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$CuPy_2Cl_2$: A Novel and Efficient Catalyst for Synthesis of Propargylamines Under the Conventional Method and Microwave Irradiation

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Abstract: $CuPy_2Cl_2$ is an efficient catalyst for the preparation of propargylamines via three-component coupling reaction of aromatic aldehydes, amines, and aromatic alkynes stirred at 95 °C without using any solvent to afford the corresponding products in good yields. The reaction mixture was irradiated at 450 W in a microwave oven to furnish the expected products in excellent yields.

Keywords: $CuPy_2Cl_2$, propargylamine, solvent free, three-component coupling

INTRODUCTION

One-pot multicomponent coupling reactions are very interesting and attractive in organic synthesis because they introduce several elements of diversity into a molecule in a single step.[1] The best example is three-component coupling of aldehydes, amines, and alkynes [A^3 coupling] via CH activation, which has received great attention in recent years.[2] The resultant propargylamines are versatile synthetic intermediates for organic synthesis to construct important natural products, therapeutic drug molecules, and biologically active compounds[3] such

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as conformationally restricted peptide isosters, oxotremorine analogs, and β-lactams. Several methods for the synthesis of propargylamines using various types of reagents have been developed, mainly transition-metal catalysts able to carryout A^3 coupling reactions, including the Ag(I) salts,[4] Au(I)/Au(III) salts,[5] Au(III)–salen complexes,[6] Cu(I) salts,[7] and Cu/Ru bimetallic system[8] under homogeneous conditions. The available methods have a number of drawbacks, such as long reaction times and low yields. Moreover, most of the reactions need to be performed under an inert atmosphere, and these reactions often proceed slowly in water. Some of the catalysts are very expensive. But, all of these systems suffer from the loss of the precious catalysts at the end of the reaction. To overcome these limitations, we found a new catalyst for the synthesis of propargylamines, $CuPy_2Cl_2$. The catalyst is stable in air and water, soluble in water, immiscible in common organic solvents, and reusable and has high thermal stability. In addition, its toxicity is low, and it can effectively promote some of the organic reactions such as the Pechmann condensation[9] and Biginelli reaction[10] in good yields.

On the other hand, microwave irradiation has been extensively used for the rapid synthesis of a variety of heterocyclic compounds, because of short reaction times and increase of yields with high purity. Microwave reactions are believed to meet the demands of green chemistry.[11] In our earlier communications, we reported several organic transformations in a domestic microwave oven.[12]

RESULTS AND DISCUSSION

Herein, we report for the first time $CuPy_2Cl_2$ as an efficient catalyst for the three-component coupling of aldehyde, alkyne, and amine to generate propargylamines, without using any other cocatalyst or additives. We examined the reaction process for the three-component coupling reaction of benzaldehyde, phenylacetylene, and morpholine in the presence of the catalyst. In method A [microwave (MW) irradiation], the reaction mixture was irradiated in a domestic microwave oven at 300 W over 30-s intervals in an open vessel for 5 min. The progress of the reaction was checked by thin-layer chromatograohy (TLC). At 300 W only 50% of the reaction was completed, whereas at 450 W, the reaction successfully completed within 2 min. In method B (conventional), when the reaction was carried out at 55 to 60 °C, no progress was observed; at 60 to 80 °C, only a part of the reaction proceeded. At 95 °C, a single product was obtained. Comparatively, MW irradiation is more advantageous than the conventional method, because it required a shorter reaction time and generated good yields with high purity.

We have carried out the reaction with varies amines such as diethyl amine, morpholine, piperdine, and piperzine. Except for piperzine, other amines displayed good activity and gave excellent yields. In this article, we report simple and ordinary reaction conditions. Therefore, we believe that our procedure is more suitable for the synthesis of propargylamines than the literature methods.

EXPERIMENTAL

The progress of the reaction was monitored by TLC. ^{1}H NMR spectra was measured on a Varian Gemini 200-MHz spectrometer using TMS as internal standard. The C, H, and N analysis of the compound was done on a Carlo Erba model EA1108. Mass spectra were recorded on a Jeol JMS D-300 spectrometer.

