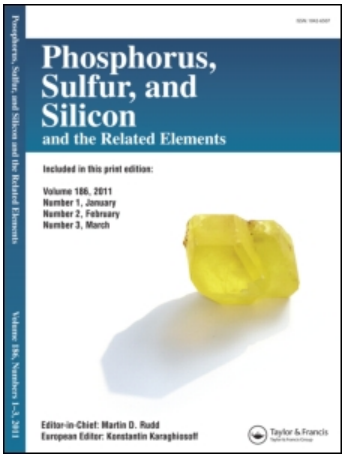

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AN EASY CONVERSION OF THE BAYLIS-HILLMAN ADDUCTS INTO *tert*-BUTYLDIMETHYLSILYL ETHERS WITH *tert*-BUTYLDIMETHYLSILYL CHLORIDE AND Li_2S

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AN EASY CONVERSION OF THE BAYLIS-HILLMAN ADDUCTS INTO *tert*-BUTYLDIMETHYLSILYL ETHERS WITH *tert*-BUTYLDIMETHYLSILYL CHLORIDE AND Li_2S

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The hydroxy group of the Baylis-Hillman adducts is protected with the t-butyldimethylsilyl (TBDMS) group using the reaction of adducts ***1a–h*** *with tert-butyldimethylsilyl chloride (TBDMSCl) in the presence of lithium sulfide under nearly acidic reaction conditions.*

Keywords: Baylis-Hillman adducts; *tert*-butyldimethylsilyl ethers; TBDMSCl; protecting group

INTRODUCTION

Recently, the key role of the Baylis-Hillman reaction[1] in the preparation of a variety of important products has been recognized by many organic chemists.[2]

The Baylis-Hillman adducts **1**, containing chemospecific functional groups in close proximity, have been extensively used in a number of transformation methodologies often involving a high level of stereoselectivity. These adducts are versatile building blocks for the synthesis of several important compounds[3] and have been exploited in the preparation of natural products such as kijanolid,[4] mycestericin E,[5] terpenticin,[6] insect pheromons[7] and nitrogen-containing heterocycles.[8,9]

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However, due to vital importance of the Baylis-Hillman adducts **1a–h** as very interesting acceptor reactants in many types of transformations, the protection of the hydroxy group may be essential in some of the reactions.

Chemists are often faced with the problem of having to use one or more protecting groups as part of a synthetic sequence. Factors that must be taken into account for identification of the most appropriate protecting groups are (1) the protecting group must withstand the reaction conditions, including those used to protect and deprotect other functional groups; (2) the protecting group must be easily introduced selectively at the desired site and in high yield; and (3) the protecting group must be easily removed selectively and in high yield.

Identification of the best protecting groups and the most appropriate conditions for performing the protection and deprotection steps becomes a relatively straightforward task. The role of silyl group has already been recognized of late as an important part of organic chemistry from both analytical and synthetic point of view, especially as protecting group in many synthesis of reasonable complexity.[11]

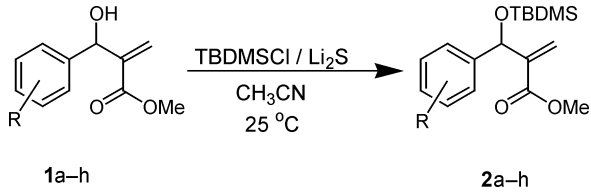
The popularity of silylation reagents is enhanced by their ease of use and formation of derivatives. In silylation, an active hydrogen is replaced by an alkylsilyl group such as trimethylsilyl (TMS) or TBDMS. Both TMS and TBDMS reagents are suitable for a wide variety of compounds, offer excellent thermal stability, and can be used under a variety of conditions and applications. Compared to their parent compounds, silyl derivatives are more volatile, less polar, and more thermally stable. The derivatives of TMS reagents are generally moisture sensitive, requiring them to be sealed to prevent deactivation. In response to this difficulty TBDMS reagents were introduced, which enabled the formation of derivatives 10,000 times more stable to hydrolysis than the TMS ethers.[12]

RESULTS AND DISCUSSION

TBDMS ethers are stable to aqueous or alcoholic base under the normal conditions for acetate saponification, and are also stable to hydrogenolysis (H_2—Pd) and mild chemical reduction (e.g., Zn—CH_3OH).[13] The specific reactions, which are outlined immediately below, provide an illustration of the stability and applicability of the TBDMS group in the protection of alcohols.

In continuation of our interest for the Baylis-Hillman adducts and transforming into a variety of natural and unnatural compounds[14] and

organosilicon compounds,[15] herein we wish to report our results for the protection of the hydroxy group of these adducts with the TBDMS group using the reaction of adducts **1a–h** with TBDMSCl and lithium sulfide (Scheme 1).

