Stereoselective reduction of 1-acyl-2-phenylacetylenes with triphenylphosphine in water: an efficient synthesis of *E*-chalcones

Svetlana N. Arbuzova, Tatyana E. Glotova, Marina Yu. Dvorko, Igor A. Ushakov, Nina K. Gusarova, and Boris A. Trofimov*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., 664033 Irkutsk, Russian Federation
E-mail: boris_trofimov@irioch.irk.ru

DOI: http://dx.doi.org/10.3998/ark.5550190.0012.b16

Abstract
1-Acyl-2-phenylacetylenes are reduced with triphenylphosphine in water under mild conditions (room temperature, without catalyst and organic solvent, 3 h) to afford (*E*)-1-acyl-2-phenylethenes (chalcones) in high yields (83-91%).

Keywords: 1-Acyl-2-phenylacetylenes, reduction, triphenylphosphine, *E*-chalcones, stereoselective synthesis

Introduction

1,3-Diaryl-2-propene-1-ones, commonly known as chalcones, represent an important group of compounds which frequently are isolated from natural sources as *E*-isomers. Chalcones are the main precursors for the biosynthesis of flavonoids and exhibit (both natural and synthetic representatives) diverse biological activities: antibacterial,[1] antifungal,[1] anticancer,[2] antituberculous,[3] antimalarial,[4] anti-inflammatory,[5] antihyperglycemic,[6] and many others. A typical representative of natural chalcones is licochalcone A isolated from the roots of *Glycyrrhiza inflata* (licorice) possessing antibacterial, antiparasitic properties and finding application in dermatological and cosmetic compositions. Chalcones are also valuable building blocks for the synthesis of azaheterocycles,[7] *i.e.* benzodiazepines, pyrazolines, isoxalines, benzimidazoles, azolopyridines and –pyrimidines, which play a significant role in biological processes. Therefore, the search for an efficient synthesis of chalcones remains a challenging task.

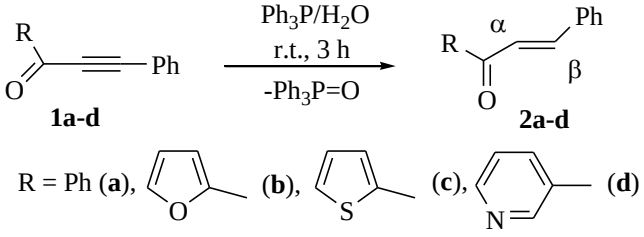
The most widely used method for the synthesis of chalcones is the Claisen-Schmidt condensation[8] of aryl methyl ketones with aromatic aldehydes, usually base-catalyzed.[8a,c,e] Another method for chalcone preparation could comprise the reduction of α-acetylenic ketones to enones.[9] However, such syntheses are laborious. For instance, the reduction of α-acetylenic

ketones by treatment with chromium(II) sulfate in aqueous DMF or chromium(II) chloride in aqueous THF requires an inert atmosphere, deoxygenated solvents, and large amounts of chromium(II) salts (6 equivalents for most reactions).[9b] An approach including hydrosilylation of alkynes and subsequent protodesilylation affording alkenes is a two-stage process and involves application of ruthenium complex $[Cp^*Ru(MeCN)_3]PF_6$ at the fist stage and CuI at the second one.[9c] The reduction of α-acetylenic ketones by the system diisobutylaluminum hydride – HMPA[9a] requires the use of anhydrous solvents, inert atmosphere and is performed at low temperatures (-50 to 0 ºC). In addition, the process is not stereoselective.[9a]

Herein we report on the efficient synthesis of *E*-chalcones based on the stereoselective reduction of available[10] 1-acyl-2-phenylacetylenes by the system Ph_3P – H_2O. To the best of our knowledge, just a single chalcone, [α,β-D_2]-1,3-diphenyl-2-propen-1-one, has been prepared by the reduction of the corresponding acetylene with the system Ph_3P – D_2O - THF (reflux, 6-10 h, 62% yield).[11]

Results and Discussion

We have found that 1-acyl-2-phenylacetylenes **1a-d** react with the system Ph_3P – H_2O under mild (biomimetic) conditions (room temperature, without catalyst and organic solvent) for 3 h to give 1-acyl-2-phenylethenes (chalcones) **2a-d** in high preparative yields as *E*-isomers (83-91%) (Scheme 1).

