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Convenient method for the preparation of 1-phenylthio-3-alken-1-ynes and 4-hydroxy-1-phenylthio-1,2-alkadienes from a common precursor

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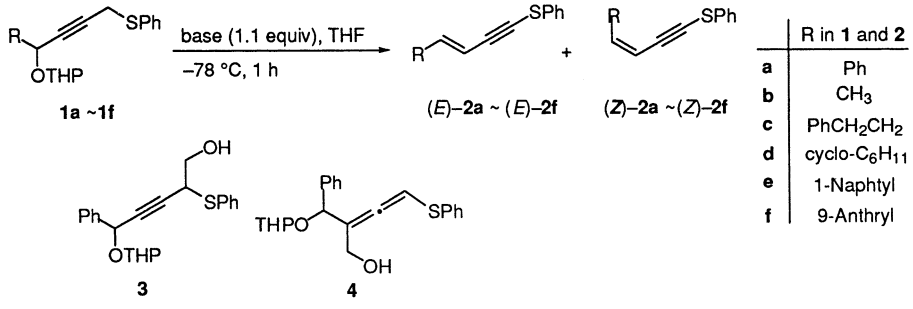
Abstract—4-Hydroxy-1-phenylthio-2-alkynes (**5**) reacted with dihydropyran to afford the corresponding 4-tetrahydropyranyloxy derivatives which, on treatment with KHMDS, gave a mixture of (*E*)- and (*Z*)-1-phenylthio-3-alken-1-ynes, with the former predominant. When MeLi was used in the place of KHMDS, the (*Z*)-isomers were formed in preference to the (*E*)-isomers. Further treatment of the mixture with a base converted the (*Z*)-isomers into (*E*)-isomers. On the other hand, the reaction of **5** with KHMDS gave the corresponding 4-hydroxy-1-phenythio-1,2-alkadienes.

Enynes, enediynes, allenes, and cumulenes are important classes of compounds in synthetic organic chemistry as well as natural product chemistry.[1–3] In this communication, we wish to report a convenient method for the preparation of 1-phenylthio-3-alken-1-ynes and 4-hydroxy-1-phenylthio-1,2-alkadienes from a common precursor.

In the course of our study to prepare nucleic acid modifying molecules, 4-phenyl-1-phenylthio-4-(2-tetrahydropyranyloxy)-2-butyne (**1a**) was reacted with *n*-BuLi (1.1 equiv.) in THF at −78°C, followed by addition of paraformaldehyde to afford 1-phenylthio-4-phenyl-3-buten-1-yne (**2a**) in 56% isolated yield as a 1:0.23 mixture of (*E*)- and (*Z*)-isomers instead of the expected alkynyl alcohol **3** or allenyl alcohol **4** (Scheme 1).

When the reaction of **1a** with KHMDS in THF at −78°C was quenched without addition of paraformaldehyde, **2a** was obtained in 76% yield as a 1.0:0.06 mixture of (*E*)-**2a** and (*Z*)-**2a** (Scheme 1, Table 1, entry 1).[4] In contrast, when MeLi was used as a base, (*Z*)-**2a** was formed as a major product in a ratio of *Z*/*E*=1:0.32 (entry 2).[5a,6]



Scheme 1.

Keywords: enynes; allenes; isomerisation; 1-phenylthio-4-hydroxy-2-alkyne.

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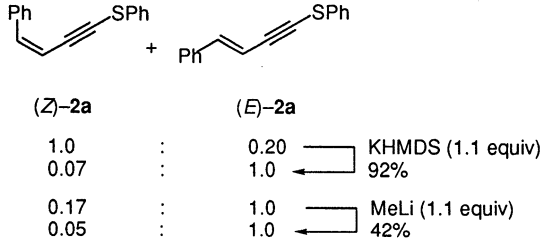
Table 1. Conversion of **1** to **2**

Entry	Substrate		Base	Product		
	No.	R		No.	Yield (%)	*E*:*Z*
1	**1a**	Ph	KHMDS	**2a**	76	1.0:0.06
2	**1a**		MeLi	**2a**	45	1.0:3.13
3	**1b**	CH_3	KHMDS	**2b**	64	1.0:1.26
4	**1b**		MeLi	**2b**	77	1.0:3.03
5	**1c**	$PhCH_2CH_2$	KHMDS	**2c**	69	1.0:0.82
6	**1c**		MeLi	**2c**	12	1.0:1.85
7	**1d**	*cyclo*-C_6H_{11}	KHMDS	**2d**	67	1.0:0.54
8	**1d**		MeLi	**2d**	21	1.0:2.38
9	**1e**	1-Naphthyl	KHMDS	**2e**	91	1.0:0.56
10	**1e**		MeLi	**2e**	43	1.0:3.85
11	**1f**	9-Anthryl	KHMDS	**2f**	64	1.0:0.83
12	**1f**		MeLi	**2f**	10	1.0:0.73

