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Ultrasound-assisted synthesis of functionalized arylacetylenes

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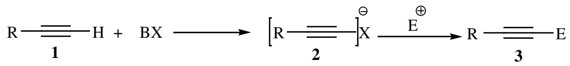
Abstract—A convenient and inexpensive ultrasound-assisted preparation of functionalized arylacetylenes using metallic lithium is reported.

Alkynes are very important synthetic intermediates that can be used as precursors to a variety of natural and complex molecules.[1] There are many methods to obtain functionalized alkynes,[2] but the most usual procedure consists on the treatment of terminal alkynes (**1**) with strong bases (i.e., *n*-BuLi, Grignard's reagents), affording the respective acetylide intermediate (**2**) which reacts with an appropriate electrophile, Scheme 1. These strongly basic conditions are incompatible with some existing functional groups in the starting materials, and undesirable side reactions can occur. Furthermore, this widely used method requires a careful balance in the stoichiometry of the reagents and it is often difficult to obtain good results.

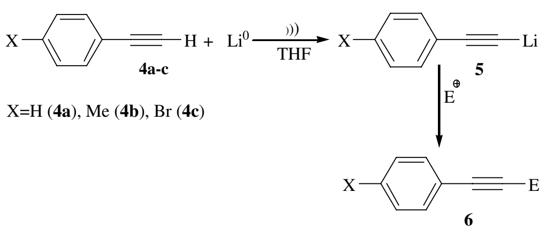
The preparation of functionalized alkynes employing silver acetylide and zirconium complex,[3] cesium salt,[4] copper salt,[5] zinc[6], zinc salt[7] or organozinc,[8] gallium triiodide/amine,[9] and $(\text{collidine})_2\text{I}^+\text{PF}_6^-$ [10] were also reported. The utilization of ultrasound energy in organic chemistry has been better known from the 70s.[11] Ultrasound effects on organic reactions are attributed to cavitation, a physical process that create, enlarge, and implode gaseous and vaporous cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressure inside the bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer. To the best of our knowledge, there is only one report using ultrasound energy to produce functionalized alkynes.[12]



Scheme 1. General method to functionalization of alkynes.

In this communication, a new methodology to obtain functionalized arylacetylenes under ultrasound irradiation, using metallic lithium, a terminal alkynes and an electrophile is reported.

As shown in Scheme 2, arylacetylene (**4**) and metallic lithium were sonicated in THF in an ultrasonic cleaning bath. The formed lithium acetylide intermediate (**5**) was then reacted with a wide range of electrophiles.[13]



Scheme 2. Reaction between arylacetylene (**4**), lithium wire and a electrophile ultrasound-assisted.

Keywords: Acetylene; Lithium acetylide; Ultrasound.

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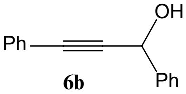
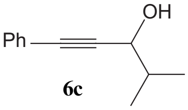
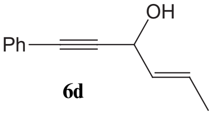
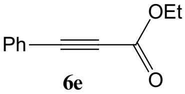
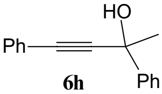
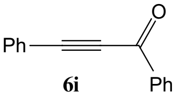
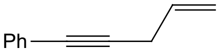
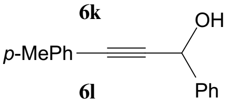
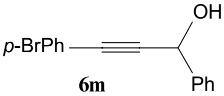
Table 1. Functionalized arylacetylenes prepared according to Scheme 2

Entry	Alkyne (**4**)	Electrophile (E^+)	Product (**6**)	Yield (%)
1	**4a**	I_2	Ph—≡—I **6a**	79
2	**4a**	Benzaldehyde	 **6b**	80
3	**4a**	Isobutiraldehyde	 **6c**	60
4	**4a**	Crotonaldehyde	 **6d**	53
5	**4a**	Ethyl chloroformiate	 **6e**	55
6	**4a**	MeSSMe	Ph—≡—SMe **6f**	77
7	**4a**	TMSCl	Ph—≡—Si(Me)$_3$ **6g**	82
8	**4a**	Acetophenone	 **6h**	57
9	**4a**	Benzoyl chloride	 **6i**	43
10	**4a**	Te/*n*-BuBr	Ph—≡—TeBu-*n* **6j**	25
11	**4a**	Allyl bromide	 **6k**	60
12	**4b**	Benzaldehyde	 **6l**	51
13	**4c**	Benzaldehyde	 **6m**	62

While traditional procedures are done in very low or high temperatures, reactions were performed at room temperature. Ultrasound irradiation also permitted a faster reaction when compared with usual methodologies. It should be stressed that reaction time depends on the size of lithium pieces: smaller pieces give rise to faster reactions. When this procedure was tested using conventional magnetic stirring instead of ultrasound irradiation, only partial lithium consumption after 24 h could be observed, demonstrating that ultrasound greatly favors the reaction between lithium and arylacetylene (**4**) to afford lithium arylacetylide.

