Efficient Ring-Closure Approach via Copper-Catalyzed Reactions of Sulfonyl Azide, Terminal Alkynes and Alcohols/Amines

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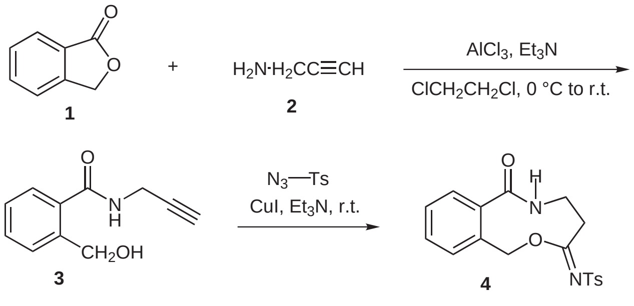
Abstract: We have developed a general and efficient method for synthesis of medium- and large-sized heterocycles via copper-catalyzed reactions of sulfonyl azide, terminal alkynes (or bisalkyne) and alcohols/amines (diamines) at room temperature, and the highly practical method provides an entry toward diverse medium- and large-sized heterocycles.

Key words: heterocycle, ring closure, copper-catalyzed, sulfonyl azide, synthetic method

Medium- and large-sized ring compounds find widespread use in many fields as biologically active natural products,[1] drug candidates[2] and materials.[3] Direct cyclization methods are often ineffective because of enthalpic (increasing strain in the transition state) and entropic influences (probability of the chain-ends meeting) unless certain conformational restraints are present in the acyclic precursor, so the generation of medium- and large-sized ring compounds possessing defined constitutions and configurations is still a challenge in organic synthesis.[1a] Of the various available methods, such as cycloaddition reactions, ring transformations and cyclization reactions, have been developed, the cyclization reactions are probably the most commonly used because of a number of possible initiators and terminators. For example, Staudinger ligation reaction, independently developed by the research groups of Bertozzi[4] and Raines,[5] might also serve as a powerful method for the facilitation of difficult lactamization reactions. The 1,3-dipolar cycloaddition of alkynes with azides, an application of the Huisgen reaction in the field of 'click chemistry', was used to construct large ring compounds.[6] Domino copper-catalyzed intermolecular N-arylation of α-lactam followed by ring expansion has been developed for the synthesis of medium-sized nitrogen heterocycles by Buchwald and co-workers.[7] Recently, both the Chang and Fokin groups have developed copper-catalyzed coupling reactions of sulfonyl azide with various terminal alkynes and amines or water or alcohols to give *N*-sulfonyl imino compounds, respectively, under mild conditions.[8] In this communication, we report a general and efficient method for the preparation of medium- and large-sized ring compounds applying copper-catalyzed three-component reactions of sulfonyl azide, terminal alkynes and alcohols or amines.

Compound **3** was prepared through reaction of phthalide with propargylamine in $ClCH_2CH_2Cl$ in the presence of $AlCl_3$ and triethylamine[9] (Scheme 1). We first used **3** and *p*-toluenesulfonyl azide (N_3Ts) as the model substrates to optimize the copper-catalyzed cyclization conditions, including optimization of the copper catalysts, bases, and solvents. Several copper salts (10 mol% relative to **3**), $CuSO_4$, CuBr, CuCl, CuI, were tested in the condensation using chloroform as the solvent, triethylamine as the base, and the results showed that CuI was the best catalyst. After the optimization process of solvents, bases and the amount of CuI, we decided that the following coupling reactions were carried out in the standard conditions, 10 mol% CuI as the catalyst, 1.2 equivalents of triethylamine as the base relative to **3**, chloroform as the solvent at room temperature. Compound **4** was obtained in 87% isolated yield after a 10 hours reaction under our standard conditions.



