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One-Pot Synthesis of Silyl-Substituted Dihydro-2H-pyran-2-ols from 3-Phenyldimethylsilyl-1-diethylaminopropyne and Epoxides

Silke Schabbert and Ernst Schaumann*

Institut für Organische Chemie, Technische Universität Clausthal
Leibnizstraße 6, D-38678 Clausthal-Zellerfeld, Germany

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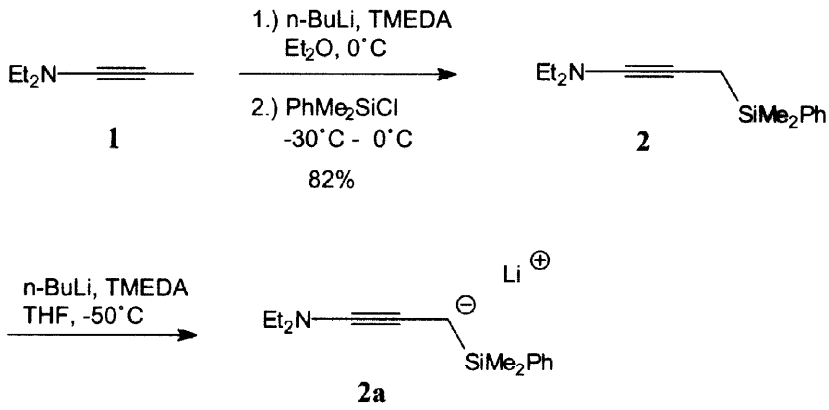
Abstract

The reaction of lithiated 3-phenyldimethylsilyl-1-diethylaminopropyne **2** with oxiranes **3** affords silyl-substituted dihydro-2H-pyran-2-ols **6** and / or **7**. The intermediates α,β-unsaturated 5-hydroxy aldehydes **5** can be isolated, but cyclize easily to the 6-membered oxacycles.

Keywords: Carbanions; Ynamines; Oxiranes; Cyclization

Ynamines are interesting and versatile building blocks in synthesis because of their extremely high reactivity [1,2,3,4,5,6]. Among the various applications, γ-metalated ynamines deserve special interest as homoenolate equivalents, but their chemistry has only been little explored [6,7]. Here we report reactions of lithiated 3-phenyldimethylsilyl-1-diethylaminopropyne **2** with various epoxides **3**. The cyclization of the resulting hydrolysis products **5** leads to unsaturated δ-lactols **6** and **7**.

The synthesis of the required silyl-substituted ynamine **2** is achieved by lithiation of 1-amino-1-propyne **1** with *n*-butyllithium / TMEDA in diethyl ether at 0 °C, followed by silylation with phenyldimethylsilyl chloride (Scheme 1) [5,7]. Compound **1** can be easily obtained by isomerization of the corresponding propargylamine [2,8].