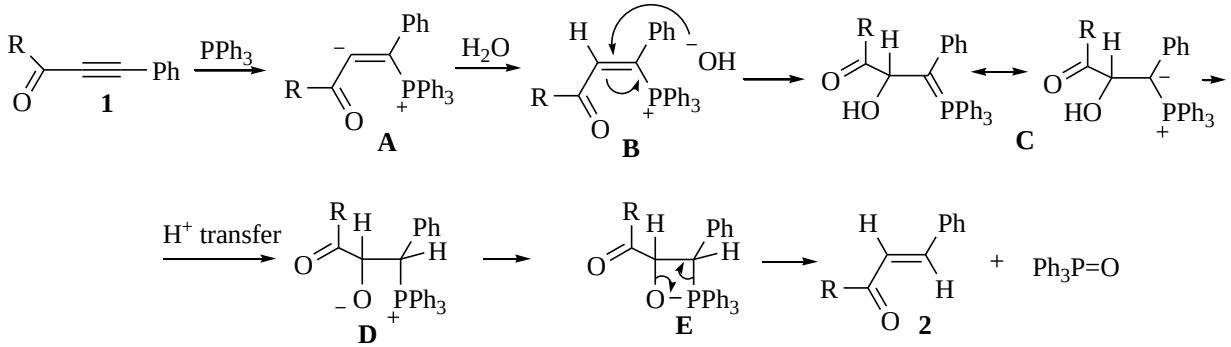


Scheme 1. Synthesis of *E*-chalcones **2** from 1-acyl-2-phenylacetylenes in the system Ph_3P – H_2O.

The process proceeds chemoselectively: only chalcone **2** (^{1}H NMR) and triphenylphosphine oxide (^{31}P NMR) are identified in the reaction mixture. The reaction is highly stereoselective: (*E*)-1-acyl-2-phenylethenes **2** are formed almost exclusively, only trace amounts of *Z*-isomers are discernible in the reaction mixtures (^{1}H NMR). The *E*-configuration of the products **2a-d** follows from ^{1}H NMR spectra: two doublets at 7.40-7.53 ppm (for H_α) and 7.81-7.88 ppm (for H_β) with coupling constant $^3J_{HH}$ 15.6-15.8 Hz being observed.

A proposed mechanism of the reaction (Scheme 2) comprises the nucleophilic addition of triphenylphosphine as a neutral nucleophile to the triple bond to give zwitterionic intermediate **A**

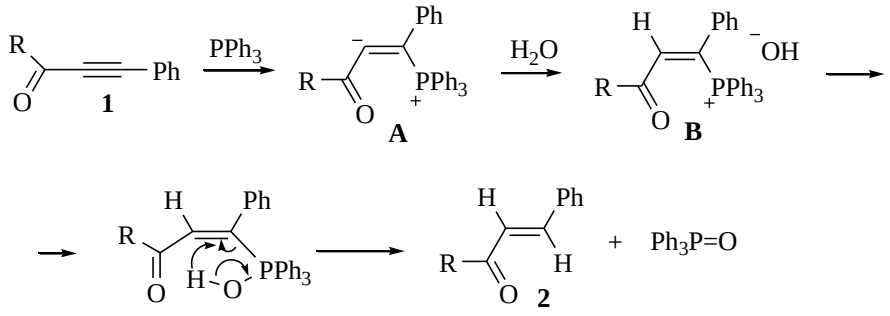
which is further protonated with water to yield vinylphosphonium hydroxide **B**. The double bond of the phoshonium cation is then attacked by the hydroxide-anion to form the phosphorane **C**. Apparently, the subsequent proton-transfer takes place to afford zwitterion (betaine) **D** which expectedly undergoes the intramolecular rearrangement via oxaphosphetane **E** (similar to the Wittig reaction) to result in triphenylphosphine oxide and 1-acyl-2-phenylethene **2**.