Scheme 1 Synthesis of a nine-membered ring compound via copper-catalyzed reaction of sulfonyl azide, terminal alkyne and alcohol

Encouraged by the excellent result above, we attempted to make some large-sized ring compounds as shown in Scheme 2. Reaction of phthalic anhydride with propargylamine in CH_2Cl_2 at room temperature produced **6**, the carboxyl of **6** was activated by ethyl chloroformate in the presence of *N*-methylmorpholine at 0 °C to provide **7**, and the treatment of the active molecule **7** with different amino alcohol (2-aminoethanol, 3-amino-1-propanol, 4-amino-1-butanol or 5-amino-1-pentanol) yielded the corresponding coupling product **9**. Under our standard

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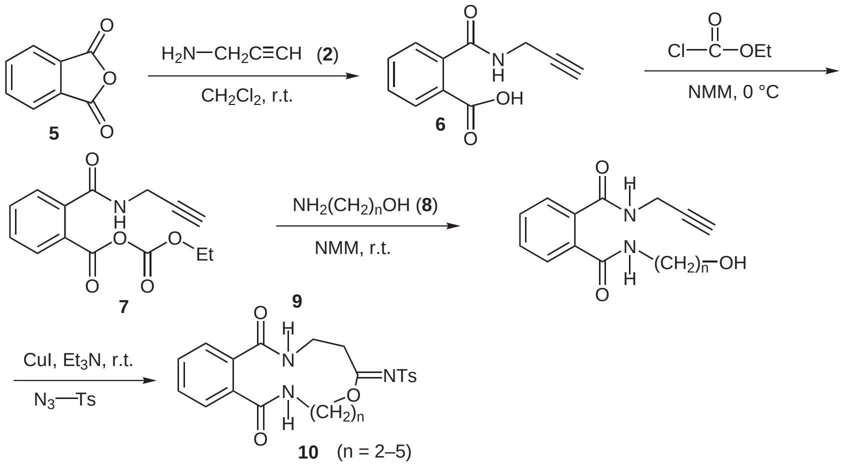


Scheme 2 Synthesis of large-sized ring compounds via copper-catalyzed reaction of sulfonyl azide, terminal alkynes and alcohols

conditions, cyclization of **9** with N_3Ts gave 12- to 15-membered cyclic compounds (**10**) in 76–83% yields (see Table 1).

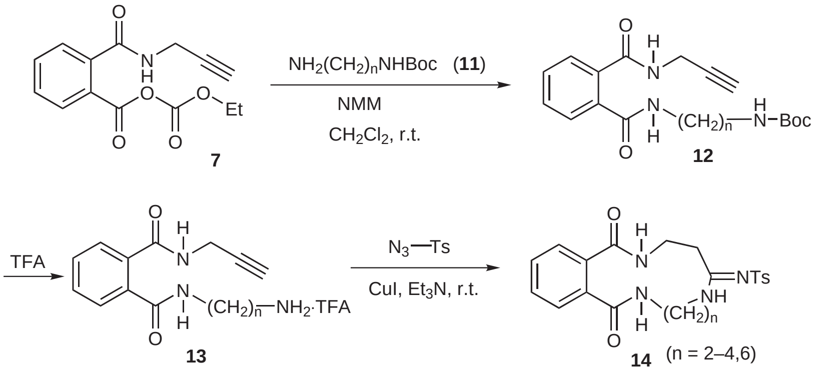
We also attempted cyclization of sulfonyl azide, terminal alkynes and amines. As shown in Scheme 3, reaction of compound **7** with different Boc-monoprotected diamine (1,2-ethanediamine, 1,3-propanediamine, 1,4-butanediamine or 1,5-pentanediamine) produced the corresponding coupling product **12**, the deprotection of **12** and the following cyclization under our standard conditions gave 12- to 14-, and 16-membered cyclic compounds (**14**) in 73–79% yields (see Table 1).

Reactions of terminal bisalkyne **15**, diamines and sulfonyl azide yielded large-sized ring compounds **17** under the optimized conditions (see Table 2). Cyclization of the diamines did not need the base (Et_3N) in the reaction system, and 1,4-butanediamine and 1,6-diaminohexane gave 18- and 20-membered macrocycles in 77% and 63% yields, respectively. The method provides a facile access to various cyclic compounds through one-step copper-catalyzed multicomponent reaction (MCR), so it is of highly practical applications.