Method A (Microwave Irradiation)

A mixture of aldehyde (1 mmol), amine (1.5 mmol), alkyne (1.5 mmol), and $CuPy_2Cl_2$ (0.01 mmol) was placed in an open vessel in a microwave oven and irradiated at 450 W for an appropriate time (Table 1). Completion of the reaction was confirmed by TLC. After completion of the reaction, reaction contents were cooled to room temperature, water (2 ml) was added and then extracted with EtOAc, and the product was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel (100–200) using hexane–EtOAc (6:2) mixture as eluent to afford the expected product as a light red oil. The pure product was confirmed by spectroscopic data.

Method B (Conventional Method)

To a mixture of aldehyde (1 mmol), amine (1.5 mmol), and alkyne (1.5 mmol), $CuPy_2Cl_2$ (0.01 mmol) was added. The reaction contents were stirred at 95 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, water (2 ml) was added and then extracted with EtOAc, and the product was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude product was purified by chromatography on silica-gel (100–200) using a hexane–EtOAc (6:2) mixture as eluent to afford the expected product as a light red oil. The pure products were confirmed by spectroscopic data.

Table 1. $CuPy_2Cl_2$–Catalyzed three-component coupling of aldehyde, alkyne, and amine

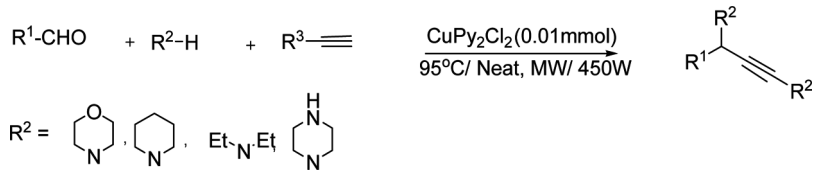
Entry	R^1	Amine	R^2	Method A		Method B	
				Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]
1	Ph	Morpholine	Ph	2	92	40	90
2	4-ClC_6H_4	Morpholine	Ph	3	91	40	88
3	4-MeC_6H_4	Morpholine	Ph	3	89	55	87
4	4-$MeOC_6H_4$	Morpholine	Ph	3	90	50	89
5	4-BrC_6H_4	Morpholine	Ph	4	92	50	91
6	4-NO2C_6H_4	Morpholine	Ph	4.5	54	75	57
7	Ph	Piperidine	Ph	3	94	45	91
8	4-MeC_6H_4	Piperidine	Ph	3	90	60	88
9	4-$MeOC_6H_4$	Piperidine	Ph	4	91	55	89
10	4-ClC_6H_4	Piperidine	Ph	3	93	45	90
11	4-BrC_6H_4	Piperidine	Ph	5	93	50	91
12	Ph	Piperzine	Ph	2	92	35	91
13	Ph	Diethyl amine	Ph	3	92	50	90
14	4-ClC_6H_4	Diethyl amine	Ph	3	90	55	87
15	4-MeC_6H_4	Diethyl amine	Ph	3	91	55	87
16	4-$MeOC_6H_4$	Diethyl amine	Ph	7	52	120	45

[a]Yields refer to isolated pure products and were characterized by comparison of NMR and mass spectral data with those of authentic samples.

Spectral Data

4-(1,3-Diphenylprop-2-ynyl)morpholine (entry1):

^1H NMR ($CDCl_3$): $\delta = 7.45$–7.60 (m, 5H), 7.25–7.39 (m, 5H), 4.75 (s, 1H), 3.60–3.78 (m, 4H), 2.50–2.70 (t, 4H); EI-MS: $m/z = 277$ (M^+). Calcd. for $C_{19}H^{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.32; H, 6.94; N, 5.01.



Scheme 1. $CuPy_2Cl_2$–catalyzed synthesis of propargylamines.

