Prop-2-yn-1-als and 1-phenylprop-2-yn-1-one in the chalcogen Baylis–Hillman reaction

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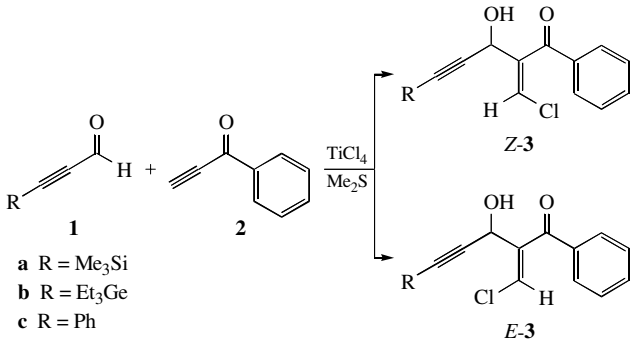
2-(*Z*,*E*-Chloromethylidene)-3-hydroxy-1-phenyl-5-organylpent-4-yn-1-ones were prepared by tandem α-hydroxyethynylation/β-chlorination of 1-phenylprop-2-yn-1-one mediated by $TiCl_4$ and Me_2S in the chalcogen Baylis–Hillman reaction.

The Baylis-Hillman (BH) reaction has attracted the attention of organic chemists[1] because it is a simple and straightforward method for generating a new C–C bond.

The C(sp^3)–C(sp^2) bond formation based on tandem conjugate addition/aldol reaction of α,β-acetylenic ketones and aliphatic or aromatic aldehydes has been promoted with $Bu_4NI/TiCl_4$,[2] $TiCl_4$,[3] TMSI and *N*-(heptafluoropropylcarbonyl)oxazaborolidine[4] or $TiCl_4/Me_2S$[5] as the catalysts in the chalcogen B–H reaction.

Propynals as aldehyde substrates in the BH reaction have not been studied previously. The incorporation of a triple bond into BH-type adducts will enrich their synthetic and biological potential. Here, we describe the synthesis of new multifunctional BH adducts from substituted prop-2-yn-1-als **1a–c** and 1-phenylprop-2-yn-1-one **2**.

An attempt to prepare compound **3a** by the reaction of **1a** and **2** in the presence of $TiCl_4$ (1.2 equiv.) in dichloromethane at room temperature was unsuccessful because of the oligomerization of the reaction mixture. The reaction of **2** with **1a** promoted with $TiCl_4$ and a catalytic amount of dimethyl sulfide (0.1 mol%) leads to 2-(*Z*/*E*-chloromethylidene)-3-hydroxy-1-phenyl-5-trimethylsilylpent-4-yn-1-one **3a** in 70% total yield.† The synthesis of **3a** was performed at −40 °C (4 h) or at 0 °C (2 h) without inert atmosphere protection (Scheme 1).



Scheme 1

Adduct **3a** is highly functionalised by six neighbouring reactive centres; these are the halogen atom, the hydroxy group, the conjugated carbon–carbon double bond, the carbonyl group, the triple bond and the Si–C_{sp} bond. It can be transformed into a variety of useful polyfunctional compounds.[6–10] Subsequent heterolysis of the Si–C_{sp} bond will afford an unknown BH-type adduct with the terminal triple bond.

The process was monitored by ^{1}H NMR spectroscopy. Crude adduct **3a** is a mixture of *Z*- and *E*-isomers in the 3.5:1 ratio. The individual *Z*- and *E*-isomers were isolated as clear yellowy oil by column chromatography on silica gel (eluent: chloroform–carbon tetrachloride, 3:1).

To determine the configuration of compound **3a**, the 2D NOESY spectra were analysed. A correlation between H_{olefin} and $H_{o\text{-}Ph}$ proton signals was observed in the *E*-isomer, whereas a correlation between H_{olefin} and H(C*H*OH) proton signals was revealed for the *Z*-isomer.

The intramolecular hydrogen bond C=O···H–O in *Z*-**3a** was detected by IR spetroscopy. In accordance with the IR and ^{1}H NMR data, compound **3a** exists predominantly in the *Z-s-trans* form. The predominance of the *Z-s-trans* conformation of *Z*-**3a** stabilised by an intramolecular H-bond is confirmed by the results of AM1[11] calculations (Scheme 2). The calculated intramolecular H-bond strength is 8 kcal mol^{-1}.