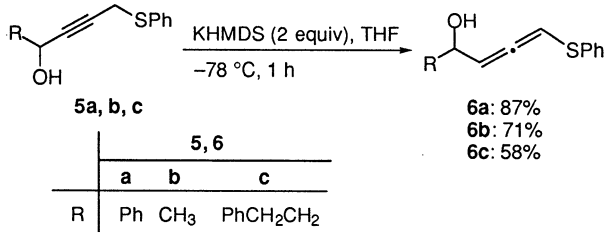
In order to study the effect of the substituent at the position 4, 1-phenylthio-4-(2-tetrahydropyranyloxy)-2-pentyne (**1b**), 6-phenyl-1-phenylthio-4-(2-tetrahydropyranyloxy)-2-hexyne (**1c**), 4-cyclohexyl-1-phenylthio-4-(2-tetrahydropyranyloxy)-2-butyne (**1d**), 4-(1-naphthyl)-1-phenylthio-4-(2-tetrahydropyranyloxy)-2-butyne (**1e**), and 4-(9-anthryl)-1-phenylthio-4-(2-tetrahydropyranyloxy)-2-butyne (**1f**) were respectively reacted with KHMDS and with MeLi in THF at −78°C to afford the corresponding (*E*)-**2** and (*Z*)-**2** as summarized in Table 1.[5a,6] As can be seen from Table 1, the stereochemistry of the reaction depends on both the substrate and the base used. Thus, KHMDS was more favorable for the formation of the (*E*)-isomer (entries 1, 5, 7, 9, 11) except for the case of **1b** (entry 3), while MeLi gave the (*Z*)-isomer in preference to the (*E*)-isomer (entries 2, 4, 6, 8, 10) with the exception of **1f** (entry 12).

When a mixture containing (*Z*)-**2a** and (*E*)-**2a** in a ratio of 1.0:0.20 was treated with KHMDS (1.1 equiv.) in THF at −78°C for 1 h, the ratio was changed to (*Z*)-**2a**/(*E*)-**2a** = 0.07:1.0 (92% yield). Similarly, when a mixture consisting of (*Z*)-**2a** and (*E*)-**2a** in a ratio of 0.17:1.0 was treated with MeLi (1.1 equiv.) under the same conditions, the ratio was converted to (*Z*)-**2a**/(*E*)-**2a** = 0.05:1.0 (42% yield) (Scheme 2).



Scheme 2.

It would be reasonable to assume that the presence of a masked hydroxyl group at the position 4 of the substrate **1** is essential for the formation of enynes **2**. As expected, 4-hydroxy-1-phenylthio-2-alkynes **5a–c** reacted smoothly with KHMDS to give the corresponding allenes **6a–c** in 87, 71, and 58% yields, respectively, instead of enynes **2** (Scheme 3).[5b,6]



Scheme 3.

In summary, a variety of 1-phenylthio-3-alken-1-ynes and 4-hydroxy-1-phenylthio-1,2-alkadienes (allenes) could be readily prepared from a common precursor, 4-hydroxy-1-phenylthio-2-alkyne.[6] Although stereoselective formation of allenes has not yet been attempted, the present reactions suggest a number of interesting possibilities for further work.

