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Novel Synthesis of Azepine Derivatives via Copper-Mediated Cyclization of 2-Aza-hepta-2,4-dien-6-ynyl Anions. Intramolecular Addition of Organocopper Centers to the C–C Triple Bond

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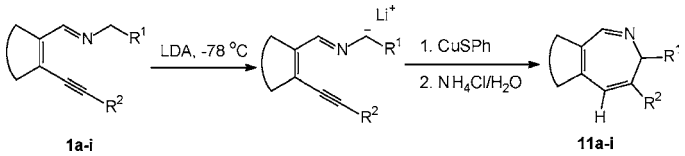
ABSTRACT



Deprotonation of alkynyl imines 1 with LDA at low temperature and subsequent transmetalation with copper thiophenolate gives the annulated azepines 11a–i in 41–73% yield after aqueous workup. The key step of the reaction is a copper-mediated intramolecular nucleophilic attack at the triple bond.

Azepine derivatives are important compounds showing manifold biological activity.[1] Therefore, the development of new and efficient synthetic routes for such compounds is of high interest in heterocyclic chemistry.[2] A straightforward novel synthesis of polysubstituted azepine derivatives via an intramolecular addition of 2-azaallyl organocopper species to the carbon−carbon triple bond is presented in this paper.

Recently, we have reported a new and unexpected rearrangement reaction taking place after the deprotonation of imines of type **1**, leading to aniline derivatives **4** (Scheme 1).[3,4] A multistep cascade mechanism via the anionic seven-membered ring intermediate **2** and the nitrile compound **3** was proposed for this reaction. From the point of azepine chemistry it would be highly desirable to obtain these seven-membered ring systems, for example, by intercepting the reaction cascade after the first cyclization step. Indeed, we were able to isolate two representative azepine derivatives after transmetalation of the lithium species derived from imines **1** using zinc chloride and trapping it with water.[4] This

(1) See, for example: (a) Smalley, R. K. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon Press: Bristol, 1984; Vol. 7, pp 545−546. (b) Meigh, J.-P. K. In *Science of Synthesis*; Weinreb, S. M., Ed.; Thieme: Stuttgart, New York, 2004; Vol. 17, pp 829−830 and references therein.

(2) (a) Surman, M. D.; Hutchings, R. H. In *Science of Synthesis*; Weinreb, S. M., Ed.; Thieme: Stuttgart, New York, 2004; Vol. 17, pp 749−823. (b) Meigh, J.-P. K. In *Science of Synthesis*; Weinreb, S. M., Ed.; Thieme: Stuttgart, New York, 2004; Vol. 17, pp 825−927. (c) Smalley, R. K. In *Methods of Organic Chemistry (Houben-Weyl)*; Schaumann, E., Ed.; Thieme: Stuttgart, New York, 1998; Vol. E9d, pp 108−199. (d) Smalley, R. K. In *Methods of Organic Chemistry (Houben-Weyl)*; Schaumann, E., Ed.; Thieme: Stuttgart, New York, 1998; Vol. E9d, pp 207−292. (e) Smalley, R. K. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon Press: Bristol, 1984; Vol. 7, pp 491−545.

(3) Sagar, P.; Fröhlich, R.; Würthwein, E.-U. *Angew. Chem.* **2004**, *116*, 5812; *Angew. Chem., Int. Ed.* **2004**, *43*, 5694.

(4) Lyaskovskyy, V.; Fröhlich, R.; Würthwein, E.-U. *Chem. Eur. J.* In press. DOI: 10.1002/chem.200601491.

