CSIRO PUBLISHING

Full Paper

www.publish.csiro.au/journals/ajc

Aust. J. Chem. **2009**, *62*, 75–81

A Simple and Economic Synthesis of Propargylamines by CuI-Catalyzed Three-Component Coupling Reaction with Succinic Acid as Additive

Gerui Ren,[A] *Jinli Zhang,*[A] *Zheng Duan,*[A] *Mengjun Cui,*[A] *and Yangjie Wu*[A,B]

[A]Department of Chemistry, Henan Key Laboratory of Chemical Biology and Organic Chemistry, Key Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University, Zhengzhou 450052, China.

[B]Corresponding author. Email: wyj@zzu.edu.cn

A practical and efficient method was developed for the synthesis of propargylamines in a one-pot procedure from aldehydes, amines, and alkynes by using CuI as catalyst and succinic acid as additive. By using this protocol, a wide range of propargylamines was obtained in high yields.

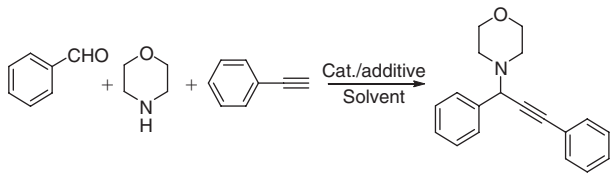
Manuscript received: 28 February 2008.
Final version: 2 July 2008.

Introduction

Propargylamines are major skeletons[1] and synthetically versatile key intermediates[2] for the preparation of many biologically active nitrogen-containing compounds such as conformationally restricted peptide isosteres, oxotremorine analogues, β-lactams, and therapeutic drug molecules.[3] Traditionally, propargylamines were synthesized by nucleophilic attack of lithium acetylides or Grignard reagents on imines or their derivatives.[4] However, these methods require strictly controlled reaction conditions. Recently, extensive attention has been paid to metal-catalyzed three-component coupling of aldehyde, amine, and alkyne (A^3 coupling)[5] for the synthesis of propargylamine. This developed synthetic method is a powerful synthetic route to access complex structures from simple precursors in a one-pot procedure and exhibits higher atom economy and selectivity.[6,7]

The extension of the scope of metal-catalyzed A^3 coupling reactions and the search for a more efficient catalyst have been one of the most popular aims for organic chemists. The recent progresses in this kind of reaction have been made by several research groups. Li[8] and Lo[9] reported their highly efficient three-component coupling reaction in green solvents, such as water, or ionic liquid.[7c] However, these methods required relatively expensive Au[8a,9] or Ag[8b,8c] as catalyst. In addition, cheaper Cu salt-catalyzed A^3 coupling reactions have also received much attention.[10] Tu[10b] and Sreedhar[10g] reported CuI-catalyzed microwave- and ultrasound-assisted A^3 coupling reactions, respectively. Recently Kidwai[10h] reported an efficient recyclable copper-nanoparticle-catalyzed A^3 coupling route using high catalyst loading (15 mol-% of Cu nanoparticles).

Herein, we report a simple CuI-, together with low-cost succinic acid as additive, catalyzed three-component coupling of aldehydes, amines, and alkynes to generate propargylamines in good to excellent yields and with lower catalyst loading (the loading of CuI could be reduced to 0.1 mol-%).



Scheme 1. A^3 coupling of benzaldehyde, morpholine, and phenylacetylene.

Results and Discussion

To find the optimal reaction conditions, the A^3 coupling syntheses of propargylamines of benzaldehyde, morpholine, and phenylacetylene with succinic acid at 100°C under various conditions were investigated (Scheme 1).

Among various copper salts screened in this three-component coupling, CuI was found to be the most effective catalyst, with 98% isolated yield, much better than other copper salts such as CuCl, CuBr, and $Cu(OAc)_2$. By screening the solvents, toluene was found to give the highest yield of 98% (Table 1, entries 1–7). We then checked the efficiency of the CuI catalyst. As shown in Table 1 (entries 7–9), when the catalyst loading was reduced to 1 mol-%, this reaction proceeded well with a slightly lower isolated yield (88%, entry 8). Even with 0.1 mol-% of CuI, the expected product was formed in 83% yield within 6 h (entry 9).