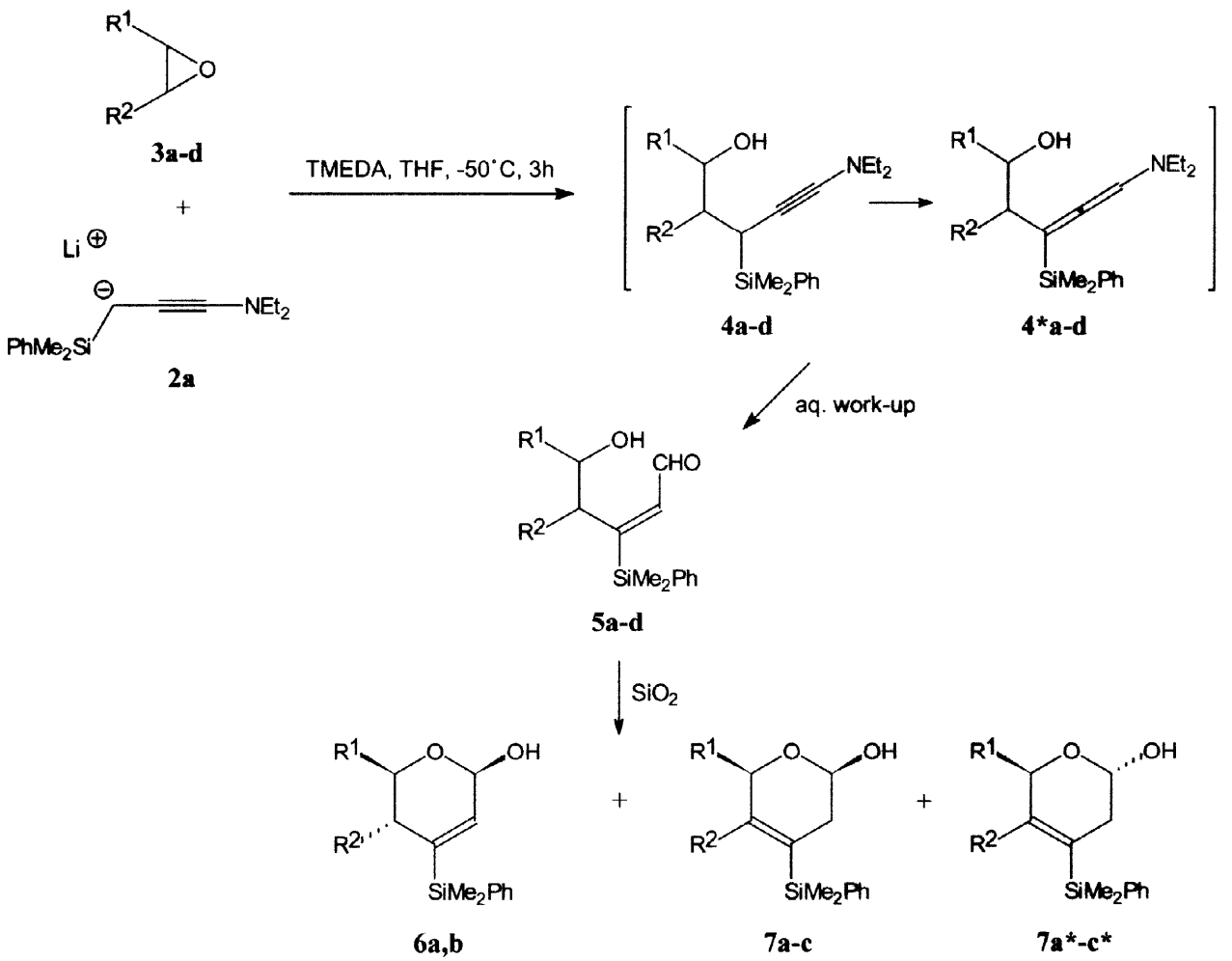
Scheme 1

PII: S0040-4020(98)01118-1

Metalation of ynamine **2** with *n*-butyllithium / TMEDA in tetrahydrofuran at -50 °C furnishes the desired silyl-stabilized alkynyl anion **2a**, which can act as nucleophile in reactions with epoxides.

This anion **2a** opens the oxiranes **3** in a completely regioselective fashion at -50 °C (Scheme 2, Table 1). Only the sterically less hindered carbon of the epoxide is attacked by the carbon adjacent to the silyl group of the ynamine anion (γ-attack), resulting in the unstable intermediate **4**. No product of α-attack of the ambident anion **2a** is observed. Rapid hydrolysis of **4** during aqueous work-up leads to α,β-unsaturated aldehydes **5** (Scheme 2). Formation of **5** can only be rationalized via an allenic intermediate **4***, followed by the usual hydrolysis of enamines. Therefore we have to conclude that ynamines **4** tautomerize to **4*** under the basic reaction conditions.

Enals **5** are isolated as single diastereomers. The *E*-configuration is assigned to the C-C double bond of these 5-hydroxy aldehydes **5** as it allows to form the cyclic hemiacetals **6** and **7**. The cyclization of **5** occurs so easily that the crude product of the epoxide ring-opening by **2a** already consists of a mixture of the corresponding cyclic compound and the 5-hydroxy aldehyde **5**. Purification of the crude material by column chromatography on silica gel completes the conversion of **5** to the hemiacetals.