In case of 3-triethylgermylprop-2-yn-1-al **1b**, desired BH adduct **3b** was not isolated under the above reaction conditions (0 °C, 3 h) because of the resinification of the reaction mixture. An increase in the amount of dimethyl sulfide from 0.1 mol% to equimolar leads to the isolation of compound **3b** by preparative chromatography on silica gel in 27% total yield in the isomer ratio *Z*:*E* = 2.5:1. The low yield of **3b** can be explained

† IR Spectra were recorded on a Specord IR-75 spectrometer in $CHCl_3$ and $C_2H_2Cl_4$ solutions (cuvette thickness of 0.01–5 cm) and films. ^{1}H, ^{13}C and ^{29}Si NMR spectra were recorded on a Bruker DPX-400 spectrometer, tetramethylsilane (TMS) was used as an internal standard. The 2D NOESY spectra were recorded on a Bruker DPX-250 spectrometer in $CDCl_3$. TLC was carried out on Silufol UV-254 plates. Dry dichloromethane and $TiCl_4$ were distilled before use.

2-(Z,E-Chloromethylidene)-3-hydroxy-1-phenyl-5-trimethylsilylpent-4-yn-1-one Z-**3a**. 3-Trimethylsilylprop-2-yn-1-al **1a** (0.38 g, 3 mmol) and dimethyl sulfide (0.08 g, 0.3 mmol) in anhydrous dichloromethane (5 ml) were added to a solution of 1-phenylprop-2-yn-1-one **2** (0.54 g, 4.2 mmol). A solution of $TiCl_4$ in dichloromethane (1.0 M, 3.6 ml, 3.6 mmol) was added dropwise at −40 °C, and the reaction mixture was stirred at this temperature for 4 h. The reaction was quenched by the dropwise addition of a saturated aqueous sodium bicarbonate solution until neutral reaction. The inorganic precipitate was removed by filtration through silica gel, and the filtrate was dried over $MgSO_4$ and concentrated at a reduced pressure. The residue was purified by column chromatography on silica gel with a chloroform–carbon tetrachloride (3:1) eluent.

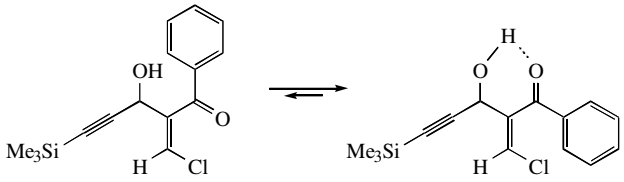
For *Z*-**3a**: yield 58%, yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.04 (s, 9H, Me_3Si), 3.50 (s, 1H, OH), 5.25 (s, 1H, C*H*OH), 6.83 (s, 1H, vinyl H), 7.49 (t, 2H, 3,5-H), 7.61 (t, 1H, 4-H), 7.98 (d, 2H, 2,6-H). ^{13}C NMR ($CDCl_3$) δ: –0.39 (Me_3Si), 63.55 (CHOH), 93.61 (Si*C*≡C), 101.79 (≡*C*–CHOH), 121.45 (=CH), 128.68 (C-3, C-5), 129.85 (C-2, C-6), 133.93 (C-4), 136.07 (C-1), 140.14 (=C), 194.88 (C=O). ^{29}Si NMR ($CDCl_3$) δ: −16.93 (Me_3Si). IR ($CHCl_3$, ν/cm^{-1}): 3500, 3400–3300 (OH), 2168 (C≡C), 1660, 1630 (C=O), 1600, 1570 (C=C, C=C phenyl), 1240, 850 (Si–C), 780 (C–Cl) and 740 (w, =CH). Found (%): C, 61.45; H, 5.82; Cl, 12.55; Si, 9.28. Calc. for $C_{15}H_{17}ClO_2Si$ (%): C, 61.52; H, 5.85; Cl, 12.11; Si, 9.59.

For *E*-**3a**: yield 12%, yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.08 (s, 9H, Me_3Si), 4.21 (s, 1H, OH), 5.59 (s, 1H, C*H*OH), 6.86 (s, 1H, vinyl H), 7.49 (t, 2H, 3,5-H), 7.62 (t, 1H, 4-H), 7.75 (d, 2H, 2,6-H).

For the preparation of compounds **3b** and **3c**, aldehydes **1b**, **1c** and dimethyl sulfide were used in a stoichiometric ratio.