The effect of chain length of dicarboxylic acids on the coupling reaction was also investigated. As shown in Fig. 1, succinic acid gave the best yield. A possible reason is that the coordination bond length and angle between succinic acid and CuI might be suitable to promote this A^3 coupling.

A variety of aldehydes, amines, and alkynes were chosen to investigate the scope and generality of this catalytic system and the results are summarized in Table 2. The substituted aldehydes with both electron-withdrawing (entries 2–7)

 10.1071/CH08086 0004-9425/09/010075

Table 1. Effect of solvents and catalyst loading on the A^3 coupling reaction

Reaction conditions: benzaldehyde (1.00 mmol), morpholine (1.2 mmol), phenylacetylene (1.5 mmol), CuI (0.03 mmol), succinic acid (0.06 mmol), reflux for 6 h

Entry	Solvent	Mol-% catalyst	Yield[A] [%]
1	THF	3	43
2	DMF	3	62
3	CH_3OH	3	68
4	H_2O	3	78
5	CH_3CN	3	81
6	1,4-dioxan	3	89
7	Toluene	3	98
8	Toluene	1	88
9	Toluene	0.1	83

[A]Isolated yields.

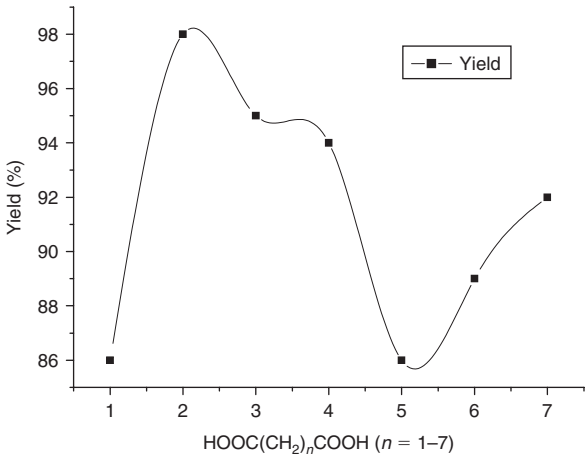


Fig. 1. Effect of various dicarboxylic acids on the three-component coupling reaction (isolated yields).

and electron-donating (entries 8, 9) groups could couple with morpholine and phenylacetylene efficiently to give the desired substituted propargylamines in good to excellent yields. The functional groups on the aldehydes, such as bromo, chloro, fluoro, and methoxyl are compatible with this three-component coupling. There is no significant effect on the reaction yield in the case of *ortho*-substituted aldehydes used (entries 2, 3).

Conclusions

In summary, we successfully developed a simple and economic three-component coupling for the synthesis of propargylamines. This one-pot procedure with aldehydes, amines, and alkynes was catalyzed efficiently by easily available CuI with succinic acid as an additive. By using this method, a diverse range of propargylamines were generated in good to excellent yields. This methodology could serve as a new avenue for the synthesis of propargylamines as useful synthetic intermediates.

Experimental

General

Melting points were measured on an XT-5 microscopic apparatus and are uncorrected. GC analysis was performed on an Agilent 4890D gas chromatograph. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker DPX 400 instrument using $CDCl_3$ as the solvent and TMS as the internal standard. Elemental analyses were conducted with a Carlo Erba 1160 elemental analyzer. High-resolution mass spectra (HRMS) were measured on a Waters Q-Tof Micro spectrometer. CuI was synthesized according to the literature.[10b] The other chemicals were reagent grade and used without further purification.

General Procedure for Three-Component Coupling Reaction

A mixture of aldehyde (1 mmol), amine (1.2 mmol), alkyne (1.5 mmol), CuI (3 mol-%), succinic acid (6 mol-%), and toluene (0.5 mL) was heated at 100°C under nitrogen for 6 h. After completion of the reaction as monitored by GC or TLC, the reaction mixture was filtered through a pad of silica gel and washed with ethyl acetate. The combined filtrates were concentrated under vacuum. The residue was purified by chromatography on silica gel using petroleum ether/ethyl acetate as eluent. The products were characterized by ^{1}H and ^{13}C NMR spectroscopy. New compounds were confirmed by HRMS or elemental analysis.