4-(1-(4-Chlorophenyl)-3-phenylprop-2-ynyl)morpholine (entry 2):

^{1}H NMR ($CDCl_3$): $\delta = 7.42$–7.56 (m, 4H), 7.23–7.39 (m, 5H), 4.81 (s, 1H), 3.65–3.81 (m, 4H), 2.55–2.74 (t, 4H); EI-MS: $m/z = 311$ (M^+). Calcd. for $C_{19}H_{18}ClNO$: C, 73.19; H, 5.82; N, 4.49. Found: C, 73.22; H, 5.77; N, 4.47.

4-(3-Phenyl-1-p-tolylprop-2-ynyl)morpholine (entry 3):

^{1}H NMR ($CDCl_3$): $\delta = 7.47$–7.61 (m, 4H), 7.28– 7.41(m, 5H), (s, 1H), 3.63–3.75 (m, 4H), 2.53–2.69 (m, 4H), 2.31 (s, 3H); EI-MS: $m/z = 291$ (M^+). Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.39; H, 7.28; N, 4.78.

4-(1-(4-Bromophenyl)-3-phenylprop-2-ynyl)morpholine (entry 5):

^{1}H NMR ($CDCl_3$): $\delta = 7.59$–7.71 (m, 4H), 7.37–7.49 (m, 5H), 4.65 (s, 1H), 3.59–3.75 (m, 4H), 2.52–2.69 (m, 4H); EI-MS: $m/z = 356$ (M^+). Calcd. for $C_{19}H_{18}BrNO$: C, 64.06; H, 5.09; N, 3.93. Found: C, 64.08; H, 5.03; N, 3.95.

4-(1-(4-Nitrophenyl)-3-phenylprop-2-ynyl)morpholine (entry 6): ^{1}H NMR ($CDCl_3$): $\delta = 7.60$–7.69 (m, 2H), 7.50–7.57 (m, 2H), 7.35–7.45 (m, 5H), 4.68 (s, 1H), 3.65–3.81 (m, 4H), 2.57–2.75 (t, 4H); EI-MS: $m/z = 322$ (M^+). Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.82; H, 5.61; N, 8.62.

1-(1,3-Diphenylprop-2-ynyl)piperidine (entry 7):

^{1}H NMR ($CDCl_3$) $\delta = 7.62$–7.68 (m, 2H), 7.49–7.57 (m, 2H),7.31–7.45 (m, 6H), 4.80(s, 1H), 2.56 (t, 4H, $J =$ 5.4 Hz), 1.55–1.65 (m, 4H), 1.44–1.53 (m, 2H); EI-MS: $m/z = 275$ (M^+). Calcd. for $C_{20}H_{21}N$: C, 87.23; H, 7.69; N, 5.09. Found: C, 87.25; H, 7.72; N, 5.05.

1-(3-Phenyl-1-p-tolylprop-2-ynyl)piperidine (entry 8):

^{1}H NMR ($CDCl_3$) $\delta = 7.62$–7.69 (m, 2H), 7.50–7.58 (m, 2H), 7.37–7.47 (m, 5H), 4.95 (s, 1H), 2.55 (t, 4H, $J =$ 5.4 Hz), 2.10 (s, 3H), 1.57–1.75 (m, 4H), 1.41–1.52 (m, 2H); EI-MS: $m/z = 289$ (M^+). Calcd. for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.12; H, 8.03; N, 4.81.

1-(1-(4-Methoxyphenyl)-3-phenylprop-2-ynyl)piperidine (entry 9):

^{1}H NMR ($CDCl_3$) $\delta = 7.68$–7.72 (m, 2H), 7.54–7.57 (m, 2H) 7.41–7.49 (m, 5H), 4.82 (s, 1H), 3.81 (s, 3H) 2.59 (t, 4H, $J = 5.4$ Hz), 1.59–1.68 (m, 4H), 1.48–1.55 (m, 2H); EI-MS: $m/z = 305$ (M^+). Calcd. for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.55; H, 7.61; N, 4.54.