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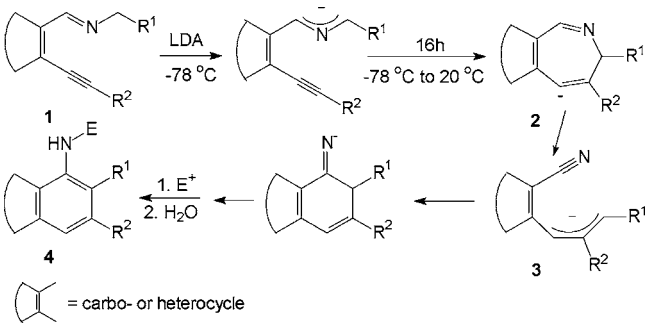
Scheme 1

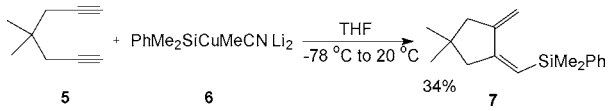


observation is convincing evidence for the proposed cascade mechanism, but it may not yet be considered as a productive, general method for azepine synthesis, as it failed in certain other cases.

Now, we have discovered a versatile synthetic route for the synthesis of azepine derivatives starting from lithium compounds derived from imines **1** by deprotonation and subsequent in situ generation of the corresponding copper-(I) species by transmetalation.

Although intermolecular additions of organocopper compounds to carbon−carbon triple bonds have often been investigated,[5] the corresponding intramolecular variant has not yet been studied intensively.

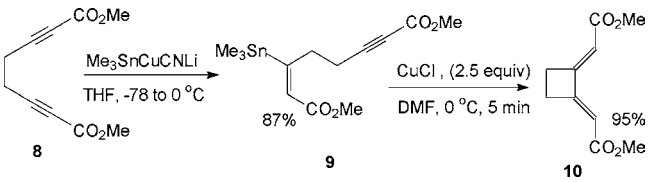
Scheme 2



One example of this reaction type is shown in Scheme 2. Here, the addition of the copper-silicon compound **6** to one of the triple bonds of 1,6-diyne **5** led to an organocopper intermediate, which reacted intramolecularly with the second triple bond giving the product **7**.[6]

Another example of an intramolecular cyclization is represented in Scheme 3. Here, the conjugate addition of a

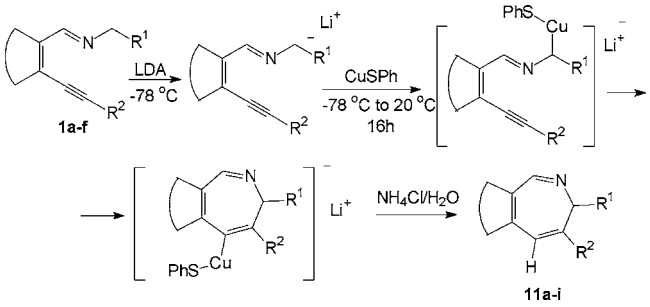
Scheme 3



stannylcuprate to ynoate **8** afforded vinylstannate **9**, which after transmetalation to the vinylcuprate cyclized in an intramolecular fashion to give product **10**.[7]

Hence, the reaction we are presenting here will be a valuable addition to the two reported examples. The general concept is outlined in Scheme 4. Mixed cuprates of type

Scheme 4



RCu(SPh)Li (instead of R_2CuLi) were used to achieve complete conversion of the imine.

The deprotonation of imines **1a**−**i**[3,4] with LDA as base was carried out in THF at −78 °C, giving the respective lithiated intermediates. At higher temperatures these would be subject of the subsequent ring opening−ring closure reaction cascade (see above, Scheme 1).[3]

The resulting 2-azaallyllithium species was added very quickly to a copper(I) thiophenolate solution at −78 °C. Then, the resulting reaction mixture was allowed to warm to room temperature during 16 h. The following trapping with ammonium chloride solution as electrophile led to the azepines **11a**−**i** in good yields (Table 1).[8]

Compounds **11a**−**i** were fully characterized by IR, mass, NMR spectra, elemental analysis, and in case of compound **11f** by X-ray structure analysis as well (Figure 1).