N-*(1,3-Diphenylprop-2-yn-1-yl)-morpholine* ***4a***[10b]

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.64–7.62 (m, 2H), 7.52–7.50 (m, 2H), 7.38–7.29 (m, 6H), 4.78 (s, 1H), 3.77–3.68 (m, 4H), 2.66–2.58 (m, 4H). δ_C (100 MHz, $CDCl_3$) 137.8, 131.9, 128.6, 128.3, 127.8, 123.0, 88.6, 85.1, 67.2, 62.1, 49.9.

N-*[1-(4-Bromophenyl)-3-phenylprop-2-yn-1-yl]-morpholine* ***4b***[10b]

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.51–7.45 (m, 6H), 7.30–7.29 (m, 3H), 4.70 (s, 1H), 3.74–3.66 (m, 4H), 2.59–2.57 (m, 4H). δ_C (100 MHz, $CDCl_3$) 136.8, 131.6131.1, 130.0, 128.2, 122.5, 121.6, 88.8, 84.1, 66.9, 61.2, 49.6.

N-*[1-(2-Bromophenyl)-3-phenylprop-2-yn-1-yl]-morpholine* ***4c***

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.60–7.59 (m, 1H), 7.58–7.57 (m, 1H), 7.51–7.48 (m, 2H), 7.33–7.31 (m, 4H), 7.16–7.14 (m, 1H), 5.07 (s, 1H), 3.74–3.64 (m, 4H), 2.71–2.62 (m, 4H). δ_C (100 MHz, $CDCl_3$) 137.0, 133.2, 131.7, 130.6, 129.3, 128.3, 126.8, 125.2, 122.7, 88.5, 84.5, 67.0, 61.2, 49.6. HRMS (positive electrospray ionization (ESI)) Calc. for $C_{19}H_{18}BrNO$ $[M + H]^+$: 356.0650. Found: 356.0657.

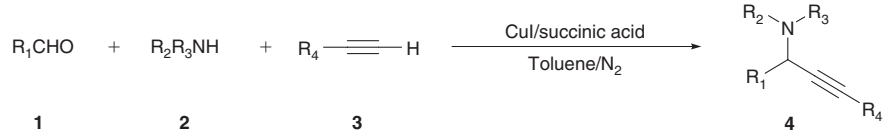
N-*[1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-yl]-morpholine* ***4d***[10b]

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.58–7.55 (m, 2H), 7.51–7.49 (m, 2H), 7.33–7.30 (m, 5H), 4.73 (s, 1H), 3.74–3.67 (m, 4H), 2.60–2.58 (m, 4H). δ_C (100 MHz, $CDCl_3$) 136.3, 133.4, 131.7, 129.7, 128.2, 122.6, 88.8, 84.2, 67.0, 61.2, 49.6.

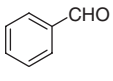
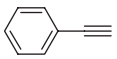
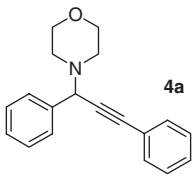
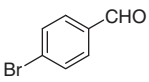
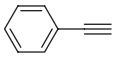
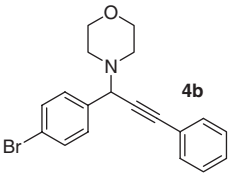
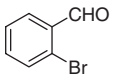
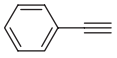
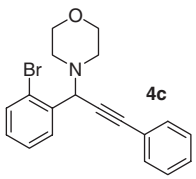
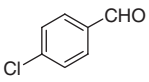
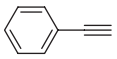
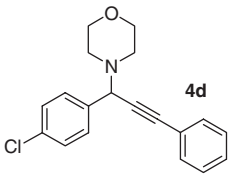
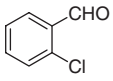
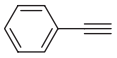
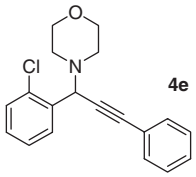
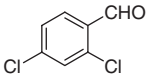
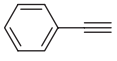
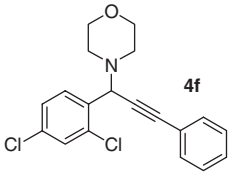
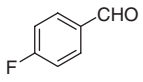
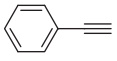
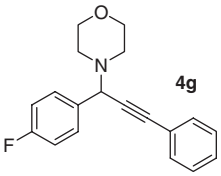
N-*[1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-yl]-morpholine* ***4e***[10b]