All the cyclic compounds prepared above contain *N*-*p*-toluenesulfonyl group, in fact desulfonylation can be successfully achieved with sodium naphthalide,[10] so the procedures above also provide efficient approaches to diverse molecules.

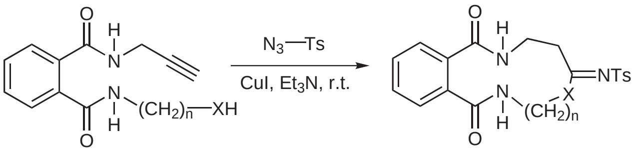
The cyclization mechanism was suggested as shown in Scheme 4 according to our results and the reaction procedures proposed by Chang et al.[8c] Reaction of alkyne with CuI unexceptionally formed copper(I) acetylide,[10] followed with treatment of N_3Ts yielded a highly reactive ketenimine intermediate or its copper complex **B** releasing an N_2.[8,11] The other possible route could also occur, i.e. the 1,3-dipolar cycloaddition of terminal alkyne with sulfonyl azide yielded a triazole[12] or its copper complex **C**, the triazole species released N_2 to give ynamides **D** whose rearrangement provided **B**.[13] Intramolecular addition of hydroxyl or amino group in **B** provided the target cyclic compound **E** (Scheme 4).

In conclusion, we have developed a general and efficient method for the synthesis of medium- and large-sized heterocycles via copper-catalyzed reactions of sulfonyl azide, terminal alkynes (or bisalkyne) and alcohols/amines (or diamines) at room temperature,[14] and the highly practical method provides an entry toward diverse medium- and large-sized heterocycles and a new strategy for the construction of diverse and complex molecules in combinatorial chemistry and medicinal chemistry. Further applications of the multicomponent cyclization method are now under investigation.



Scheme 3 Synthesis of large-sized ring compounds via copper-catalyzed reactions of sulfonyl azide, terminal alkynes and amines

Table 1 Copper-Catalyzed Synthesis of Large-Sized Ring Compounds via Reactions of Sulfonyl Azide, Terminal Alkynes and Alcohols or Amines[a]



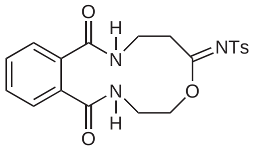
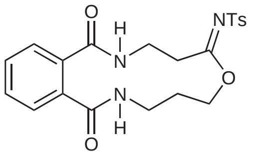
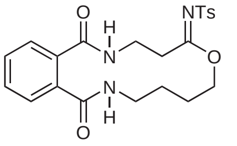
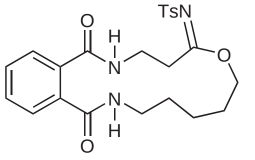
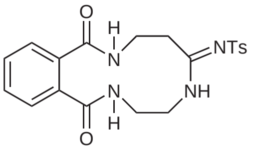
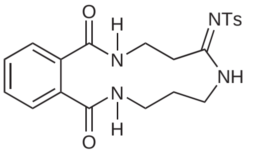
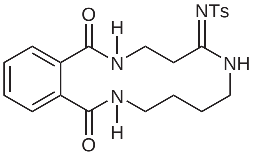
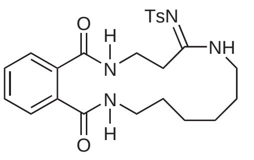
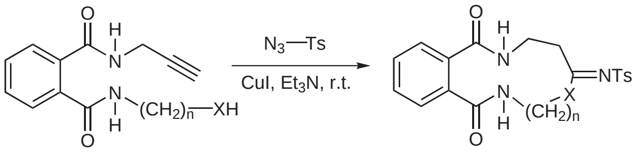
Entry	X (n)	Time (h)	Compound	Yield (%)[b]
1	O (2)	9	 **10a**	76
2	O (3)	10	 **10b**	83
3	O (4)	10	 **10c**	78
4	O (5)	8	 **10d**	76
5	NH (2)	12	 **14a**	79
6	NH (3)	10	 **14b**	73
7	NH (4)	9	 **14c**	77
8	NH (6)	11	 **14d**	74