Scheme 2

Table 1.
Reactions of **2a** with epoxides

Entry	R^1	R^2	5-Hydroxy aldehyde	5,6-Dihydro-pyran-2-ol	3,6-Dihydro-pyran-2-ol	Ratio **6:7:7***	Yield[a] (%)
1	Me	H	**5a**	**6a**	**7a,a***	2.5 : 1 : 1	65
2	Et	H	**5b**	**6b**	**7b,b***	2.5 : 1 : 1	57
3	$BnOCH_2$	H	**5c**	---	**7c,c***	0 : 1 : 1	42
4	$-(CH_2)_4-$		**5d**	---	---		4[b]

a) Total isolated yield of oxacycles
b) Isolated yield of pure **5d**

In contrast to the present results, the reported reactions of the corresponding lithiated trimethylsilyl-substituted ynamine with aldehydes and ketones and subsequent hydrolysis lead not only to the corresponding 4-hydroxy aldehydes (γ-attack), but also to α-hydroxy ketones as products of an α-attack of the ynamine anion [9]. The *Z*-configuration of the isolated unsaturated 4-hydroxy aldehydes was suggested by the author because no cyclic hemiacetals were detected. In our case, the presence of the bulky phenyldimethylsilyl substituent obviously favors the *E*-configuration of **5**, which is required for the observed formation of the oxacycles **6** and **7**.

In addition, our investigations show that the formation of different products **6** or **7** by cyclization depends on the bulk of the substituent R^1 in **5**. If R^1 is a methyl or ethyl group (R^2 = H, Table 1, entries 1,2), a mixture of three cyclic compounds (ratio 2.5 : 1 : 1) is observed. One diastereomer of 5,6-dihydro-2H-pyran-2-ol **6a,b** as main product is formed selectively, in which the alkyl substituent at C-6 as well as the hydroxy group at C-2 are in equatorial positions. Moreover, two diastereomers of 3,6-dihydro-2H-pyran-2-ols **7a/a***, **b/b*** are obtained in a 1:1 ratio because of an allylic rearrangement of the double bond in **5a,b** prior to cyclization.

If R^1 is a sterically more demanding substituent as in the reaction of benzylglycidol (**3c**) with **2a** (R^2 = H, Table 1, entry 3), the corresponding α,β-unsaturated 5-hydroxy aldehyde **5c** can be isolated analogously. The following cyclization of **5c** by purification on silica gel furnishes both diastereomeric 3,6-dihydro-2H-pyran-2-ols **7c/c*** in 1:1 ratio selectively via allylic rearrangement. No formation of a 5,6-dihydro-2H-pyran-2-ol is observed in this case.

The sluggish reaction of cyclohexene oxide (**3d**) with ynamine anion **2a** (Table 1, entry 4) requires to raise the temperature to -30 °C. Unfortunately, the expected hydroxy aldehyde **5d** is then isolated only in very poor yield (4%) and a cyclic hemiacetal of **5d** is not detected. We suppose a *Z*-configuration of the double bond of this hydroxy aldehyde because of its bulky alkyl substituents R^1 / R^2.

Experimental Section

^1H and ^{13}C NMR: Bruker DPX-200 and AMX 400. - Infrared spectra: Bruker Vektor 22 spectrometer, as neat films. - Elemental analyses: Institut für Pharmazeutische Chemie, TU Braunschweig. - Column Chromatography: Merck silica gel (70-230 mesh), petroleum ether (PE) of boiling range 60-70 °C and ethyl acetate (EE) were used.

General Procedure: A solution of 1 equiv. of freshly synthesized ynamine **2** in dry THF (10 ml/mmol) is cooled to -50 °C. Then 1.2 equiv. of TMEDA and 1.2 equiv. of *n*-BuLi (1.6 *M* solution in *n*-hexane) are added slowly and the mixture is stirred for 1.5 h to form the orange anion **2a** completely. At -50 °C, 1.1 equiv. of epoxide **3** are added and for completion of the reaction stirring is continued at this temperature for 3 h. The cold mixture is hydrolyzed by addition of aqueous 1% K_2CO_3 solution and diethyl ether. After separation, the organic layer is washed with aq. NH_4Cl and brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting crude product, consisting of 5-hydroxy aldehyde and hemiacetal, is purified by column chromatography on silica gel (PE:EE, 10:1) to furnish the corresponding oxacycles exclusively.

