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CHLOROETHOXY(TRIMETHYL)SILANE : A HARD-BASE TRAP WHICH PRESERVES TMS ETHER GROUPS AND IMPROVES THE WITTIG METHYLENATION OF GIBBERELLINS

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SUMMARY: A reagent, 2-chloroethoxy(trimethyl)silane (CETS), has been devised which ensures the preservation of TMS ether groups during Wittig methylenation in protic media and which makes this formerly capricious reaction with 16-keto gibberellins a reliable and straightforward procedure.

In this letter we report the development of a reagent [viz. $Me_3SiOCH_2CH_2Cl$ (1)] which renders trimethylsilyl (TMS) protecting groups for alcohols compatible with Wittig methylenation in protic media. The reagent traps oxide bases and is operationally equivalent to chlorotrimethylsilane, but with attenuated reactivity.

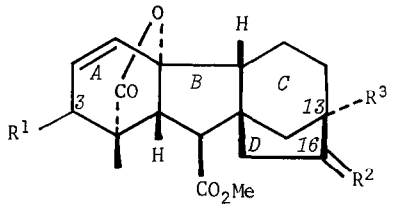
The general need for such a hard-base trap became apparent when we experienced considerable difficulty with Wittig methylenation of the D-ring cyclopentanone function in gibberellins, e.g. (2) → (3). Bicyclooctanones of this type are notoriously unreactive, and in simpler related substrates the use of salt-free ylide,[1] HMPA cosolvent,[2] or Me_2SO solvent[3] have been recommended with excesses of reagent at elevated temperature. These forcing conditions, however, are incompatible with the A-ring functionality of most gibberellins.

A gentle procedure which we have adopted for substrates unencumbered at C(13) involves titrating the ketone in THF with the yellow solution of ylide from $Ph_3P^+CH_3Br^-$ and *t*-BuOK using *t*-BuOH as cosolvent.[4] Thus, gibberellin A_7 and A_4 intermediates (4) and (10) were converted into their respective C(16)-methylene derivatives (5) and (11) within a few minutes at 20°.[5] Transformation of the more hindered[6] A_1 substrate (12) into (13), required 5 eq. of ylide for 20-30 min, but occasionally the yield was low, and above 20° inversion at C(3) began to occur.[7]

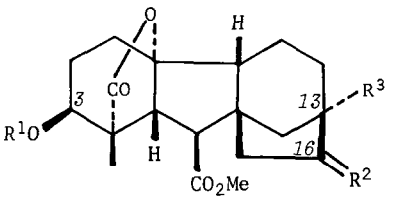
With the much more sensitive A_3 norketone (6) it was impossible to carry out methylenation to (7) under our usual conditions without considerable epimerization at C(3) to give (8).[8] Although the corresponding C(3)-benzoate (2) could be converted into (3), the reaction was extremely capricious and often gave a *seco*-diene mixture (14)[7] as the major product, especially on scales $\lesssim$ 20 μM.

Since the need to methylenate highly functionalized substrates arises quite often during synthesis, we have sought a general solution to the difficulties outlined above.

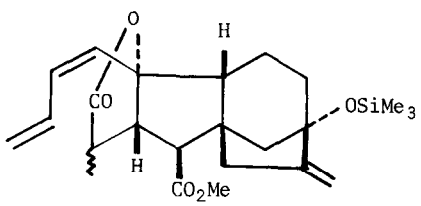
To probe the mechanism of the C(3) inversion in silyl ethers (6) and (12), a 1:1 mixture of the bis-silyl ether (7)[9] (methyl gibberellate, Me_3SiCl, *i*-Pr_2NEt, CH_2Cl_2) with the d_{18}-derivative (9)[9] was subjected to the Wittig conditions used for (6), then the silyl ether mixture analysed by mass spectrometry. The observed ratio of M^+ (d_0:d_9:d_{18}) ≈ 1:2:1 indicated that TMS group-transfer was intermolecular. Furthermore, *t*-BuOK alone, rapidly cleaved the silyl ethers. It seemed, therefore, that a trace of *t*-BuO^- (in equilibrium with the ylide), or some adventitious base, was triggering a chain reaction by cleaving the 3β-silyl ether to form the 3β-alkoxide which then undergoes a retro-aldol/aldol epimerization to the thermodynamically more-stable 3α-alkoxide. This intermediate then attacks further 3β-silyl ether, perpetuating the chain process.