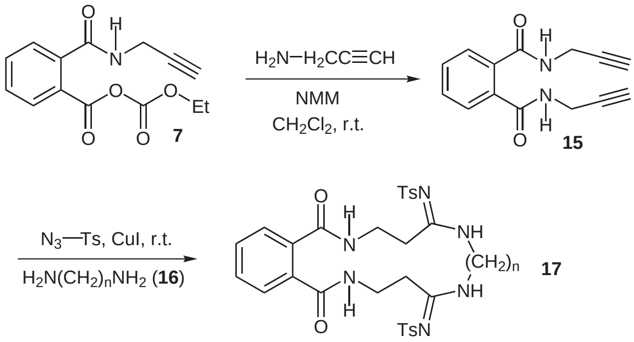
Table 1 Copper-Catalyzed Synthesis of Large-Sized Ring Compounds via Reactions of Sulfonyl Azide, Terminal Alkynes and Alcohols or Amines[a] (continued)

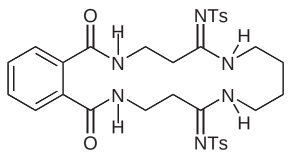
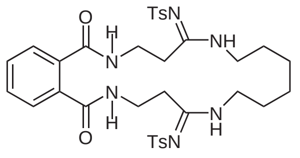


[a] Reaction conditions: *p*-methylbenzensulfonyl azide (1.2 mmol), **9** or **13** (1 mmol), CuI (0.1 mmol) and Et_3N (1.2 mmol for **9**, 2.4 mmol for **13**) in $CHCl_3$ (3 mL).

[b] Isolated yield.

Table 2 Copper-Catalyzed Synthesis of Macrocycles via Reaction of Sulfonyl Azide, Terminal Bisalkyne and Diamines[a]



Entry	n	Time (h)	Compound	Yield (%)[b]
1	4	5	 **17a**	77
2	6	7	 **17b**	63

[a] Reaction conditions: *p*-methylbenzenesulfonyl azide (2.4 mmol), **17** (1 mmol), CuI (0.2 mmol) in $CHCl_3$ (3 mL).

[b] Isolated yield.

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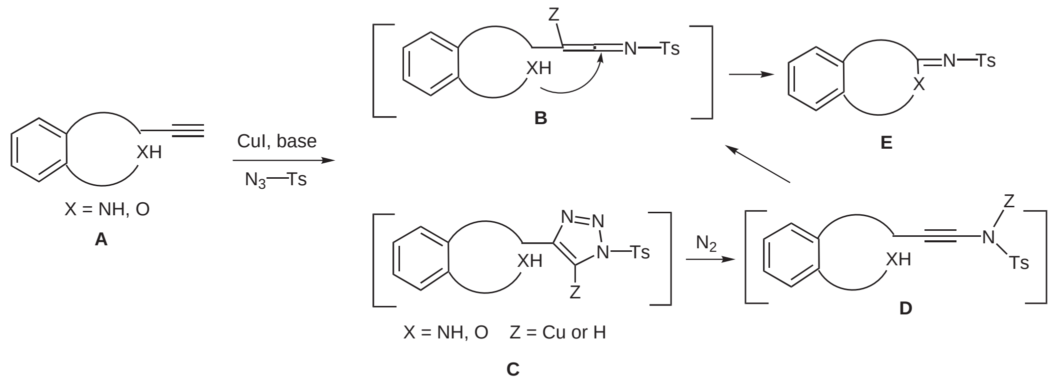