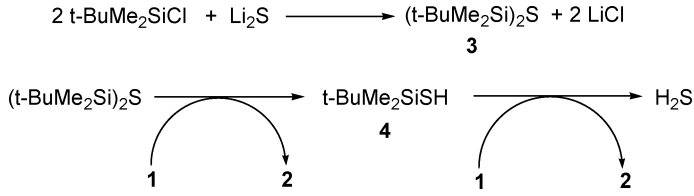


SCHEME 1

The procedure generally used for the preparation of TBDMS ethers involves treatment of alcohols with TBDMSCl in the presence of imidazole in dimethylformamide solution. The silylation of tertiary and allylic alcohols were, however sluggish under these conditions.[16] In the case of Baylis-Hillman type allylic alcohols used in this study, after addition of the silylating reagent and Li_2S in acetonitrile, the reactions were completed in 5–8 h in all the cases studied (**1a–h**). The results are summarized in Table I.

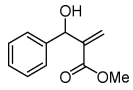
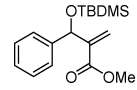
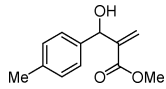
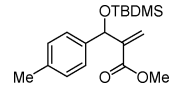
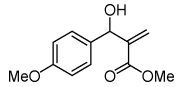
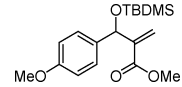
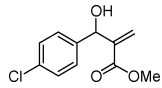
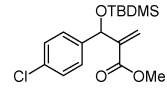
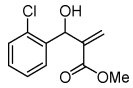
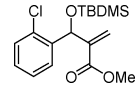
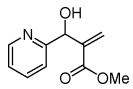
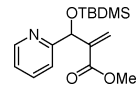
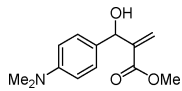
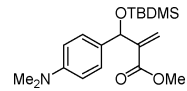
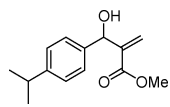
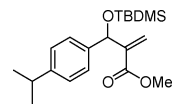
Silylation of the Baylis-Hillman adducts took place very smoothly at ambient temperature when a mixture of alcohol, TBDMSCl, and Li_2S (in a 1:2:1.5 molar ratio) in dry acetonitrile was stirred overnight. Yields were generally high, and the method provided an extremely mild, simple, and inexpensive way of *tert*-butyldimethylsilylation under weakly acidic conditions.[17]

The proposed mechanism of this reaction and the role of Li_2S is not clear, but a proposed mechanism of this transformation is depicted in Scheme 2. The reaction is initiated through the formation of a complex with the sulfide and TBDMSCl, resulting in in situ formation of a disilathiane-type equivalent **3**, which would be responsible for the remarkable silylating power of the reagent.[18] A rapid reaction with



SCHEME 2 A proposed mechanism of the silylation with *t*-$BuMe_2SiCl$ and Li_2S.

TABLE I Product Distribution Data and the Yield of the Products

Entry	Alcohols (**1**)	Products (**2**)[a]	Time (h)	% yield[b]
a			6	88[c]
b			7	85
c			7.5	84
d			5	90
e			6	82
f			6.5	79
g			7	78
h			8	80

[a]All compounds have been fully characterized spectroscopically by ^{1}H NMR, IR, and elemental analyses.

[b]Isolated yields.

[c]Analyzed by comparition of its spectroscopic data (^{1}H NMR, IR) with those of an authentic sample (Annunziata et al.[9]).

alcohol then ensues, leading to the hydrogensulfide silylating species **4** and concomitant release of the corresponding TBDMS ether and H_2S.

In conclusion, a practical, highly efficient, and convenient protocol with mild conditions (25°C) has been developed for *tert*-butyldimethylsilylation of the Baylis-Hillman adducts. This reaction can be applied to the protection of hydroxy groups and the synthesis of multiple-point pharmacophores of natural and unnatural compounds.

EXPERIMENTAL

General

Chemicals were purchased from Merck and Fluka. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN—O-Rapid analyzer. IR spectra were determined on a Shimadzu IR-470 spectrometer. ^{1}H NMR spectra were recorded on a 500 MHz Bruker DRX-500 instrument in $CDCl_3$ as solvent and TMS as internal standard. Preparative thin layer chromatography (TLC) was prepared from Merck Kieselgel 60 H, F_{254}, Art No 7730. GC was carried out using Buck Scientific 910 (capillary column, MXT-5, 15 m). All solvents used were dried and distilled according to standard procedures.

General Procedure for *tert*-Butyldimethylsilylation of Baylis-Hillman Adducts

To a well-stirred suspension of lithium sulfide (0.345 g, 7.5 mmol) in dry acetonitrile (15 ml) was added *tert*-butyldimethylsilylchloride (1.5 g, 10 mmol) under a nitrogen atmosphere. To this mixture was then added a solution of the corresponding alcohol **1** (5.0 mmol) in acetonotrile (5 ml), and the stirring continued until the reaction was completed. The reaction mixture was diluted with ether (20 ml), washed successively with water (2 × 20 ml) and brine (10 ml), and dried over anhydrous sodium sulfate. Evaporation of the ethereal extract afforded pure TBDMS ethers, which were further purified by vacuum distillation or recrystalization to afford pure silyl ether **2**. The isolated yield for each product is given in parentheses, and the IR and ^{1}HNMR data for the compounds **2b–h** are given below.

