Tetrahedron Letters, Vol. 22, No. 14, pp 1303 - 1306,1981 Printed in Great Britain 0040-4039/81/141303-04\$02.00/0 ©1981 Pergamon Press Ltd.

A CLASS OF NEW SILVLATING AGENTS. II. A HIGHLY REACTIVE REAGENT FOR INTRODUCTION OF THE TRIMETHYLSILVL GROUP.¹

Tarik Veysoglu and Lester A. Mitscher* Department of Medicinal Chemistry, Kansas University, Lawrence, Kansas 66045

Abstract. Trimethylsilyl enol ethers of pentane-2,4-dione and methyl acetoacetate react rapidly with alcohols at room temperature without the need for catalytic assistance to give high isolated yields of trimethylsilyl ethers.

The silylation of organic compounds-the replacement of protons attached to oxygen, nitrogen, sulfur, etc., by triorganosilyl (most often trimethylsilyl) groups--generally results in enhanced volatility, thermal stability, solubility in nonpolar solvents, and may alter reactivity towards attacking reagents, either at the site of the newly introduced silyl substituent or in adjacent positions of the molecule.² The recognition of these facts has led to an exponential increase³ in use and demand for silylating agents in chemistry and biochemistry laboratories for analysis by gas chromatography and mass spectrometry. Many excellent general purpose reagents and procedures employing trimethylchlorosilane (TMCS), trimethylsilylimidazole (TMSI), hexamethyldisilazane (HMDZ), and other silylamines, N-O-bis(trimethylsilyl)acetamide (BSA) and other silylamides (MTSA) and bis(trimethylsilyl)trifluoroacetamide), bis(trimethylsilyl)urea (BSU), and trimethylsilyldiphenylurea (TDPU) have been developed and are widely used to introduce the trimethylsilyl group. 4 Others, such as hexamethyldisiloxane⁵ and trimethylsilyltrifluoromethanesulfonate find more limited use. However, an ongoing quest to circumvent some of the drawbacks of these reagents is amply evidenced by the continuing appearance of publications describing newer and more superior reagents. Most recently trimethylsilylacetate-tetra-<u>n</u>-buty1-ammonium fluoride (ETSA-TBAF), 6 ketene methyl trialkylsilyl acetals 7 and ally1silanes 8 were introduced. Superior as they are, however, they also suffer from some drawbacks. first is not compatible with some functional groups, the ketene trialkylsilyl acetals are very tedious to prepare, and finally the allylsilanes require heating (70-80°C) with the substrate in the presence of an acid catalyst. As an extension of our work on the <u>t</u>-butyldimethylsilyl group, described in the preceding paper, we have discovered that the 0-trimethylsilyl ethers derived from 2,4-pentanedione and acetoacetate esters are extremely potent trimethylsilylating agents. These new silyl transfer reagents react quantitatively in several minutes at room temperature without catalytic assistance to give trimethylsilyl ethers of primary, secondary, and tertiary alcohols as shown in Scheme I. Also, they are very simple and inexpensive to prepare and generate only easy to remove, volatile and neutral byproducts in the reaction medium. Thus, other sensitive functional groups in the molecule would not be

 $\begin{array}{cccc} & & & & & & \\ & & & & \\ R & & & & \\ R & & \\ R & & \\ \end{array} \begin{array}{ccccc} & & & & & \\ R & & & \\ R & & & \\ R &$

affected by the use of these reagents.