In agreement with our previous studies, we assume an electrocyclic ring-closure reaction of the organometallic intermediate during the warming from −78 °C to room temperature.[9] The transmetalation reaction from lithium to

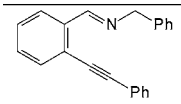
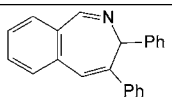
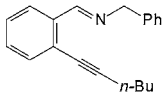
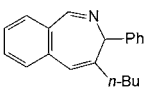
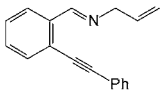
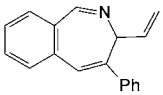
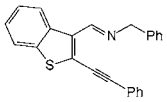
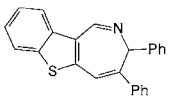
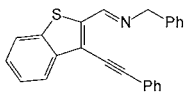
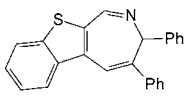
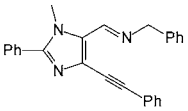
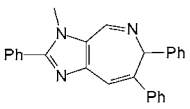
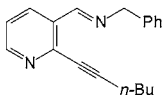
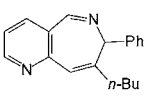
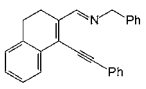
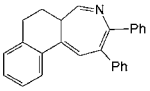
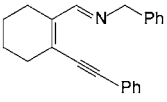
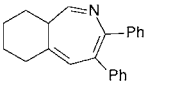
(5) See, for example: Krause, N.; Hoffman-Röder, A. In *Modern Organocupper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 145−166.

(6) Fleming, I.; de Marigorta, E. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 889.

(7) Piers, E.; Boehringer, E. M.; Yee, J. G. K. *J. Org. Chem.* **1998**, *63*, 8642.

(8) **General Procedure for the Preparation of Compounds 11.** A solution of LDA was prepared by adding *n*-BuLi (0.625 mL, 1.00 mmol, 1.6 M solution in *n*-hexane) to diisopropylamine (0.10 g, 1.00 mmol) in dry THF (25 mL) at −78 °C. The imine **1** (1.00 mmol), dissolved in 10 mL of THF, was added dropwise over a period of 30 min, and the misture was stirred for 1 h, resulting in a deep violet solution. In another flask a stirred suspension of 0.19 g of CuI (1.01 mmol, 99.999% purity) in 30 mL of THF was treated with 1.01 mmol of freshly prepared PhSLi (from 1.01 mmol PhSH and 1.01 mmol of *n*-BuLi solution in 5 mL of THF), resulting in a clear yellow solution within 5 min. To this solution of CuSPh was quickly added at −78 °C the violet solution of the imine lithium compound using a Teflon tube. The resulting mixture was allowed to warm to 20 °C during 16 h. Then it was treated with 60 mL of diluted ammonium chloride solution and 30 mL of Et_2O. The precipitate was filtered off, and the filtrate was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with 2 N sodium hydroxide solution and then with brine and were dried over magnesium sulfate. The solvent was evaporated, and the residue was purified by flash chromatography, giving the respective compounds **11**.

Table 1. Compounds **1a**−**i** and **11a**−**i** and Yields of **11a**−**i**

imines **1**	azepines **11**	yield of **11**
 **1a**	 **11a**	70%
 **1b**	 **11b**	58%
 **1c**	 **11c**	41%
 **1d**	 **11d**	65%
 **1e**	 **11e**	63%
 **1f**	 **11f**	73%
 **1g**	 **11g**	50%
 **1h**	 **11h**	41%
 **1i**	 **11i** and **isomer**	58%

copper is expected to take place in the low-temperature part of this range.[10]

The scope of this cyclization reaction seems to be quite general and various carbo- and heterocyclic imines were successfully converted into the respective azepines (Table 1). Both benzothiophene- and pyridine-derived imines gave good results, despite the very different electronic and molecular structure of these heterocyclic systems. The nature

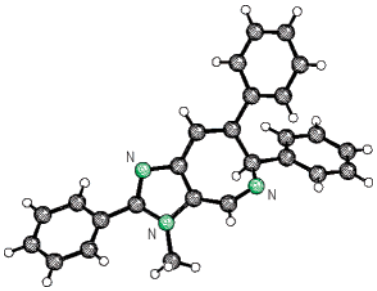


Figure 1. Molecular structure of **11f** as obtained by X-ray diffraction.

of substituent R^2 at the triple bond (aromatic or aliphatic) also did not influence the yields strongly. Allylic imines (**1c**) reacted in the same way as the benzyl derivatives (**1a,b**, **1d**−**i**).