Acknowledgements

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3. For reviews of enediyne antibiotics and related compounds, see for example: (a) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387–1416; (b) Maier, M. E. *Synlett* **1995**, 13–26; (c) Grissom, J. M.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453–6518.
4. Van Boom et al. have demonstrated that the thioethers $RS–CH_2–C{\equiv}C–CH_2–OR^1$ reacted with EtO^- in liquid NH_3 to afford $RS–C{\equiv}C–CH{=}CH_2$ by the isomerization of initially formed cumulene, $RS–CH{=}C{=}C{=}CH_2$ (R = alkyl). As a possible alternative route, they also proposed 1,4-elimination of EtOH from allene intermediate $EtS–CH{=}C{=}CH–CH_2OEt$. See: (a) Van Boom, J. H.; Brandsma, L; Arens, J. F. *Rec. Trav. Chim.* **1966**, *85*, 580–600. See also: (b) Montione, R.; Alves, A.; Montijin, P. P.; Wildschut, G. A.; Bos, H. J. T.; Brandsma, L. *Rec. Trav. Chim.* **1970**, *89*, 97–109.
5. (a) Reaction of 1-phenylthio-4-(tetrahydro-2*H*-pyran-2-yloxy)-2-butyn (**1a**) with KHMDS and with MeLi. The reaction was carried out in parallel manner. 4-Phenyl-1-phenylthio-4-(tetrahydropyranyloxy)-2-butyn (**1a**: 0.0931 g, 0.312 mmol and 0.1004 g, 0.308 mmol) was placed in two-necked flask A and in flask B. The flasks were sealed with a rubber septum. After flushing with Ar, 2.8 mL or 3.0 mL of THF was injected through the septum into the flasks, which were then cooled to −78°C. KHMDS (0.5 M toluene solution; 0.61 mL, 0.3 mmol) was injected into the flask A and MeLi (1.14 M diethyl ether solution, 0.29 mL, 0.33 mmol) was injected into the flask B. After stirring at −78°C for 1 h, the reactions were quenched by the addition of saturated aqueous ammonium chloride. For flask A, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. The products were separated by column chromatography (*n*-hexane–EtOAc = 30:1) to afford a mixture of (*E*)- and (*Z*)-4-phenyl-1-phenylthio-3-buten-1-yne [(*E*)-**2a** and (*Z*)-**2a**] in 76% yield (0.0491 g) in a ratio of 1.0:0.06 (Table 1, entry 1). By a similar procedure, the reaction in flask B gave a mixture of (*E*)-**2a** and (*Z*)-**2a** in a yield of 45% (0.0317 g) in a ratio of 1.00:3.13. HRMS of purified mixture; Found: *m*/*z* 236.0614. Calcd for $C_{16}H_{12}S$: 236.0660. ^{1}H NMR. For (*Z*)-**2a** δ 5.89 (1H, d, $J_{3,4}$ = 12 Hz, H-3), 6.64 (1H, d, $J_{4,3}$ = 12 Hz, H-4), 7.22–7.50 (10H, m, aromatic H). For (*E*)-**2a** δ 6.39 (1H, d, $J_{3,4}$ = 16 Hz, H-3), 7.02 (1H, d, $J_{4,3}$ = 16 Hz, H-4), 7.22–7.50 (10H, m, aromatic H).

(b) Preparation of 4-hydroxy-4-phenyl-1-phenylthio-1,2-butadiene (**6a**). To a solution of 4-phenyl-1-phenylthio-2-butyn-4-ol (**5a**: 0.2035 g, 0.8 mmol)) in THF (8.0 mL) at −78°C was added KHMDS (0.5 M solution in toluene, 3.2 mL, 1.6 mmol). After the mixture was stirred at this temperature for 1 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane–ethyl acetate = 7:1) to afford **6a** as a diastereomer mixture (syrup, 0.1771 g, 87%) in a ratio of ca. 1:1 as determined by NMR. HRMS of the diastereomer mixture; Found: *m*/*z* 254.0681. Calcd for $C_{16}H_{14}OS$: 254.0766. ^{1}H NMR (500 MHz; $CDCl_3$; TMS = 0.00 ppm). For diastereomer A: δ 5.25 (1H, dd, $J_{1,4}$ = 2.29, $J_{3,4}$ = 5.96 Hz, H-4), 5.67 (1H, dd, $J_{1,3} = J_{3,4}$ = 5.96 Hz, H-3), 6.16 (1H, dd, $J_{1,3}$ = 5.96, $J_{1,4}$ = 2.29 Hz). For diastereomer B: δ 5.22 (1H, dd, $J_{1,4}$ = 2.29, $J_{3,4}$ = 5.96 Hz, H-4), 5.64 (1H, dd, $J_{1,3} = J_{3,4}$ = 5.96 Hz, H-3), 6.15 (1H, dd, $J_{1,3}$ = 5.96, $J_{1,4}$ = 2.29 Hz). IR: ν 1970 cm^{-1}.
6. 4-Hydroxy-1-phenylthio-2-alkynes **5** could be readily prepared by treatment of 1-phenylthio-2-propyne with EtMgBr, followed by reaction with an aldehyde. The reaction of alcohol **5** with dihydropyran gave **1**.