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.76–7.73 (m, 1H), 7.50–7.46 (m, 2H), 7.40–7.37 (m, 1H), 7.32–7.29 (m, 3H), 7.24–7.22 (m, 2H), 5.12 (s, 1H), 3.73–3.63 (m, 4H), 2.67–2.65 (m, 4H). δ_C (100 MHz, $CDCl_3$) 135.4, 134.5, 131.7,

Table 2. Three-component coupling of various aldehydes, amines, and alkynes

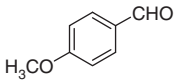
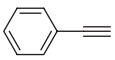
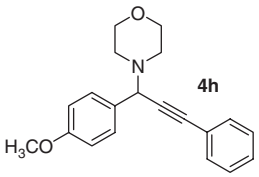
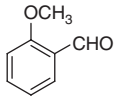
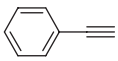
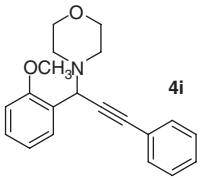
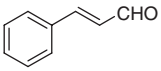
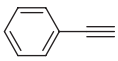
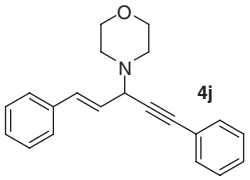
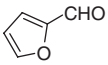
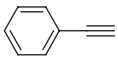
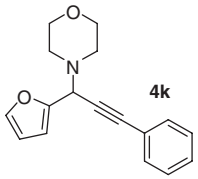
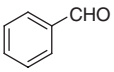
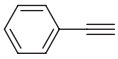
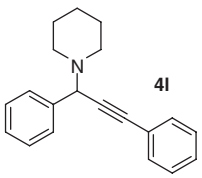
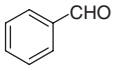
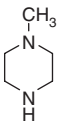
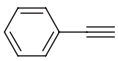
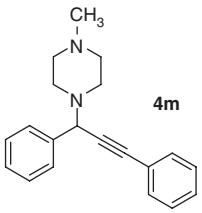
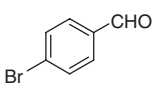
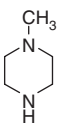
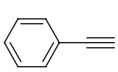
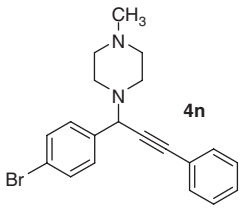


1 **2** **3** **4**

Entry[A]	Aldehyde	Amine	Alkyne	Product	Yield [%][B]
1				 **4a**	98
2				 **4b**	99
3				 **4c**	99
4				 **4d**	99
5				 **4e**	84
6				 **4f**	82
7				 **4g**	86

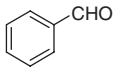
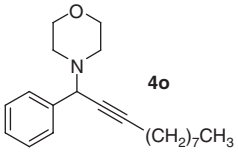
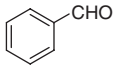
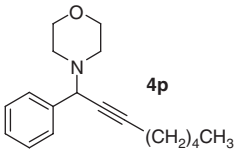
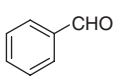
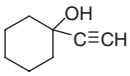
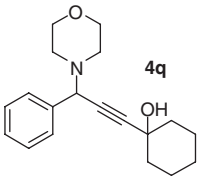
(*Continued*)

Table 2. (Continued)

Entry[A]	Aldehyde	Amine	Alkyne	Product	Yield [%][B]
8				 **4h**	85
9				 **4i**	98
10				 **4j**	71
11				 **4k**	61
12				 **4l**	86
13				 **4m**	96
14				 **4n**	85

(*Continued*)

Table 2. (Continued)

Entry[A]	Aldehyde	Amine	Alkyne	Product	Yield [%][B]
15			$CH_3(CH_2)_7C\equiv CH$	 **4o**	86
16			$CH_3(CH_2)_4C\equiv CH$	 **4p**	85
17				 **4q**	78

[A]Reaction conditions: aldehyde (1.00 mmol), amine (1.2 mmol), alkyne (1.5 mmol), CuI (0.03 mmol), succinic acid (0.06 mmol), toluene (0.5 mL), reflux for 6 h.
[B]Isolated yields.