	R^1	R^2	R^3
(2)	β-OCOPh	O	$OSiMe_3$
(3)	β-OCOPh	CH_2	$OSiMe_3$
(4)	β-OCOPh	O	H
(5)	β-OCOPh	CH_2	H
(6)	β-$OSiMe_3$	O	$OSiMe_3$
(7)	β-$OSiMe_3$	CH_2	$OSiMe_3$
(8)	α-$OSiMe_3$	CH_2	$OSiMe_3$
(9)	β-$OSi(CD_3)_3$	CH_2	$OSi(CD_3)_3$



	R^1	R^2	R^3
(10)	PhCO	O	H
(11)	PhCO	CH_2	H
(12)	Me_3Si	O	$OSiMe_3$
(13)	Me_3Si	CH_2	$OSiMe_3$



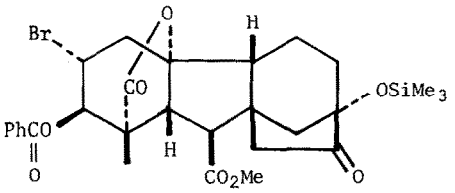
(14)

To circumvent this problem, an electrophile was needed which would intercept either bases nucleophilic towards the 3β-TMS ether, or the 3β-alkoxide before isomerization, without generating another nucleophilic species or rapidly destroying the Wittig reagent. We reasoned that chloroethoxy(trimethyl)silane [CETS(1)] could fulfill our requirements, because nucleophilic attack on silicon should give ethylene oxide and chloride ion.[10]

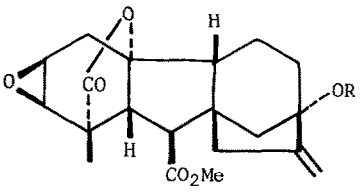
In practice (see below), the addition of 20 eq. of CETS(1) to a THF solution of ketone (6)[11] essentially suppressed epimerization of the 3β-TMS ether during Wittig methylenation. Isolation of the resulting olefin (7)[9] was extremely easy and, moreover, the hydroxy groups were readily unmasked by brief treatment with weak acid to give methyl gibberellate in almost quantitative yield.

Remarkably, when benzoate (2)[11] was subjected to methylenation in the presence of CETS, debenzoylation and TMS group-transfer occurred to give the bis-TMS olefin (7) directly, in virtually quantitative yield, with no sign of *seco*-dienes (14), and only a trace of the 3α-epimer (8).[9] CETS(1) has a profound effect upon the behaviour of bromo-benzoate (15)[11] during the Wittig reaction: when (15) was treated with 1 eq. Wittig reagent before adding (1), and then more ylide, the precursor (7) to gibberellic acid was obtained; when (1) was added before any ylide, however, (15) gave the epoxide (16)[9] which was readily converted into gibberellin A_6 methyl ester (17).[9,12]

Thus, the problems associated with the use of TMS ethers during Wittig reactions in hydroxylic media have been overcome through the addition of CETS. In view of the merits of TMS ethers for hydroxy-protection in complex labile molecules we expect that CETS will find, general use in synthesis. With the specific examples in hand, the once capricious Wittig methylenation of 16-keto gibberellins has become a thoroughly reliable, high yielding, and convenient operation.