Reaction of propene oxide (**3a**) gave a mixture of **6a** (1 diastereomer H-6_{ax}, H-2_{ax}) and **7a/a*** (2 diastereomers H-6_{ax}, H-2_{ax}, H-2_{eq}*) as colorless oil, ratio 2.5 : 1 : 1* (65%).
IR: 3398, 3069, 2969, 2903, 1428, 1383, 1249, 1113, 1068, 1029, 1006, 833, 816, 773, 733, 701 cm^{-1}; $C_{14}H_{20}O_2Si$ (248.40): calcd. C 67.69, H 8.11; found C 67.63, H 8.48

6-Methyl-4-phenyldimethylsilyl-5,6-dihydro-2H-pyran-2-ol (6a):
^1H NMR (400 MHz): δ, 0.38 (*s*, 6H, $SiMe_2$); 1.21 (*d*, *J* = 6.0 Hz, 3H, CH_3); 1.89 (*dddd*, *J* = 18.0, 10.4, 2.6, 1.4 Hz, 1H, H-5_{ax}); 1.99 (*ddd*, *J* = 18.0, 3.2, 1.2 Hz, 1H, H-5_{eq}); 3.60 (br.*s*, 1H, OH); 4.02 (*dqd*, *J* = 10.4, 6.0, 3.2 Hz, 1H, H-6_{ax}); 5.37 (br.*s*, 1H, H-2_{ax}); 6.07 (*td*, *J* = 2.6, 1.2 Hz, 1H, HC=C); 7.5 (*m*, 5H, arom. H); ^{13}C NMR (50 MHz): δ, -4.0 ($SiMe_2$); 21.0 (CH_3); 33.6 (CH_2); 62.8 (CHO); 89.2 (OCHO); 134.5 (*H*C=C); 140.1 (*C*=CH); 127.8, 129.2, 133.9 (arom. CH); 136.8 (arom. C); MS (m/z): 248 (1%, M^+); 233 (15%, M^+- CH_3); 135 (100%, $SiMe_2Ph$)

6-Methyl-4-phenyldimethylsilyl-3,6-dihydro-2H-pyran-2-ol (7a/a*):
^1H NMR (400 MHz): δ, 0.36, 0.37 (*s*, each 6H, $SiMe_2$); 1.27* (*d*, *J* = 6.8 Hz, 3H, CH_3*); 1.30 (*d*, *J* = 6.8 Hz, 3H, CH_3); 2.07* (*m*, 1H, H-3_{ax}*); 2.11 (*dddd*, *J* = 17.0, 8.4, 3.6, 2.4 Hz, 1H, H-3_{ax}); 2.25 (*dtd*, *J* = 17.0, 3.0, 1.2 Hz, 1H, H-3_{eq}); 2.37* (*dddd*, *J* = 17.2, 4.0, 3.2, 2.4 Hz, 1H, H-3_{eq}*); 3.60 (br.*s*, each 1H, OH); 4.42 (*m*, 1H, CHO); 4.51* (*m*, 1H, CHO*); 4.95 (*dd*, *J* = 8.4, 3.0 Hz, 1H, H-2_{ax}); 5.32* (*dd*, *J* = 4.0, 2.4 Hz, 1H, H-2_{eq}*); 5.86 (*m*, 1H, HC=C); 5.99* (*m*, 1H, HC=C*); 7.5 (*m*, each 5H, arom. H); ^{13}C NMR (50 MHz): δ, -3.97, -3.93 ($SiMe_2$); 20.5, 20.8 (CH_3); 31.7, 33.7 (CH_2); 65.0*, 72.3 (CHO); 89.9*, 93.5 (OCHO); 130.8, 133.1 (*C*=CH); 139.5*, 139.8 (*H*C=C); 127.8, 127.8, 129.1, 129.2, 133.6, 133.8 (arom. CH); 137.1, 137.2 (arom. C); MS (m/z): 230 (10%, M^+- H_2O); 215 (58%, M^+- H_2O-CH_3); 135 (100%, $SiMe_2Ph$)
No data of the intermediate hydroxy aldehyde **5a** can be given because of its rapid cyclization.