130.4, 129.8, 129.0, 128.2, 126.2, 122.7, 88.2, 84.6, 67.0, 58.8, 49.7.

N-*[1-(2,4-Dichlorophenyl)-3-phenylprop-2-yn-1-yl]-morpholine* ***4f***

Slightly yellowish solid, mp 79–80°C. δ_H (400 MHz, $CDCl_3$) 7.68 (d, *J* 8.3, 1H), 7.49–7.47 (m, 2H), 7.41 (s, *J* 2.1, 1H), 7.33–7.30 (m, 3H), 7.26–7.24 (d, *J* 8.4, 1H), 5.04 (s, 1H), 3.72–3.64 (m, 4H), 2.65–2.62 (m, 4H). δ_C (100 MHz, $CDCl_3$) 135.3, 134.3, 131.8, 131.3, 129.7, 128.5, 128.4, 126.6, 122.6, 88.7, 84.0, 67.0, 58.5, 49.8. HRMS (positive ESI) Calc. for $C_{19}H_{17}Cl_2NO$ $[M+H]^+$: 346.0765. Found: 346.0771.

N-*[1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-yl]-morpholine* ***4g***

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.61–7.58 (m, 2H), 7.51–7.49 (m, 2H), 7.32–7.30 (m, 3H), 7.06–7.01 (m, 2H), 4.74 (s, 1H), 3.76–3.66 (m, 4H), 2.61–2.58 (m, 4H). δ_C (100 MHz, $CDCl_3$) 162.2 (d, *J* 245), 133.5 (d, *J* 3.1), 131.7, 130.0 (d, *J* 8.1), 128.2, 122.7, 114.9 (d, *J* 21), 88.6, 84.6, 67.0, 61.2, 49.6. HRMS (positive ESI) Calc. for $C_{19}H_{18}FNO$ $[M+H]^+$: 296.1451. Found: 296.1453.

N-*[1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl]-morpholine* ***4h***[10b]

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.55–7.50 (m, 4H), 7.33–7.30 (m, 3H), 6.91–6.89 (m, 2H), 4.73 (s, 1H), 3.80 (s, 3H), 3.76–3.70 (m, 4H), 2.64–2.60 (m, 4H). δ_C (100 MHz, $CDCl_3$) 159.1, 131.7, 129.8, 129.6, 128.2, 128.1, 123.0, 113.5, 88.2, 85.3, 67.0, 61.3, 55.1, 49.7.

N-*[1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-yl]-morpholine* ***4i***

Slightly yellowish solid, mp 74–75°C. (Found: C 78.15, H 6.89. Calc. for $C_{20}H_{21}NO_2$: C 78.13, H 6.96%.) δ_H (400 MHz, $CDCl_3$) 7.64 (d, *J* 7.6, 1H), 7.47–7.45 (m, 2H), 7.29–7.24 (m, 4H), 6.97 (m, 1H), 6.90–6.87 (m, 1H), 5.19 (s, 1H), 3.82 (s, 3H), 3.71–3.68 (m, 4H), 2.74–2.60 (m, 4H). δ_C (100 MHz, $CDCl_3$) 157.2, 131.7, 130.2, 129.1, 128.2, 128.0, 126.0, 123.2, 120.2, 111.2, 86.7, 86.6, 67.1, 55.9, 55.0, 50.1.

N-*[1,5-Diphenylpent-1-en-4-yn-3-yl]-morpholine* ***4j***

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.52–7.50 (m, 2H), 7.43–7.41 (m, 2H), 7.33–7.23 (m, 6H), 6.89 (d, *J* 16, 1H), 6.31–6.26 (dd, *J* 16, 5.4, 1H), 4.37–4.36 (q, *J* 1.1, 5.3, 1H), 3.80–3.73 (m, 4H), 2.80–2.75 (m, 2H), 2.66–2.61 (m, 2H). δ_C (100 MHz, $CDCl_3$) 136.3, 133.3, 131.7, 128.5, 128.2, 127.8, 126.5, 122.8, 88.4, 84.2, 67.0, 59.8, 49.9. HRMS (positive ESI) Calc. for $C_{21}H_{21}NO$ $[M+H]^+$: 304.1701. Found: 304.1706.