As can be seen in Table 1, functionalized arylacetylenes were obtained in fair to good yields. Due to the high synthetic interest of 1-iodo-1-alkynes,[14] we first tested iodine as electrophile. As expected, the iodoalkyne **6a** was obtained in good yield (79%; entry 1).

When carbonylic compounds were used as electrophiles to afford propargyl alcohol derivatives (entries 2–4 and 8), better results were obtained with benzaldehyde (80%; entry 2). This reaction was also carried out in a scale of 20 mmol and compound **6b** (entry 2) was obtained with a somewhat good yield (70%).

The chemoselectivity of this methodology was analyzed using crotonaldehyde as electrophile. Interestingly, reaction is chemospecific to 1,2-addition, affording the allylic alcohol **6d** (entry 4). Unfortunately, α,β-unsaturated carbonylic compounds (entries 5 and 9) were not obtained in satisfactory yields. We also tested DMF as electrophile, but the yield was lower than 10%.

The good results obtained with methyl disulfide (77%; entry 6) prompted us to investigate other chalcogen species. The reactions with phenyl diselenide and phenylselenoyl bromide did not afford the expected products. Similar results were obtained using elemental selenium. Although consumption of the metal could be verified, it was impossible to isolate the alkynyl selenide. We also tested elemental tellurium. In this case the alkynyl telluride was obtained in poor yields (entry 10).

In order to extend the scope of this reaction other alkynes like heptyne, decyne, and propargyl alcohol were tested. Unfortunately, under the same conditions used with arylacetylenes, consumption of lithium wire was not observed. These results surely demonstrate that the presence of the aromatic ring is of paramount importance in the formation of the lithium acetylide.

In summary, it was demonstrated here that ultrasound-promoted reaction of arylacetylenes and metallic lithium with a variety of electrophiles provides an efficient, mild, practical, and inexpensive route to obtain functionalized arylacetylenes, avoiding the use of strong bases such as *n*-BuLi or Grignard's reagents. Extension of this reaction to aliphatic alkynes and mechanistic studies are currently in progress and will be reported in due course.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.01.161.

References and notes

1. (a) Kuijpers, B. H. M.; Groothuys, S.; Keereweer, A. R.; Quaedflierg, P. J. L. M.; van Blaauw, R. H.; Delft, F. L.; Rutjes, F. P. J. T. *Org. Lett.* **2004**, *6*, 3123; (b) Woerpel, K. A.; Clark, T. B. *J. Am. Chem. Soc.* **2004**, *126*, 9522; (c) Malinakova, H. C.; Lu, W. *J. Org. Chem.* **2004**, *69*, 4701; (d) Vorogushin, A. V.; Predeus, A. V.; Wulff, W. D.; Hansen, H. J. *J. Org. Chem.* **2003**, *68*, 5826; (e) Chan, K. K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497; (f) Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 3548; (g) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341.
2. (a) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1971; (b) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenic, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981.
3. Shahi, S. P.; Koide, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 2525.
4. (a) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193; (b) Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463.
5. (a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763; (b) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem.* **2002**, *114*, 2651; *Angew. Chem., Int. Ed.* **2002**, *41*, 2535; (c) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797; (d) Bieber, L. W.; Silva, M. F.; Menezes, P. H. *Tetrahedron Lett.* **2004**, *45*, 2735; (f) Suárez, A.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3580.
6. Sugita, H.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 2769.
7. Jiang, B.; Si, Y.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 216.
8. (a) Pu, L.; Li, Z.-B. *Org. Lett.* **2004**, *6*, 1065; (b) Dahmen, S. *Org. Lett.* **2004**, *6*, 2113.
9. Han, Y.; Huang, Y.-Z. *Tetrahedron Lett.* **1995**, *36*, 7277.
10. Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* **1995**, *36*, 2619.
11. (a) Margulis, M. A. *High Energ. Chem.* **2004**, *38*, 135; (b) Mason, T. J. *Chem. Soc. Rev.* **1997**, *26*, 443.
12. Tuncay, A.; Anaclerio, B. M.; Zolodz, M. *Tetrahedron Lett.* **1999**, *40*, 599.
13. General Experimental Procedure: lithium-wire (17.5 mg; 2.5 mmol) and phenylacetylene (0.55 mL; 2.0 mmol) were placed in 5 mL THF and sonicated (Ultrasonic Cleaner apparatus, Model-3510, with frequency of 40 KHz and a nominal power of 130 W) under a nitrogen atmosphere at 15–20 °C until lithium consumption (20–30 min). The electrophile (2 mmol) was then added and sonication continued for 30 min at the same temperature. After work up with aqueous satd NH_4Cl (10 mL) and extraction with ethyl acetate (3×20 mL), products were purified by distillation or flash chromatography.
14. (a) Delavarenne, S. Y.; Viehe, H. G. In *The Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; p 651, Chapter 10; (b) Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984**, *49*, 3429; (c) Bjorkling, F.; Norin, T.; Unelius, R. *Synth. Commun.* **1985**, *15*, 463; (d) Boutin, R. H.; Rapoport, H. J. *J. Org. Chem.* **1986**, *51*, 5320.