Reaction of 1,2-butene oxide (**3b**) gave a mixture of **6b** (1 diastereomer H-6_{ax}, H-2_{ax}) and **7b/b*** (2 diastereomers H-6_{ax}, H-2_{ax}, H-2_{eq}*) as colorless oil, ratio 2.5 : 1 : 1* (57%).
IR: 3387, 3069, 2964, 2933, 1428, 1250, 1115, 1068, 1046, 1026, 998, 835, 819, 780, 731, 700 cm^{-1}; $C_{15}H_{22}O_2Si$ (262.42): calcd. C 68.65, H 8.45; found C 68.66, H 8.62

6-Ethyl-4-phenyldimethylsilyl-5,6-dihydro-2H-pyran-2-ol (6b):
^1H NMR (400 MHz): δ, 0.37 (*s*, 6H, $SiMe_2$); 1.09 (*t*, *J* = 7.2 Hz, 3H, CH_3); 1.50 (*m*, 2H, CH_2-CH_3); 1.70 (br.*s*, 1H, OH); 1.87 (br.*dd*, *J* = 17.2, 11.2, 1H, H-5_{ax}); 1.98 (br.*dd*, *J* = 17.2, 2.8 Hz, 1H, H-5_{eq}); 3.77 (*m*, 1H, H-6_{ax}); 5.36 (br.*s*, 1H, H-2_{ax}); 6.07 (*m*, 1H, HC=C); 7.4 - 7.5 (*m*, 5H, arom. H); ^{13}C NMR (100 MHz): δ, -4.0 ($SiMe_2$); 12.5 (CH_3); 28.3 (CH_2-CH_3); 31.5 (CH_2); 67.9 (CHO); 89.2 (OCHO); 127.8, 129.2, 133.9 (arom. CH); 136.9 (arom. C); 134.8 (*H*C=C); 140.2 (*C*=CH)

6-Ethyl-4-phenyldimethylsilyl-3,6-dihydro-2H-pyran-2-ol (7b/b*):
^{1}H NMR (400 MHz): δ, 0.35, 0.36 (each *s*, 6H, $SiMe_2$); 1.11, 1.12 (each *t*, *J* = 7.2 Hz, 3H, CH_3); 1.50 (*m*, each 2H, CH_2-CH_3); 1.70 (br.*s*, each 1H, OH); 2.07, 2.25 (each br.*d*, *J* = 16.8 Hz, each 1H, CH_2); 2.36 - 2.46 (*m*, each 1H, CH_2); 4.24, 4.29* (each *m*, CHO); 4.93 (*dd*, *J* = 8.2, 3.2 Hz, 1H, H-2_{ax}); 5.32* (*dd*, *J* = 4.0, 2.0 Hz, 1H, H-2_{eq}*); 5.88, 6.02* (each *m*, 1H, HC=C); 7.4 - 7.5 (*m*, each 5H, arom. H); ^{13}C NMR (100 MHz): δ, -3.98, -3.93 ($SiMe_2$); 13.0, 13.1 (CH_3); 27.7, 28.0 (CH_2-CH_3); 30.4, 31.9 (CH_2); 74.4, 77.2 (CHO); 90.1, 93.5 (OCHO); 127.8, 127.8, 129.1, 129.2, 133.9, 133.9 (arom. CH); 137.2, 137.2 (arom. C); 131.4, 133.7 (*C*=CH); 138.5, 138.9 (H*C*=C)
5-Hydroxy-3-phenyldimethylsilyl-hept-2-enal (5b): oil
IR: 3416, 3069, 3050, 2961, 2929, 1678, 1428, 1252, 1114, 1067, 835, 732, 701 cm^{-1}; ^{1}H NMR (200 MHz): δ, 0.55, 0.57 (each *s*, 3H, $SiMe_2$); 0.92 (*m*, 3H, CH_3); 1.48 (*m*, 2H, CH_2-CH_3); 1.9 (br.*s*, 1H, OH); 2.58 (*d*, *J* = 7.2 Hz, 2H, CH_2); 3.62 (*m*, 1H, CHOH); 6.57 (*d*, *J* = 8.4 Hz, 1H, HC=C); 7.3 (*m*, 5H, arom. H); 9.77 (*d*, *J* = 8.4 Hz, 1H, H-C=O)