Compound **11h** differs from the other 2*H*-azepines, as it has the substructure of a 3*H*-azepine, resulting from a hydrogen shift after the initial ring closure reaction (Figure 2). Quantum chemical DFT calculations (B3LYP/6-311G-

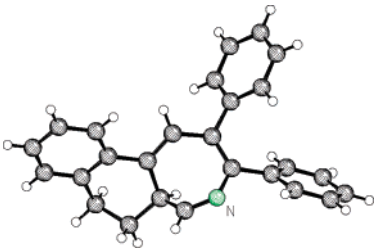


Figure 2. Molecular structure of **11h** as obtained by X-ray diffraction.

(d,p) optimizations, including zero point correction)[11] prefer the observed 3*H*-structure by 6.8 kcal/mol over the corresponding 2*H*-isomer.

Similarly, we obtained from the cyclohexene derivative **1i** predominantly compound **11i** together with a second tautomer (83:17). Inter alia, the structure of **11i** was characterized by a $^1H\{^{15}N\}$-gHMQC long-range coupling experiment. According to the DFT calculations, **11i** is preferred by 4.3 kcal/mol over the corresponding 2*H*-azepine.

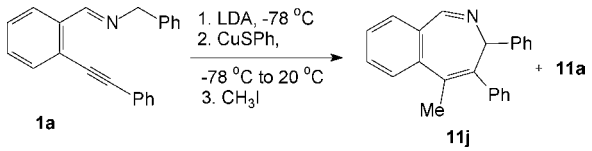
Besides water as electrophile, the use of methyl iodide was also studied in this reaction. The deprotonation of imine **1a** with subsequent transmetalation using copper thiophenolate at low temperature and allowing the reaction to warm it to 20 °C for 16 h led, after addition of methyl iodide, to

(9) (a) Klötgen, S.; Würthwein, E.-U. *Tetrahedron Lett.* **1995**, *36*, 7085. (b) Klötgen, S.; Fröhlich, R.; Würthwein, E.-U. *Tetrahedron* **1996**, *52*, 14801. (c) Gerdes, K.; Sagar, P.; Fröhlich, R.; Wibbeling, B.; Würthwein, E.-U. *Eur. J. Org. Chem.* **2004**, 3465.

(10) See examples in: Lipshutz, B. H. In *Organomethallics in Synthesis. A Manual*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester, 2004; pp 674−685.

a mixture of two products, which were identified by NMR as the mixture of compounds **11j** and **11a** (ratio 85:15, Scheme 5). Apparently, a part of the organocopper intermediate reacted with some proton donors present (probably diisopropylamine) during the 16 h reaction time, forming compound **11a**. Reducing the reaction time (warming to 0 °C for 30 min and stirring for an additional 1 h at this temperature) to minimize the protonation reaction and subsequent workup led again to a mixture of (methylated) **11j** and (protonated) **11a**, but at this time in a 94:6 ratio. Purification of this mixture by column chromatography afforded pure azepine **11j** in 30% yield. Additionally, some fractions containing **11j** together with **11a** were obtained.

Scheme 5



We have disclosed a new and straightforward synthetic pathway for the preparation of annulated benzazepine derivatives by electrocyclization of copper(I) intermediates, derived from imines **1** upon deprotonation and subsequent transmetalation. To interrupt the multistep reaction cascade, leading to aniline derivatives (see Scheme 1), the transmetallation of the initial lithium species to the corresponding copper(I) compounds proved to be of great synthetic potential. The new azepine derivatives **11** were fully characterized by spectroscopic methods including X-ray diffraction studies of **11f** and **11h**.

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Supporting Information Available: Details of experimental procedures, spectral data, quantum chemical calculations, copies of NMR spectra for compounds **11a**−**j**, and crystallographic data for compounds **11f** and **11h** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL063081Y

(11) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.