Scheme 4 Possible copper-catalyzed cyclization mechanism

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(14) **Preparation of Compounds 4 and 10a–d**

Et_3N (1.2 mmol) was slowly added to a stirred mixture of *p*-methylbenzenesulfonyl azide (1.2 mmol), **3** or **9** (1 mmol) and CuI (0.1 mmol) in $CHCl_3$ (3 mL) at r.t. under an N_2 atmosphere. Later (8–10 h), the solvent was removed in vacuo, and the crude residue was purified by flash column chromatography on silica gel with an appropriate eluting solvent system (CH_2Cl_2–MeOH 15:1 to 20:1) to give the target product **4** or **10**.

Compound **10a**: eluent: CH_2Cl_2–MeOH (15:1); white solid, yield 76%. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 7.93 (br s, 2 H), 7.29–7.71 (m, 8 H), 3.97 (t, 2 H, *J* = 2.40 Hz), 3.50 (d, 2 H, *J* = 2.73 Hz), 3.39 (d, 2 H, *J* = 2.40 Hz), 2.83 (t, 2 H, *J* = 2.73 Hz), 2.27 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ = 175.1, 169.2, 168.9, 143.6, 139.6, 136.9, 136.5, 130.1, 130.0, 129.8, 127.8, 127.2, 126.7, 67.7, 37.2, 36.9, 34.4, 21.5. HRMS: *m/z* calcd for $C_{20}H_{22}N_3O_5S$ $[M + H]^+$: 416.1280; found: 416.1287.

Preparation of Compounds 14a–d

Et_3N (2.4 mmol) was slowly added to a stirred mixture of *p*-methylbenzenesulfonyl azide (1.2 mmol), **13** (1 mmol) and CuI (0.1 mmol) in $CHCl_3$ (3 mL) at r.t. under an N_2 atmosphere. Later (9–12 h), the solvent was removed in vacuo, and the crude residue was purified by flash column chromatography on silica gel with an appropriate eluting solvent system (CH_2Cl_2–MeOH, 15:1 to 20:1) to give the target product **14**.

Compound **14b**: eluent: CH_2Cl_2–MeOH (20:1); white solid, yield 73%, ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 8.40 (br s, 2 H), 8.22 (br s, 1 H), 7.28–7.68 (m, 8 H), 3.52 (m, 2 H), 3.27 (m, 4 H), 2.82 (m, 2 H), 2.32 (s, 3 H), 1.67 (m, 2 H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ = 168.9, 168.7, 166.6, 142.1, 136.6, 135.6, 130.5, 130.2, 129.8, 128.4, 128.0, 126.2, 42.5, 36.6, 34.9, 27.7, 21.4. HRMS: *m/z* calcd for $C_{21}H_{25}N_4O_4S$ $[M + H]^+$: 429.1597; found: 429.1605.

Preparation of Compounds 17a,b

A solution of diamine (1.2 mmol) in $CHCl_3$ (1 mL) was slowly added to a stirred mixture of *p*-methylbenzenesulfonyl azide (2.4 mmol), **15** (1 mmol) and CuI (0.2 mmol) in $CHCl_3$ (3 mL) at r.t. under an N_2 atmosphere. After a 5–7 h stirring, the solvent was concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel with an appropriate eluting solvent system to give **17**.

Compound **17a**: eluent: CH_2Cl_2–MeOH (20:1); white solid, yield 77%. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 8.78 (br t, 2 H), 8.62, (br t, 2 H), 7.32–7.70 (m, 12 H), 3.58 (m, 4 H), 3.07 (m, 4 H), 2.90 (m, 4 H), 2.34 (s, 6 H), 1.38 (m, 4 H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ = 169.2, 167.2, 142.2, 142.0, 136.1, 130.2, 129.7, 128.2, 126.1, 41.5, 37.5, 34.1, 26.0, 21.4. HRMS: *m/z* calcd for $C_{32}H_{39}N_6O_6S_2$ $[M + H]^+$: 667.2372; found: 667.2376.