Scheme 2. Proposed mechanism for the formation of *E*-chalcones **2.**

In support to this scheme, it is relevant to mention that stable compounds similar to phosphorane **C** have previously been isolated[12] from three-component reaction of triphenylphosphine, acetylenedicarboxylates and C-[12b,d], N-[12c-h], O-[12a] and S[12e,h]-centered nucleophiles. However, this scheme does not explain properly the stereoselectivity of the reaction. In addition, intramolecular proton-transfer affording betaine **D** is not so plausible in the presence of water.

An alternative simpler way of the reduction can be represented by the direct rearrangement of hydroxy phosphonium intermediate **B** (Scheme 3). The high stereoselectivity of the process can be rationalized by the formation of initial zwitterionic intermediate **A** of *trans*-configuration (in accordance with *trans*-nucleophilic addition rule[13]) that provides finally the *E*-configuration of alkene **2**.



Scheme 3. An alternative way for the formation of *E*-chalcones **2**.

Conclusions

In summary, stereoselective reduction of 1-acyl-2-phenylacetylenes with triphenylphosphine in water, proceeding under mild conditions (room temperature, without catalyst and organic solvent) provides a facile synthesis of (*E*)-1-acyl-2-phenylethenes belonging to a class of chalcones, compounds with a variety of biological activities. Particular advantages of the method are its chemo- and stereoselectivity and also environmentally benign conditions.

Experimental Section

General. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DPX 400 spectrometer (400.13, 101.61 and 161.98 MHz, respectively) in $CDCl_3$ solutions and referenced to internal HMDS (^{1}H, ^{13}C NMR) and external 85% H_3PO_4 (^{31}P NMR). IR spectra were run on a Bruker Vertex 70 spectrometer in KBr pellets. 1-Acyl-2-phenylacetylenes **1** were synthesized according to the protocol.[12]

General procedure for the synthesis of (*E*)-1-acyl-2-phenylethenes (2a-d)
A suspension of finely divided triphenylphosphine (0.52 g, 2 mmol) and acylacetylene **1** (2 mmol) in water (10 mL) was stirred vigorously at room temperature for 3 h. The dark oil obtained was extracted with Et_2O (3x10 mL) and the extract was dried over $MgSO_4$. The partial evaporation of the solvent (to ~10 mL) and keeping the product at 5-8 ºC for 5-6 h caused precipitation of most of triphenylphosphine oxide (~0.3-0.4 g) which was filtered off. The residue was purified by column chromatography on Al_2O_3 using Et_2O/petroleum ether (1:9) as eluent to give after removing the solvents (*E*)-1-acyl-2-phenylethenes **2a-d** as crystals. *Z*-isomers of **2** were not isolated but their presence (in amounts from trace to 5%) in the crude reaction mixtures followed from ^{1}H NMR spectra: two doublets at 6.53-6.61 ppm (for H_α) and 6.94-7.07 ppm (for H_β) with coupling constant $^{3}J_{HH}$ 12.8-13.0 Hz were observed.
(*E*)-1,3-Diphenyl-2-propen-1-one (2a). White crystals, yield 91%, 0.38 g, mp 55-57 ºC; IR (ν_{max}, cm^{-1}): 1664 (C=O), 1607, 1574, 1495, 1448, 1336, 1308, 1287, 1215, 1181, 1033, 1014, 751, 688, 659, 562, 491. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 7.53 (1H, d, $^{3}J_{HH}$ 15.6 Hz, H_α), 7.81 (1H, d, $^{3}J_{HH}$ 15.6 Hz, H_β), 7.41, 7.49, 7.64, 8.03 (10H, m, Aryl). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ_C 122.0, 128.3, 128.4, 128.5, 128.9, 130.4, 132.7, 134.8, 138.1, 144.7, 190.4. Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81%. Found: C, 86.38; H, 5.66%.
(*E*)-1-(2-Furyl)-3-phenyl-2-propen-1-one (2b). White crystals, yield 83%, 0.33 g, mp 80-82 ºC; IR (ν_{max}, cm^{-1}): 1657 (C=O), 1604, 1573, 1561, 1497, 1465, 1447, 1394, 1338, 1288, 1250, 1164, 1086, 1052, 1014, 994, 980, 929, 864, 770, 760, 721, 688, 604, 570, 488. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 7.46 (1H, d, $^{3}J_{HH}$ 15.8 Hz, H_α), 7.88 (1H, d, $^{3}J_{HH}$ 15.8 Hz, H_β), 6.59, 7.28, 7.34, 7.41, 7.65 (8H, m, Aryl, Furyl). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ_C 121.3, 112.6, 117.6,

128.6, 129.0, 130.6, 134.8, 146.6, 153.8, 144.0, 178.0. Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09%. Found: C, 78.45; H, 5.24%.