Reaction of benzylglycidol (**3c**) gave **7c/c*** (2 diastereomers H-6_{ax}, H-2_{ax}, H-2_{eq}*) as colorless oil, ratio 1 : 1* (42%).
6-Benzyloxymethyl-4-phenyldimethylsilyl-3,6-dihydro-2H-pyran-2-ol (7c/c*):
IR: 3415, 3067, 3028, 2956, 2923, 2860, 1453, 1428, 1249, 1113, 1028, 833, 816, 774, 734, 700 cm^{-1}; $C_{21}H_{26}O_3Si$ (354.52): calcd. C 71.14, H 7.39; found C 70.66, H 7.56; ^{1}H NMR (200 MHz): δ, 0.37 (*s*, each 6H, $SiMe_2$); 2.00 (br.*s*, each 1H, OH); 2.14, 2.23, 2.34, 2.44 (each *m*, 1H, CH_2); 3.56 (d, J = 5.2, 2H, CH_2O); 3.57 (d, J = 4.8, 2H, CH_2O); 4.55 (m, each 1H, CHO); 4.59 (br.*s*, each 2H, $PhCH_2$); 5.03 (*dd*, *J* = 6.8, 3.6 Hz, 1H, H-2_{ax}); 5.39* (*m*, 1H, H-2_{eq}*); 5.92, 6.00 (each br.*q*, *J* = 1.6 Hz, 1H, HC=C); 7.4 (*m*, each 10H, arom. H); ^{13}C NMR (50 MHz): δ,-4.08, -4.04 ($SiMe_2$); 31.7, 33.4 (CH_2); 68.6, 74.7 (CHO); 72.1, 72.2, 73.2, 73.3 ($BnOCH_2$, $PhCH_2$); 90.0, 92.5 (OCHO); 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 129.0, 129.1, 133.8, 133.9 (arom. CH); 133.6, 135.3 (*C*=CH); 134.7, 135.1 (H*C*=C); 136.9, 137.0, 137.8, 138.0 (arom. C)
6-Benzyloxy-5-hydroxy-3-phenyldimethylsilyl-hex-2-enal (5c): oil
IR: 3423, 3068, 3029, 2957, 2922, 1676, 1454, 1428, 1252, 1112, 837, 819, 734, 700 cm^{-1}; ^{1}H NMR (200 MHz): δ, 0.54, 0.56 (each *s*, 3H, $SiMe_2$); 2.4 (br.*s*, 1H, OH); 2.55 (*d*, *J* = 6.2 Hz, 2H, CH_2); 3.39 (*m*, 2H, CH_2O); 3.93 (*m*, 1H, CHOH); 4.53 (br.*s*, 2H, $PhCH_2$); 6.59 (*d*, *J* = 8.2 Hz, 1H, HC=C); 7.3 - 7.5 (*m*, 10H, arom. H); 9.75 (*d*, *J* = 8.2 Hz, 1H, H-C=O)

Reaction of cyclohexene oxide (**3d**) at -50°C to -30°C gave **5d** (1 diastereomer) as clear oil (4%).
3-(2-Hydroxy-cyclohexyl)-3-phenyldimethylsilyl-prop-2-enal (5d):
IR: 3406, 3069, 2959, 2932, 2858, 1673, 1627, 1449, 1428, 1252, 1117, 1088, 822, 782, 732, 700 cm^{-1}; ^{1}H NMR (200 MHz): δ, 0.55, 0.57 (each *s*, 3H, $SiMe_2$); 1.20, 1.70, 2.00 (*m*, 10H, CH_2, CH, OH); 3.68 (*td*, J = 10.0, 4.4 Hz, 1H, CHOH); 6.62 (*d*, *J* = 8.4 Hz, 1H, HC=C); 7.4 (*m*, 5H, arom. H); 9.78 (*d*, *J* = 8.4 Hz, 1H, HC=O)

Acknowledgements

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