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ScienceDirect
Mendeleev Commun., 2011, **21**, 339–340
Mendeleev Communications

Convenient synthesis of diarylpropargyl alcohols

Valerii Z. Shirinian,*[a] Aleksei A. Shimkin,[a] Artur K. Mailyan,[b] Evgeniya S. Leonova[b] and Mikhail M. Krayushkin[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: shir@ioc.ac.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2011.11.016

Reaction between benzophenones and sodium acetylide in THF in the presence of 18-crown-6 gives the corresponding diarylpropargyl alcohols.

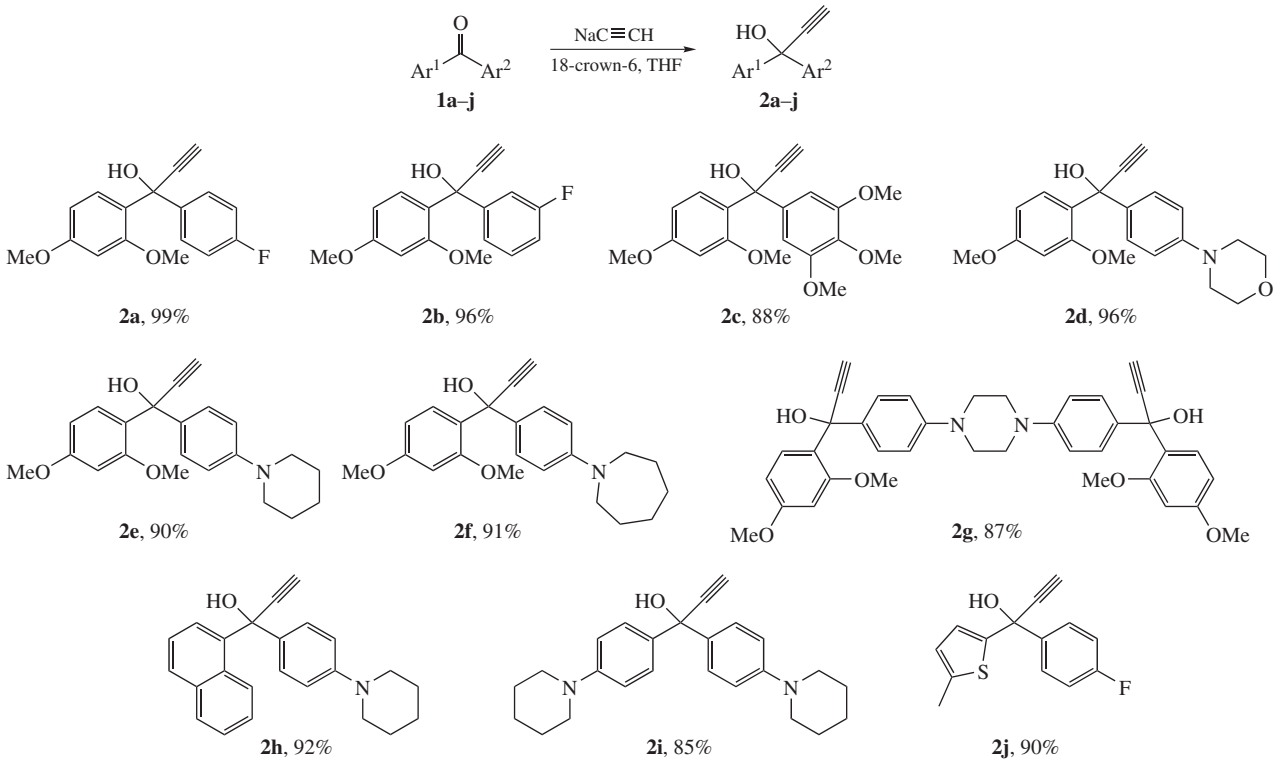
The tertiary propargylic alcohols are widely used in the synthesis of photochromic naphthopyrans[1] and other heterocyclic compounds.[2] The Meyer–Schuster rearrangement of propargylic alcohols provides an access to α,β-unsaturated carbonyl compounds.[3] Cycloisomerization of prop-2-yn-1-ols leads to furans or pyrroles,[4] benzofurans,[5] indoles[6] and cyclopentadienes.[7] Propargylic alcohols, especially steroid derivatives, often show high biological activity.[8]