(*E*)-3-Phenyl-1-(2-thienyl)-2-propen-1-one (2c). Yellowish crystals, yield 86%, 0.37 g, mp 78-80 °C; IR (ν_{max}, cm^{-1}): 1651 (C=O), 1592, 1574, 1518, 1447, 1414, 1354, 1335, 1241, 1219, 1066, 973, 857, 849, 761, 725, 708, 682, 566, 542, 489. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 7.40 (1H, d, $^3J_{HH}$ 15.8 Hz, H_α), 7.83 (1H, d, $^3J_{HH}$ 15.8 Hz, H_β), 7.16, 7.39, 7.61, 7.65, 7.84 (8H, m, Aryl, Thienyl). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ_C 121.7, 128.3, 128.5, 129.0, 130.6, 131.9, 133.9, 134.8, 145.6, 144.1, 182.1. Anal. Calcd for $C_{13}H_{10}OS$: C, 72.87; H, 4.70; S, 14.96%. Found: C, 72.54; H, 4.78; S, 14.69%.

(*E*)-3-Phenyl-1-(3-pyridinyl)-2-propen-1-one (2d). White crystals, yield 86%, 0.36 g, mp 79-81 °C; IR (ν_{max}, cm^{-1}): 1667 (C=O), 1607, 1585, 1495, 1483, 1449, 1415, 1351, 1331, 1290, 1234, 1206, 1114, 1049, 1018, 987, 822, 752, 697, 690, 679, 621, 571, 481. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ_H 7.50 (1H, d, $^3J_{HH}$ 15.6 Hz, H_α), 7.86 (1H, d, $^3J_{HH}$ 15.6 Hz, H_β), 7.45, 7.66, 8.30, 8.81, 9.24 (9H, m, Aryl, Pyridinyl). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ_H 121.4, 123.6, 128.6, 129.0, 130.9, 131.9, 132.1, 135.8, 145.9, 149.8, 153.1, 189.0. Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69%. Found: C, 80.65; H, 5.24; N, 6.43%.

Acknowledgements

This work was supported by the President of the Russian Federation [programs for the support of leading scientific schools (grant NSh-3230.2010.3)].

References

1. Nowakowska, Z.; Kedzia, B.; Schroeder, G. *Eur. J. Med. Chem.* **2008**, *43*, 707.
2. (a) Bois, F.; Beney, C.; Boumendjel, A.; Mariotte, A. M.; Conseil, G.; DiPietro, A. *J. Med. Chem.* **1998**, *41*, 4161. (b) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 699. (c) Fu, Y.; Hsieh, T. C.; Guo, J.; Kunicki, J.; Lee, M. Y.; Darzynkiewicz, Z.; Wu, J. M. *Biochem. Biophys. Res. Commun.* **2004**, *322*, 263.
3. Lin, L.-M.; Zhou, Y.; Flavin, M. T.; Zhou, L.-M.; Nie, W.; Chen, F.-C. *Bioorg. Med. Chem.* **2002**, *10*, 2795.
4. (a) Dominguez, J.; Leon, C.; Rodrigues, J.; Dominguez, N. G.; Gut, J.; Rosenthal, P. *J. Med. Chem.* **2005**, *48*, 3654. (b) Narender, T.; Shweta; Tanvir, K.; Rao, M. S.; Srivastava, K.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2453. (c) Mishra, N.; Arora, P.; Kumar, B.; Mishra, L. C.; Bhattacharya, A.; Awasthi, S. K.; Bhasin, V. K. *Eur. J. Med. Chem.* **2008**, *43*, 1530.
5. (a) Hsieh, H.-K.; Lee, T.-H.; Wang, J.-P.; Wang, J.-J.; Lin, C.-N. *Pharm. Res.* **1998**, *15*, 39. (b) Herencia, F.; Ferrándiz, M. L.; Ubeda, A.; Domínguez, J. N.; Charris, J. E.; Lobo, G. M.;