N-*[1-(2-Furanyl)-3-phenylprop-2-yn-1-yl]-morpholine* ***4k***[10b]

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.51–7.48 (m, 2H), 7.44–7.43 (m, 1H), 7.34–7.26 (m, 3H), 6.51–6.50 (m, 1H), 6.36–6.35 (m, 1H), 4.88 (s, 1H), 3.82–3.72 (m, 4H), 2.70–2.62 (m, 4H). δ_C (100 MHz, $CDCl_3$) 150.7, 142.8, 131.8, 128.4, 128.3, 122.5, 110.1, 109.7, 87.0, 82.8, 66.9, 56.0, 49.6.

N-*(1,3-Diphenylprop-2-yn-1-yl)-piperidine* ***4l***[10b]

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.64–7.62 (m, 2H), 7.51–7.49 (m, 2H), 7.33–7.27 (m, 6H), 4.79 (s, 1H), 2.56 (s, 4H), 1.63–1.52 (m, 4H), 1.44–1.41 (m, 2H). δ_C (100 MHz, $CDCl_3$)

138.5, 131.7, 128.4, 128.2, 128.0, 127.3, 123.2, 87.8, 86.0, 62.3, 50.6, 26.1, 24.4.

1-Methyl-4-(1,3-diphenylprop-2-yn-1-yl)-piperazine ***4m***

Slightly yellowish solid, mp 39–41°C. δ_H (400 MHz, $CDCl_3$) 7.63–7.62 (m, 2H), 7.50–7.48 (m, 2H), 7.34–7.32 (m, 2H), 7.28–7.7.26 (m, 4H), 4.81 (s, 1H), 2.66 (s, 4H), 2.46 (s, 4H), 2.25 (s, 3H), 1.44–1.41 (m, 2H). δ_C (100 MHz, $CDCl_3$) 138.0, 131.6, 128.3, 128.0, 127.9, 127.9, 127.7, 127.4, 122.9, 88.1, 85.1, 61.4, 55.0, 49.1, 45.8. HRMS (positive ESI) Calc. for $C_{20}H_{22}N_2$ $[M+H]^+$: 291.1861. Found: 291.1859.

1-Methyl-4-[1-(4-bromophenyl)-3-phenylprop-2-yn-1-yl]-piperazine ***4n***

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.52–7.46 (m, 6H), 7.30–7.26 (m, 3H), 4.77 (s, 1H), 2.66 (s, 4H), 2.50 (s, 4H), 2.30 (s, 3H). δ_C (100 MHz, $CDCl_3$) 137.3, 131.8, 131.2, 130.1, 128.2, 122.7, 121.5, 88.8, 84.4, 60.9, 55.0, 45.8. HRMS (positive ESI) Calc. for $C_{20}H_{21}BrN_2$ $[M+H]^+$: 369.0966. Found: 369.0963.

N-*(1-Phenyl-2-undecyn-1-yl)-morpholine* ***4o***

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.56–7.54 (m, 2H), 7.34–7.30 (m, 2H), 7.27–7.23 (m, 1H), 4.52 (s, 1H), 3.72–3.65 (m, 4H), 2.53–2.50 (m, 4H), 2.32–2.28 (m, 2H), 1.61–1.54 (m, 2H), 1.45–1.40 (m, 2H), 1.32–1.28 (m, 8H), 0.88 (t, *J* 6.8, 3H). δ_C (100 MHz, $CDCl_3$) 138.5, 128.6, 128.1, 127.6, 88.8, 75.4, 67.2, 61.7, 49.8, 31.9, 29.3, 29.1, 29.1, 29.0, 22.7, 18.8, 14.2. HRMS (positive ESI) Calc. for $C_{21}H_{31}NO$ $[M+H]^+$: 314.2484. Found: 314.2487.