2-(Z,E-Chloromethylidene)-3-hydroxy-1-phenyl-5-triethylgermylpent-4-yn-1-one **3b**, yellow viscous oil, preparative yield 28%, *Z*/*E* = 2.5:1 (for crude adduct). IR (film, ν/cm^{-1}): 3400 (OH), 2160 (C≡C), 1660 (C=O), 1590, 1570 (C=C, C=C phenyl), 1250, 830 (C–Ge). For *Z*-**3b**: ^{1}H NMR ($CDCl_3$) δ: 0.80–1.2 (m, 15H, Et_3Ge), 4.14 (s, 1H, OH), 5.63 (s, 1H, C*H*OH), 6.85 (s, 1H, vinyl H), 7.87 (d, 2H, 2,6-H), 7.50–7.65 (m, 4H, Ph). For *E*-**3b**: ^{1}H NMR ($CDCl_3$) δ: 0.80–1.20 (m, 15H, Et_3Ge), 4.14 (s, 1H, OH), 5.67 (s, 1H, C*H*OH), 6.97 (s, 1H, vinyl H), 7.85 (d, 2H, 2,6-H), 7.50–7.65 (m, 3H, Ph).

2-(Z,E-Chloromethylidene)-3-hydroxy-1,5-diphenylpent-4-yn-1-one **3c**: dark yellow oil, preparative yield 52%, *Z*/*E* = 5.7:1 (for crude adduct). IR (film, ν/cm^{-1}): 3400 (OH), 2230 (C≡C), 1660 (C=O), 1600, 1580 (C=C, C=C phenyl). For *Z*-**3c**: ^{1}H NMR ($CDCl_3$) δ: 3.90 (s, 1H, OH), 4.97 (s, 1H, C*H*OH), 6.42 (s, 1H, vinyl H), 7.0–7.8 (m, 10H, Ph). For *E*-**3c**: ^{1}H NMR ($CDCl_3$) δ: 3.90 (s, 1H, OH), 5.40 (s, 1H, C*H*OH), 6.52 (s, 1H, vinyl H), 7.0–7.8 (m, 10H, Ph).



Z-s-cis *Z-s-trans*

Scheme 2

by the heterolysis of the Ge–C_{sp} bond in **1b** to form unstable reaction products. The lability of this bond in germanium acetylenic compounds under the action of acids was described earlier.[12,13]

Phenyl analogue **3c** was prepared in 52% yield similarly to **3b**. As in the case of BH adducts **3a** and **3b**, the *Z*-stereoselectivity was predominantly observed for **3c** (the ratio *Z*/*E* = = 5.7:1 for crude adduct).

Thus, we found that propynals can be successfully used in the chalcogen Baylis–Hillman reaction with α,β-acetylenic ketones to afford multyfunctional adducts as potentially important synthetic building blocks.

References

1 D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, 1996, **52**, 8001.
2 M. Taniguchi, T. Hino and Y. Kishi, *Tetrahedron Lett*., 1986, **27**, 4767.
3 H.-W. Wei, S. H. Kim, T. D. Caputo, D. W. Purkiss and G. Li, *Tetrahedron*, 2000, **56**, 2397.
4 G. Li, H.-X. Wei, B. S. Phelps, D. W. Purkiss and S. H. Kim, *Org. Lett*., 2001, **3**, 823.
5 T. Kataoka, H. Kinoshita, S. Kinoshita, T. Iwamura and S.-ichi Watanabe, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 2358.
6 U. Shadakshari and S. K. Nayak, *Tetrahedron*, 2001, **57**, 4599.
7 C. R. Mateus, R. S. Hyma, K. Padmaya and M. Krishnamacharyuli, *Tetrahedron*, 1999, **55**, 6971.
8 N. S. Kim, T. Y. Kim, K. Y. Lee, Y. M. Chung, H. J. Lee and J. N. Kim, *Tetrahedron Lett*., 2000, **41**, 2613.
9 N. J. Lawrence, J. P. Crump, A. T. McGown and J. A. Hadfield, *Tetrahedron Lett*., 2001, **42**, 3939.
10 D. Basavaiah and R. M. Reddy, *Tetrahedron Lett*., 2001, **42**, 3025.
11 J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. I. Stewart, *J. Am. Chem. Soc*., 1985, **107**, 3902.
12 A. S. Medvedeva, *DSc Dissertation*, Irkutsk Institute of Organic Chemistry, SB RAS, 1988.
13 M. Lesbre, P. Mazerolles and J. Satge, *Organicheskie soedineniya germaniya* (*The Organic Compounds of Germanium*), Mir, Moscow, 1974, p. 65 (in Russian).

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