Alcaraz, M. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1169. (c) Hsieh, H.-K.; Tsao, L.-T.; Wang, J.-P. *J. Pharm. Pharmacol.* **2000**, *52*, 163.
6. Satyanarayana, M.; Tiwari, P.; Tripathi, B. K.; Srivastava, A. K.; Pratap, R. *Bioorg. Med. Chem.* **2004**, *12*, 883.
7. Chebanov, V. A.; Desenko, S. M.; Gurley, T. W. *Azaheterocycles based on α,β-unsaturated carbonyls*; Springeer, 2008.
8. For recent examples, see: (a) Srinivasan, M.; Perumal, S.; Selvaraj, S. *Arkivoc* **2006**, (*x*), 21. (b) Thirunarayanan, G.; Vanangamudi, G. *Arkivoc* **2006**, (*xii*), 58. (c) Giasuddin Ahmed, M.; Romman, U. K. R.; Mosaddeq Ahmed, S.; Kawsari Akhter; Ershad Halim, Md. *Bangladesh J. Sci. Ind. Res.* **2007**, *42*, 45. (d) Narender, T.; Papi Reddy, K. *Tetrahedron Lett.* **2007**, *48*, 3177. (e) Rateb, N. M.; Zohdi, H. F. *Synth. Commun.* **2009**, *39*, 2789.
9. (a) Tsuda, T.; Yoshida, T.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 1624. (b) Smith, A. B.; Levenberg, P. A.; Suits, J. Z. *Synthesis* **1986**, 184. (c) Trost, B. M.; Zachary, T. B.; Thomas, J. *J. Am. Chem. Soc.* **2002**, *124*, 7922.
10. (a) Chowdhury, C.; Kundu, N. G. *Tetrahedron* **1999**, *55*, 7011. (b) Glotova, T. E.; Dvorko, M. Yu.; Ushakov, I. A.; Chipanina, N. N.; Kazheva, O. N.; Chekhlov, A. N.; Dyachenko, O. A.; Gusarova, N. K.; Trofimov, B. A. *Tetrahedron* **2009**, *65*, 9814.
11. Richards, E. M.; Tebby, J. C.; Ward, R. S.; Williams, D. H. *J. Chem. Soc. (C)* **1969**, 1542.
12. (a) Ramazani, A.; Souldozi, A.; Marandi, F.; Kazemizadeh, A. R. *Asian J. Chem.* **2005**, *17*, 293. (b) Ramazani, A.; Dolatyari, L.; Kazemizadeh, A. R.; Ahmadi, E. *Asian J. Chem.* **2005**, *17*, 297. (c) Yavari, I.; Zabarjad-Shiras, N. *Mol. Divers.* **2006**, *10*, 23. (d) Heydari, R.; Maghsoodlou, M. T.; Yami, R. N. *Phosphorus, Sulfur, Silicon and Relat. Elem.* **2008**, *183*, 2578. (e) Kazemian, M. A.; Nassiri, M.; Ebrahimi, A.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Vasheghani-Farahani, F. *Arkivoc* **2008**, (*xvii*), 173. (f) Hassanabadi, A.; Anary-Abbasinejad, M.; Dehghan A. *Synth. Commun.* **2009**, *39*, 132. (g) Habibi-Khorassani, S. M.; Ebrahimi, A.; Maghsoodlou, M. T.; Charati, F. R.; Kazemian, M. A.; Karimi, P. *Phosphorus, Sulfur, Silicon and Relat. Elem.* **2010,** *185*, 559. (h) Habibi-Khorassani, S. M.; Ebrahimi, A.; Maghsoodlou, M. T.; Zakarianezhad, M.; Ghasempour, H.; Ghahghayi, Z. *Curr. Org. Chem.* **2011**, *15*, 942.
13. Dickstein, J. I.; Miller, S. I. In *The Chemistry of the Carbon-Carbon Triple Bond*; Patai, S., Ed.; Wiley: Chichester, U.K., 1978; Ch. 19, pp 813-955.

