2 mmol) in the presence of $CuCl_2$ (0.03 mmol) at 100 °C in air for 10 h.

also a good yield with n-butylamine as base (Table 3, entry 5). Therefore, the optimal solvent-free system for this reaction involves Et_3N (3 mol%) and $CuCl_2$ (3 mol%).

Encouraged by the efficiency of the reaction protocol described above, we investigated the substrate scope. A variety of terminal alkynes including aromatic and aliphatic acetylenes were tested under the optimized conditions. The results show that the solvent-free $CuCl_2$-catalyzed homocoupling reaction tolerates a variety of functional groups. As shown in Table 4, the catalytic oxidative homocoupling of phenylacetylenes **1a–h**, which contain electron-donating as well as electron-withdrawing substituents, proceeded readily to afford the corresponding diyne derivatives **2a–h** in 50–99% yields (entries 1–8). The reaction of the heteroatom-containing alkyne **1i** also proceeded efficiently (entry 9), but the desired product of the heteroatom-

containing alkyne **1j** was isolated in 70% yield, due to the partial carbonization of the substrate (entry 10). When aliphatic acetylenes were used, the yields were somewhat lower (entries 11 and 12). Alkynes based on propargylic alcohols also gave the corresponding diynes, but the yields were low (entries 13 and 14). Interestingly, we successfully extended the procedure to higher-boiling alkynes such as ferrocenylacetylene, and the yield of the obtained product being 99% (entry 15). In addition, the crude products of symmetric 1,3-diynes can be purified by

Table 5 Solvent-free synthesis of various unsymmetric conjugate 1,3-diynes by catalytic amounts of Cu(II) salt and base[a]

$$R_1\text{—}\equiv\text{—} + \equiv\text{—}R_2 \xrightarrow[\substack{\text{solvent-free 10 h} \\ 60\,°C, \text{ air}}]{\substack{\text{CuCl}_2\ (3\ \text{mol\%}) \\ \text{Et}_3\text{N}\ (3\ \text{mol\%})}} R_1\text{—}\equiv\text{—}\equiv\text{—}R_2$$

Entry	R_1	R_2	Product	Yield (%)[b]
1	4-CH$_3$OC$_6$H$_4$	C$_6$H$_5$	**3a**	70
2	HOCH$_2$	C$_6$H$_5$	**3b**	35
3	4-CH$_3$OC$_6$H$_4$	3-CH$_3$C$_6$H$_4$	**3c**	55
4	4-n-C$_5$H$_{11}$OC$_6$H$_4$	C$_6$H$_5$	**3d**	72
5	HOC(CH$_3$)$_2$	C$_6$H$_5$	**3e**	32
6	4-CH$_3$OC$_6$H$_4$	Thiophen-3-yl	**3f**	56
7	n-C$_4$H$_9$	C$_6$H$_5$	**3g**	Trace
8	n-C$_4$H$_9$	4-CH$_3$OC$_6$H$_4$	**3h**	Trace

[a] The reaction was carried out using R^{1}C≡CH (0.5 mmol), R^{2}C≡CH (3 mmol) and Et$_3$N (0.03 mmol) in the presence of CuCl$_2$ (0.03 mmol) at 60 °C in air. [b] Isolated yields after column chromatography.

reduced pressure distillation (except 1,4-diferrocenylbuta-1,3-diyne **2o**) – reduced pressure distillation is simpler and more environmentally friendly than column chromatography.

The cross-coupling of two different terminal alkynes was also investigated in the catalytic system by using an excess of one of the terminal alkyne substrates. As shown in Table 5, unsymmetric 1,3-diynes were produced in 32–72% yield. Phenylacetylene **1a** successfully cross-coupled with some alkynes including alkoxy alkynes (entries 1 and 4), propargylic alcohols (entries 2 and 5); *p*-methoxyphenylacetylene **1b** could also be cross-coupled with aromatic acetylenes (entries 1 and 3) and a heteroatom-containing alkyne (entry 6), although the yields were somewhat lower. The reaction between **1l** and **1a** (or **1b**) only gives trace product (entries 7 and 8). It should be noted that the crude products of unsymmetric 1,3-diynes only can be purified by column chromatography – reduced pressure distillation does not work for these compounds.

Finally, we examined the recovery and reuse of CuCl$_2$. The catalyst can be recovered by filtration, acidification, and drying under vacuum, and can then be reused. After five recycles, the activity of the recovered catalyst decreased slightly to 85%. The average catalyst recovery was about 80% (Table 6).

Table 6 Recovery and reuse of CuCl$_2$

$$\mathbf{1a} \xrightarrow[\substack{\text{solvent-free, 6 h} \\ 60\,°C, \text{ air}}]{\substack{\text{CuCl}_2\ (3\ \text{mol\%}) \\ \text{Et}_3\text{N}\ (3\ \text{mol\%})}} \mathbf{2a}$$

Run	Product yield (%)	Catalyst recovery (%)
1	96	75
2	90	78
3	90[b]	80
4	88[b]	82
5	85[b]	85

[a] Isolated yields after reduced-pressure distillation. [b] The reaction time was 10 h.

Conclusion

In conclusion, we have developed an environmentally friendly, economical and efficient method for transforming terminal acetylenes into 1,3-diynes under solvent-free conditions with catalytic amounts of CuCl$_2$ and triethylamine. The procedure is suitable for many substrates, and various conjugate 1,3-diynes can be produced conveniently with excellent yields. This catalytic system can also be used for the synthesis of unsymmetrical 1,3-diynes, although the yields are not perfect. The catalyst can also be recycled five times with only a moderate reduction in activity, making it acceptable for industrial-scale production.

Experimental

General

Solvents were dried and degassed by standard methods, and all alkynes are readily available. Flash column chromatography was performed using silica gel (300–400 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 200–400 mesh silica gel impregnated with a fluorescent indicator (254 nm).

Typical experimental procedure for the homocoupling reaction under solvent-free conditions

Typical reaction procedure: to a mixture of CuCl$_2$ (3.0 mol%) and Et$_3$N (3.0 mol%), phenylacetylene (1.0 mmol) was added. The mixture was stirred at 60 °C under air for 6 h.

Purification of crude product by Method 1. After cooling to room temperature, the mixture was diluted with ethyl acetate and filtered. The filtrate was removed under reduced pressure to give the crude product, which was further purified by silica gel chromatography (petroleum ether–ethyl acetate as eluent) to yield the corresponding 1,3-diynes.

Purification of crude product by Method 2. After cooling to room temperature, the mixture was diluted with dichloromethane and filtered. The filtrate was washed with water and the organic phase was dried using MgSO$_4$. Dichloromethane and unreacted phenylacetylene were removed under reduced pressure to give the purified product.

Acknowledgements

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