The reagents react very rapidly with water, so normal precautions in their preparation and handling must be taken. Thus, reagent $\underline{1}_{\underline{4}}$ was prepared as follows: 27.4 g (1.15 equiv.) of freshly distilled trimethylchlorosilane was added to a mixture of 15.162 g of imidazole in 125 mL of dry THF under an argon atmosphere in a rigorously dried two-necked reaction flask fitted with a reflux condenser and a rubber septum. A jelly-like precipitate formed. Distilled 2,4-pentanedione (22 g; 22 mmoles) was injected through the septum and the septum was then replaced by a teflon-lined glass stopper. The reaction mixture was magnetically stirred under gentle reflux overnight. The end of the reaction was indicated by the replacement of the gel by crystalline imidazole hydrochloride. Cooling, followed by filtration through a sintered glass funnel filled with anhydrous Na₂SO₄ and then evaporation under reduced pressure (dry argon back flush) gave 48 g of a very mobile yellowish liquid. Fractional distillation using a 20 cm Vigreaux column gave 32.7 g (86% yield) of pure $\underline{1}_{\underline{4}}$ (b.p. 63 C/3 Torr (Lit. 66-8 C/4 Torr⁹ and 61-3 C/3 Torr¹⁰) which consists of the <u>cis</u> and <u>trans</u> isomers in a 3:1 ratio.¹¹ A very convenient and high yield preparation of $\underline{1}_{\underline{4}}$ from HMDZ was also recently described by Chu and Huckin.¹⁰ $\underline{1}_{\underline{5}}$ was obtained in the same manner and in similar yields: b.p. 73-5 C/8 Torr.

These reagents were tested with a representative primary (2-phenylethanol), secondary (trans-2methylcyclopentanol), and a tertiary (linalool (2a)) alcohol as well as with a base-sensitive glycol (terrein (3a)). The reactions were monitored by GLC, however, all the products were isolated and characterized. Both reagents reacted quantitatively in several minutes at room temperature without catalytic assistance with all the substrates, even the notoriously difficult linalool, 7,12 providing the useful trimethyl ethers (see table). The absence of extraneous by-products makes the resulting ethers extremely easy to isolate and analyze. Besides its volatility, the considerable water solubility of 2,4-pentanedione is, also, of significant advantage in this respect. When the alcohol is in excess, the reagent is consumed rapidly to give the silylated products at room temperature with or without solvent. Since the silylation reactions are basically equilibrium reactions, ^{3c,11} the polarity of the solvent was expected to exert some effect on the reaction. Indeed, reactions with these reagents are facilitated by more polar solvents (DMF) acetonitrile)THF) dichloromethane). In DMF, even linalool (a tertiary allylic alcohol) was quantitatively silylated in 5-6 minutes with stoichiometric amounts of la. When the silyl reagent is present in sufficient excess, the alcohol is silylated quantitatively and even more rapidly. In the extreme case represented by <u>neat</u> linalool, an 80% excess of 1a was required to give quantitative reaction in 10-15 minutes. Reagent 1a is more reactive than 1b. Both 1a and 1b, though stable for months, react rapidly with water, and therefore excess reagent is destroyed easily when necessary.

The following examples demonstrate the typical procedure used: 1. A slight molar excess of reagent <u>1a</u> (182 mg) was added to a solution of terrein (77 mg; 0.5 mmole) in dry DMF (1.5 ml) in a 4 ml vial with a teflon septum. The solution was shaken for 20 mins. and the volatile compounds were removed under reduced pressure to give 163 mg of a liquid which was dissolved in 3 ml CCl₄, filtered through a sintered glass funnel and concentrated to give 143 mg (96%) of glc and analytically pure oily terrein ditrimethylsilyl ether (<u>3b</u>): nmr (CCl₄) T9.80 (s, 18H), 8.10 (d, J=6 Hz, 3H), 5.93 (d, J=3 Hz, 1H), 4.20 (s, 1H), and 3.30-3.77 (m, 2H); ir (CCl₄) 2980, 1720, 1642, 1590, 1442, 1360, 1335, 1245, 1170, 1134, 1100, 1040, 955, 895, 870, and 830 cm⁻¹; eims (m/e) 298, 293, 193, 179,

Alcohol	Reagent	Conditions for Quantitative Conversion to Product as Judged by GLC ¹²	Isolated Yie
2-phenylethanol	la	5-6 mins., neat, r.t. 3-5 mins., DMF, r.t.	84% ¹⁴
	1b	5-6 mins., neat, r.t. 3-5 mins., DMF, r.t.	
<u>trans</u> -2-methylcyclopentanol	la	8-10 mins., neat, r.t. 5-6 mins., DMF, r.t.	80% ¹⁴
	1b	8-10 mins., neat, r.t. 5-6 mins., DMF, r.t.	
linalool (2a)	la	8-10 mins., DMF, r.t.	75-85% ¹⁴
terrein (3a)	la	20 mins., DMF, r.t.	96%