The usual synthetic strategy for the preparation of prop-2-yn-1-ols includes interaction between ketone and metal acetylide. The most frequently used reagents are lithium acetylide (as ethylenediamine complex),[9] sodium acetylide (suspension in xylene),[10] lithium or magnesium derivatives prepared *in situ* from acetylene and *n*-butyllithium or Iotsich reagent.[11] While the application of commercially available acetylides is very attractive, yields of propargylic alcohols are usually moderate, the large excess (up to 10 equiv.[10(a)]) of metal acetylide or passing of acetylene gas through reaction mixture[10(b)] being necessary.

Here we report an improved procedure for the synthesis of diarylpropargyl alcohols using commercially available sodium acetylide in the presence of 18-crown-6 (Scheme 1).

The reaction of benzophenone **1a** with ethylenediamine complex of lithium acetylide in anhydrous THF at room temperature leads to propargylic alcohol **2a** in only 43% yield. The reaction time was extremely long, while the conversion of the starting ketone on using of 4 equiv. of lithium acetylide over two weeks was no more than 60%. Apparently, the complex of lithium acetylide with ethylenediamine is very stable, in which the C–Li bond is rather covalent, resulting in poor nucleophilicity of this acetylene 'anion'.

To strengthen the nucleophilic properties of acetylide, we assumed that the more polar bond between metal and carbon atom is needed. Testing of commercially available sodium acetylide (as suspension in xylene) brought about much better results: yield of propargylic alcohol **2a** was 75%. We have tested various reaction conditions (without solvent, in benzene, dioxane, DMSO,



Scheme 1

acetonitrile, HMPA), however, in many cases the target product has not been detected at all. Molecules of both benzene and dioxane are non-polar and do not provide the sufficient solvation of the acetylide anion, whereas the solubility in the other solvents is very high. We supposed that the poor yields of the target diarylpropargyl alcohols in polar solvent might be explained by the reversibility of this reaction. Indeed, we have found that 1,1-diphenylprop-2-yn-1-ol on treatment with sodium hydride in HMPA gave benzophenone. Probably, in very polar solvents the equilibrium is shifted to starting ketones. On balance, among the tested solvents THF is the most suitable for our purpose. Further optimization on using 18-crown-6 as the catalyst provided 99% yield of **2a** within one week of the reaction. To avoid loss of acetylene as a result of the decomposition of sodium acetylide, the vessel should be tightly closed. The developed procedure was applied to the preparation of a series of other diarylpropargyl alcohols **2b–j**, which were obtained in high yields (85–99%).†

The structures of the obtained compounds were confirmed by ^{1}H NMR spectroscopy, mass spectrometry and elemental analysis.† The characteristic signal of acetylenic hydrogen atom of propynols **2a–j** in ^{1}H NMR spectra is observed at 2.77–2.90 ppm.

In conclusion, we have developed a simple and efficient procedure for the synthesis of diarylpropargyl alcohols by the reaction of diarylketones with sodium acetylide in the presence of catalytic amount of 18-crown-6.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.11.016.

† *General procedure for the synthesis of diarylpropargyl alcohols* **2a–j**. Benzophenone **1** (15 mmol or 7.5 mmol for **1g**) and 18-crown-6 (0.27 g, 1 mmol) were added to a stirred mixture of sodium acetylide (18% suspension in xylene, 8 g, 30 mmol) in anhydrous THF (50 ml). The flask was closed with a stopper; the reaction mixture was stirred for 7 days at room temperature, and then poured into crushed ice (200 g). The precipitate was filtered off, washed with water (3×50 ml), and dried in air. If oil instead of precipitate emerged, the mixture was extracted with ethyl acetate (3×50 ml). The combined extracts were washed with water (3×50 ml) and evaporated *in vacuo*. The crude product was purified by flash chromatography. For the characteristics of all the prepared compounds, see Online Supplementary Materials.

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Received: 23rd June 2011; Com. 11/3749