2b: yellow solid, m.p. 85–87°C, 85%. Found: C, 67.46; H, 8.81. $C_{18}H_{28}O_3Si$ requires: C, 67.50; H, 8.75%. IR (film, cm^{-1}): 3100, 2900, 2800, 1722, 1610, 1254. ^{1}H NMR ($CDCl_3$, δ): −0.1 (s, 3H), 0.00 (s, 3H), 0.99 (s, 9H), 3.62 (s, 3H), 5.63 (t, br., 1H), 6.13 (t, br., 1H), 6.26 (t, br., 1H), 6.77 (d, 2H, $J = 7.6$ Hz), 7.11 (d, 2H, $J = 7.6$ Hz).

2c: yellow solid, m.p. 89–91°C, 84%. Found: C, 64.20; H, 8.35. $C_{18}H_{28}O_4Si$ requires: C, 64.28; H, 8.33%. IR (film, cm^{-1}): 3100, 2900, 2800, 1720, 1612, 1253. ^{1}H NMR ($CDCl_3$, δ): −0.1 (s, 3H), 0.00 (s, 3H), 0.99 (s, 9H), 3.62 (s, 3H), 3.7 (s, 3H), 5.61 (t, br., 1H), 6.11 (t, br., 1H), 6.24 (t, br., 1H), 6.8 (d, 2H, $J = 7.7$ Hz), 7.13 (d, 2H, $J = 7.7$ Hz).

2d: white solid, m.p. 99–101°C, 90%. Found: C, 59.80; H, 7.44. $C_{17}H_{25}ClO_3Si$ requires: C, 59.91; H, 7.34%. IR (film, cm^{-1}): 3100, 2900, 2800, 1721, 1613, 1250. ^{1}H NMR ($CDCl_3$, δ): −0.1 (s, 3H), 0.00 (s, 3H),

0.99 (s, 9H), 3.66 (s, 3H), 5.65 (t, br., 1H), 6.15 (t, br., 1H), 6.26 (t, br., 1H), 7.12 (d, 2H, $J = 7.9$ Hz), 7.23 (d, 2H, $J = 7.9$ Hz).

2e: white solid, m.p. 96–98°C, 82%. Found: C, 59.83; H, 7.35. $C_{17}H_{25}ClO_3Si$ requires: C, 59.91; H, 7.34%. IR (film, cm^{-1}): 3109, 2900, 2800, 1722, 1615, 1253. ^1H NMR ($CDCl_3$, δ): −0.1 (s, 3H), 0.00 (s, 3H), 0.99 (s, 9H), 3.66 (s, 3H), 5.65 (t, br., 1H), 6.15 (t, br., 1H), 6.26 (t, br., 1H), 7.12–7.25 (m, 4H).

2f: green solid, m.p. 110–112°C, 79%. Found: C, 62.55; H, 8.27. $C_{16}H_{25}NO_3Si$ requires: C, 62.54; H, 8.14%. IR (film, cm^{-1}): 3150, 2900, 2800, 1725, 1625, 1256. ^1H NMR ($CDCl_3$, δ): −0.1 (s, 3H), 0.00 (s, 3H), 0.99 (s, 9H), 3.66 (s, 3H), 5.65 (t, br., 1H), 6.15 (t, br., 1H), 6.26 (t, br., 1H), 7.45–8.70 (m, 4H).

2g: green solid, m.p. 101–103°C, 78%. Found: C, 65.25; H, 8.97. $C_{19}H_{31}NO_3Si$ requires: C, 65.32; H, 8.88%. IR (film, cm^{-1}): 3100, 2900, 2800, 1720, 1621, 1252. ^1H NMR ($CDCl_3$, δ): −0.1 (s, 3H), 0.00 (s, 3H), 0.99 (s, 9H), 2.9 (s, 6H), 3.69 (s, 3H), 5.63 (t, br., 1H), 6.12 (t, br., 1H), 6.23 (t, br., 1H), 6.70 (d, 2H, $J = 7.8$ Hz), 7.11 (d, 2H, $J = 7.8$ Hz).

2h: yellow solid, m.p. 89–91°C, 80%. Found: C, 68.87; H, 9.30. $C_{20}H_{32}O_3Si$ requires: C, 68.96; H, 9.19%. IR (film, cm^{-1}): 3100, 2900, 2800, 1720, 1612, 1252. ^1H NMR ($CDCl_3$, δ): −0.1 (s, 3H), 0.00 (s, 3H), 0.99 (s, 9H), 1.3 (d, 6H), 3.10 (m, 1H), 3.62 (s, 3H), 5.63 (t, br., 1H), 6.13 (t, br., 1H), 6.26 (t, br., 1H), 7.10 (d, 2H, $J = 7.6$ Hz), 7.19 (d, 2H, $J = 7.6$ Hz).

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