N-*(1-Phenyl-2-octyn-1-yl)-morpholine* ***4p***[10b]

Slightly yellowish oil; δ_H (400 MHz, $CDCl_3$) 7.56–7.54 (m, 2H), 7.35–7.31 (m, 2H), 7.28–7.24 (m, 1H), 4.52 (s, 1H), 3.73–3.66 (m, 4H), 2.54–2.51 (m, 4H), 2.32–2.28 (m, 2H), 1.60–1.57 (m, 2H), 1.44–1.34 (m, 4H), 0.91 (t, *J* 7.2, 3H). δ_C (100 MHz, $CDCl_3$) 138.5, 128.6, 128.1, 127.6, 88.8, 75.4, 67.2, 61.7, 49.8, 31.2, 28.8, 22.2, 18.8, 14.1.

N-*[3-(1-Hydroxycyclohexyl)-1-phenylprop-2-yn-1-yl]-morpholine* ***4q***

Slightly yellowish solid, mp 90–92°C. (Found: C 76.22, H 8.42. Calc. for $C_{19}H_{25}NO_2$: C 75.97, H 8.58%.) δ_H (400 MHz, $CDCl_3$) 7.56–7.54 (m, 2H), 7.35–7.32 (m, 2H), 7.29–7.25 (m, 1H), 4.61 (s, 1H), 3.74–3.66 (m, 4H), 2.56 (s, 1H), 2.54–2.52 (m, 4H), 2.03–1.97 (m, 2H), 1.75–1.72 (m, 2H), 1.66–1.56 (m, 5H), 1.27–1.23 (m, 1H). δ_C (100 MHz, $CDCl_3$) 137.7, 128.4, 128.1, 127.6, 92.4, 79.1, 68.8, 67.0, 61.3, 49.6, 40.2, 25.2, 23.5.

Accessory Publication

General methods, general procedure for the synthesis of propargylamines, ^1H and ^{13}C NMR figures for all new compounds, and Gaussian models are available from the journal's website.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (Project 20772114) and the Innovation Fund for Outstanding Scholars of Henan Province (Project 0621001100) for the financial support given to the present research.

References

[1] (a) M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. D. VanDuyne, J. Clardy, *J. Am. Chem. Soc.* **1990**, *112*, 3715. doi:10.1021/JA00165A097
(b) M. A. Huffman, N. Yasuda, A. E. DeCamp, E. J. J. Grabowski, *J. Org. Chem.* **1995**, *60*, 1590. doi:10.1021/JO00111A016
(c) A. A. Boulton, B. A. Davis, D. A. Durden, L. E. Dyck, A. V. Juorio, X.-M. Li, I. A. Paterson, P. H. Yu, *Drug Dev. Res.* **1997**, *42*, 150. doi:10.1002/(SICI)1098-2299(199711/12)42:3/4<150::AID-DDR6>3.0.CO;2-P

[2] (a) B. Nilsson, H. M. Vargas, B. Ringdahl, U. Hacksell, *J. Med. Chem.* **1992**, *35*, 285. doi:10.1021/JM00080A013
(b) K. Hattori, M. Miyata, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 1151. doi:10.1021/JA00056A051
(c) A. Jenmalm, W. Berts, Y. L. Li, K. Luthman, I. Csoregh, U. Hacksell, *J. Org. Chem.* **1994**, *59*, 1139. doi:10.1021/JO00084A037
(d) M. Miura, M. Enna, K. Okuro, M. Nomura, *J. Org. Chem.* **1995**, *60*, 4999. doi:10.1021/JO00121A018

[3] I. Naota, H. Takaya, S. I. Murahashi, *Chem. Rev.* **1998**, *98*, 2599. doi:10.1021/CR9403695

[4] (a) C. W. Ryan, C. Ainsworth, *J. Org. Chem.* **1961**, *26*, 1547. doi:10.1021/JO01064A058
(b) F. Tubéry, D. S. Grierson, H.-P. Husson, *Tetrahedron Lett.* **1987**, *28*, 6457. doi:10.1016/S0040-4039(00)96887-4
(c) M. E. Jung, A. Huang, *Org. Lett.* **2000**, *2*, 2659. doi:10.1021/OL0001517
(d) T. Murai, Y. Mutoh, Y. Ohta, M. Murakami, *J. Am. Chem. Soc.* **2004**, *126*, 5968. doi:10.1021/JA048627V