147 (base), 75 and 59; found: C, 56.05; H, 8.60. 2. <u>la</u> (3.490 g; 20.2 mmole) was added to distilled linalool (3.01 g; 20 mmole) in 20 ml dry DMF. After shaking 10 mins. the solution was extracted with ligroin (5 x 10 ml), the combined extracts were cooled and then washed with cold water (4 x 10 ml), dried (Na_2SO_4), and concentrated. The resulting product was distilled to give 3.758 g of <u>2b</u>: b.p. 134 C/98 Torr; nmr (CCl₄) T9.90 (s, 9H), 8.56 (s, 3H), 8.46 (s, 3H), 8.35 (s, 3H), 4.8-5.23 (2H), and 3.95-4.43 (2H); ir (CCl₄) 2950, 2925, 2885, 1450, 1410, 1370, 1250, 1175, 1115, 1045, 990, 860, and 830 cm⁻¹; eims (m/e) 226, 211, 183(base), 121, 93, 80, 75, and 73; found: C, 68.80; H, 11.60.

OR

$$2a, R=H$$

 $2b, R=(CH_3)_3Si$
Che ease of preparation of these reagents, their high react:

3b, R=(CH₃)₃S1 The ease of preparation of these reagents, their high reactivity and the ease with which pure products can be obtained persuade us that these new silylating agents will find substantial use. Our present efforts in this area involve a survey of the reactivity of other functional groups toward these and analogous reagents.

Acknowledgement: This work was supported by USPHS Grant GM/HL 26553. References:

1. Paper I. T. Veysoglu and L. A. Mitscher, <u>Tetrahedron</u> Letters, preceeding paper (1981).

2a) J. F. Klebe, <u>Accounts Chem. Res.</u>, 3, 299 (1970); b) C. A. Roth, <u>Ind. Eng. Chem. Prod. Res. Develop.</u> 11, 134 (1972); c) S. S. Washburne, <u>J. Organomet. Chem.</u>, 83, 155 (1974); d) <u>idem, ibid.</u>, 123, 1 (1976); e) E. W. Colvin, <u>Chem. Soc. Reviews</u>, 7, 15 (1978); and f) A. Hosomi, <u>Kagaku No Ryoiki</u>, 29, 528 (1975).

3. B. E. Cooper, Chem. Ind., 1978, 794.

4a) A. E. Pierce, "Silylation of Organic Compounds," 1968, Pierce Chemical Co., Rockford, Illinois;
b) B. Arkles, "<u>Techniques for Silylation</u>" in <u>Silicon Compounds, Register and Review,</u> 1979, Petrarch Systems, Levitton, Pa.; and c) J. F. Klebe, H. Finkbeiner and D. M. White, <u>J. Am. Chem</u>. 1306

Soc., 88, 3390 (1966).

- 5. H. W. Pinnick, B. S. Bal, and N. H. Lajis, Tetrahedron Lett., 1978, 4261.
- 6. S. E. Nakamura, T. Murofushi, M. Shimizu, and I. Kuwajima, J. Am. Chem. Soc., 98, 2346 (1976).
- 7. Y. Kita, J. Haruta, J. Segawa and Y. Tamura, Tetrahedron Lett., 1979, 4311.
- 8. T. Morita, Y. Okamoto, and H. Sakurai, Tetrahedron Lett., 1980, 835.
- 9. R. West, J. Am. Chem. Soc., 80, 3246 (1958).
- 10. D. T. W. Chu and S. N. Huckin, Can. J. Chem., 58, 138 (1980).
- 11. T. J. Pinnavaia, W. T. Collins, and J. J. Howe, <u>J. Am. Chem. Soc</u>., <u>92</u>, 4544 (1973).
- 12. R. G. Visser, H. J. T. Bos, and L. Brandsma, Rec. Tray. Chim. Pays. Bas., 99, 70 (1980).
- 13. The reactions were monitored and purity was established in all cases using a Varian Model 3700 Gas Chromatograph; flame ionization detector; He; a 3% Se-30 on Chromasorb W 80/100 column and column temps. of 70-210 C.
- 14. The actual yields are considerably higher, loss in isolated yields incurred because of small quantities distilled.

(Received in USA 3 November 1980)