1-(1-(4-Bromophenyl)-3-phenylprop-2-ynyl)piperidine (entry 11):

^{1}H NMR ($CDCl_3$) $\delta = 7.65$–7.75 (m, 2H), 7.52–7.60 (m, 2H),7.32–7.47 (m, 5H), 4.85 (s, 1H), 2.61 (t, 4H, $J = 5.4$ Hz), 1.60–1.69 (m, 4H), 1.51–1.58 (m, 2H); EI-MS: $m/z = 354$ (M^+). Calcd. for $C_{20}H_{20}BrN$: C, 67.80; H, 5.69; N, 3.95. Found: C, 67.83; H, 5.62; N, 3.91.

N,N-Diethyl-1,3-diphenylprop-2-yn-1-amine (entry 12):

^{1}H NMR ($CDCl_3$) $\delta = 7.65$–7.69 (m, 2H), 7.47–7.55 (m, 2H),7.21–7.38 (m, 6H), 5.03 (s, 1H), 2.51–2.68 (m, 4H), 1.08 (t, 6H, $J = 7.1$ Hz); EI-MS: $m/z = 263$ (M^+). Calcd. for $C_{19}H_{21}N$: C, 86.65; H, 8.04; N, 5.32. Found: C, 86.61; H, 8.09; N, 5.28.

1-(4-Chlorophenyl)-N,N-diethyl-3-phenylprop-2-yn-1-amine (entry 13):

^{1}H NMR ($CDCl_3$) $\delta = 7.61$–7.66 (m, 2H), 7.48–7.55 (m, 2H),7.30–7.44 (m, 5H), 4.99 (s, 1H), 2.48–2.67 (m, 4H), 1.07 (t, 6H, $J =$ 7.1 Hz); EI-MS: $m/z = 297$ (M^+). Calcd. for $C_{19}H_{20}ClN$: C, 76.62; H, 6.77; N, 4.70. Found: C, 76.65;H, 6.75; N, 4.73.

N,N-Diethyl-3-phenyl-1-p-tolylprop-2-yn-1-amine (entry 14):

^{1}H NMR ($CDCl_3$) $\delta = 7.53$–7.64 (m, 4H), 7.31–7.39 (m, 3H),7.14–7.21 (m, 2H), 5.04(s, 1H), 2.51–2.74 (m, 4H), 2.37 (s, 3H), 1.13(t, 6H, $J = 7.1$ Hz); EI-MS: $m/z = 277$ (M^+). Calcd. for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.54;H, 8.39; N, 5.08.

N,N-Diethyl-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-amine (entry 15):

^{1}H NMR ($CDCl_3$) $\delta = 7.56$–7.59 (m, 2H), 7.48–7.54 (m, 2H),7.29–7.38 (m, 3H), 6.86–6.89 (m, 2H), 4.98 (s, 1H), 3.81 (s, 3H), 2.50–2.66 (m,

4H), 1.07 (t, 6H, $J = 7.1$Hz); EI-MS: $m/z = 293$ (M^+). Calcd. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.83;H, 7.92; N, 4.81.

1-(1,3-Diphenylprop-2-ynyl)piperazine (entry 16):

^{1}H NMR ($CDCl_3$) $\delta = 7.45$–7.58 (m, 5H), 7.23–7.38 (m, 5H), 4.89 (s, 1H), 2.45–2.51 (m, 4H), 2.61–2.70 (m, 4H); EI-MS: $m/z = 276$ (m^+). Calcd. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.52; H, 7.31; N, 10.11.

CONCLUSIONS

In summary, we have successfully developed a facile economic and green method for construction of propargylamines by employing a three-component coupling of aldehyde, amine, and alkyne in the presence of $CuPy_2Cl_2$ under solvent-free conditions. The notable factors of this reaction are (a) reasonably good yields, (b) fast reaction, and (c) easy recovery of the catalyst, $CuPy_2Cl_2$. Thus, we believe that our procedure will find important application in the synthesis of propargylamines through a one-pot coupling reaction to cater to the needs of academia as well as pharmaceutical industries.

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