[5] (a) A^3 coupling, see: H. Z. S. Syeda, R. Halder, S. S. Karla, J. Das, J. Iqbal, *Tetrahedron Lett.* **2002**, *43*, 6485. doi:10.1016/S0040-4039(02)01240-6
(b) L. W. Bieber, M. F. da Silva, *Tetrahedron Lett.* **2004**, *45*, 8281. doi:10.1016/J.TETLET.2004.09.079
(c) L. Pin-Hua, W. Lei, *Chin. J. Chem.* **2005**, *23*, 1076. doi:10.1002/CJOC.200591076
(d) M. L. Kantam, B. V. Prakash, C. Reddy, V. Reddy, B. Sreedhar, *Synlett* **2005**, 2329. doi:10.1055/S-2005-872677
(e) K. Mohan-Reddy, N. Seshu-Babu, I. Suryanarayana, P. S. Sai-Prasad, N. Lingaiah, *Tetrahedron Lett.* **2006**, *47*, 7563. doi:10.1016/J.TETLET.2006.08.094
(f) W. J. Yan, R. Wang, Z. Q. Xu, J. K. Xu, L. Lin, Z. Q. Shen, Y. F. Zhou, *J. Mol. Catal. Chem.* **2006**, *255*, 81. doi:10.1016/J.MOLCATA.2006.03.055
(g) N. Gommermann, P. Knochel, *Chem. Eur. J.* **2006**, *12*, 4380. doi:10.1002/CHEM.200501233

[6] (a) For metal-catalyzed multi-component reactions, see: A. B. D. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474. doi:10.1002/CBER.189002301243
(b) C. Mannich, W. Kosche, *Arch. Pharm.* **1912**, *250*, 647. doi:10.1002/ARDP.19122500151
(c) I. Ugi, C. Steinbrueckner, *Chem. Ber.* **1961**, *94*, 2802. doi:10.1002/CBER.19610941032
(d) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123. doi:10.1021/AR9502083
(e) L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 366. doi:10.1055/S-1999-2612
(f) I. Ugi, A. Domling, B. Werner, *J. Heterocycl. Chem.* **2000**, *37*, 647.

[7] B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259. doi:10.1002/ANIE.199502591

[8] (a) C. M. Wei, C. J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584. doi:10.1021/JA0359299
(b) C. M. Wei, Z. Li, C. J. Li, *Org. Lett.* **2003**, *5*, 4473. doi:10.1021/OL035781Y
(c) Z. Li, C. M. Wei, L. Chen, R. S. Varma, C. J. Li, *Tetrahedron Lett.* **2004**, *45*, 2443. doi:10.1016/J.TETLET.2004.01.044

[9] V. K. Y. Lo, Y. Liu, M. K. Wong, C. M. Che, *Org. Lett.* **2006**, *8*, 1529. doi:10.1021/OL0528641

[10] (a) C. J. Li, C. M. Wei, *Chem. Commun.* **2002**, 268. doi:10.1039/B108851N
(b) L. Shi, Y. Q. Tu, M. Wang, F. M. Zhang, C. A. Fan, *Org. Lett.* **2004**, *6*, 1001. doi:10.1021/OL049936T
(c) J. S. Yadav, B. V. S. Reddy, V. Naveenkumar, R. S. Rao, K. Nagaiah, *N. J. Chem.* **2004**, *28*, 335. doi:10.1039/B312785K
(d) B. M. Choudary, C. Sridhar, M. L. Kantam, B. Sreedhar, *Tetrahedron Lett.* **2004**, *45*, 7319. doi:10.1016/J.TETLET.2004.08.004
(e) Y. H. Ju, C. J. Li, R. S. Varma, *QSAR Comb. Sci.* **2004**, *23*, 891. doi:10.1002/QSAR.200420034
(f) S. B. Park, H. Alper, *Chem. Commun.* **2005**, 1315. doi:10.1039/B416268D
(g) B. Sreedhar, P. S. Reddy, B. V. Prakash, A. Ravindra, *Tetrahedron Lett.* **2005**, *46*, 7019. doi:10.1016/J.TETLET.2005.08.047
(h) M. Kidwai, V. Bansal, N. K. Mishra, A. Kumar, S. Mozumdar, *Synlett* **2007**, 1581. doi:10.1055/S-2007-980365