(15)



	R
(16)	$SiMe_3$
(17)	H

GENERAL PROCEDURE

(a) *2-Chloroethoxy(trimethyl)silane:* CETS was prepared by adding at 5° under N_2, $HOCH_2CH_2Cl$ (6.7 ml, 0.1 mol) to Me_3SiCl (13.2 ml, 0.105 mol) and *i*-Pr_2NEt (18.3 ml, 0.105 ml) in CH_2Cl_2 (75 ml), then diluting with ether-pentane (4:1, 100 ml), filtering off the salt, washing with aqueous $NaHCO_3$ (10%), and drying. Distillation gave a colourless liquid (13 g, 95%), bp 132°C (lit.[13] 72-73°, 33 mm); NMR δ 0.12 (s, 9H), 3.56 (t, J = 6 Hz, 2H), 3.84 (t, J = 6 Hz, 2H); MS *m/z* (relative intensity) 137 (36), 93 (100), 73 (34); HRMS 137.0193, calcd for ($C_5H_{13}{}^{35}ClOSi$ -Me) 137.0190.

(b) *$Ph_3P{=}CH_2$ reagent (0.1 M):* dry $Ph_3\overset{+}{P}CH_3\bar{B}r$ (357 mg, 1.0 mmol) was stirred in THF (6.75 ml) and treated at 20°C under N_2 with *t*-BuOK in *t*-BuOH (0.75 ml, 1 M solution from K and *t*-BuOH, 0.75 mmol). After 0.5 h, the flask was cooled to 14°C and the precipitate allowed to settle (∿ 0.5 h). The clear yellow supernatant was withdrawn through a septum as required.

(c) *Methylenation Procedure:* a colourless solution of ketone (0.1 mmol) in dry THF (2.5 ml) containing CETS (304 mg, 2 mmol) was stirred under N_2 at 20°C and treated dropwise with the $Ph_3P{=}CH_2$ reagent until pale yellow (indicating that adventitious water had been consumed); then, 1.0 ml (0.1 mmol) reagent was added during 5 min followed at hourly intervals by aliquots of 0.5 ml (0.05 mmol) to complete the methylenation (and debenzoylation plus TMS transfer where appropriate; silica TLC, pentane:EtOAc, 6:1). The concentrated (∿ 0.3 ml) reaction mixture was then passed quickly through a column of silica (100 mm x 10 mm, activity 3) with pentane:EtOAc (6:1), the eluate (10 ml) concentrated, and the residue subjected to reduced pressure (0.05 mmHg) for 18 h to afford essentially pure olefinic product.

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3. R. Greenwald, M. Chaykovsky and E.J. Corey, *J. Org. Chem.*, 28, 1128 (1963).
4. *t*-BuOH ensures reprotonation of the enolate which forms readily from C(16) carbonyl function. Moreover, protic media have been noted to enhance generally the rate and yield of Wittig reactions, see: M. Schlosser and K.F. Christmann, *Angew. Chem. internat. Edit.*, 3, 636 (1964); J.-M. Conia and J.-C. Limasset, *Bull. Soc. chim. Fr.*, 1936 (1967); R.J. Anderson and C.A. Henrick, *J. Am. Chem. Soc.*, 97, 4327 (1975).
5. A.L. Cossey, L. Lombardo and L.N. Mander, *Tetrahedron Lett.*, 21, 4383 (1980); data for (5) ref. 9.

6. C(13)-OH protection is necessary to prevent a keto-carbinol rearrangement[7] but the options are limited: large C(13)-groups (e.g. THP ether) severely inhibit methylenation and mild conditions are mandatory for unmasking the C(13)-alcohol function.
7. L. Lombardo, L.N. Mander and J.V. Turner, *J. Am. Chem. Soc.*, 102, 6626 (1980).
8. Corey has noted the lability of TMS ethers in Wittig reactions and has advocated the use of the more stable *t*-butyldimethylsilyl group, [see: E.J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 94, 6190 (1972)] but we were unable to add this, or a triethylsilyl group to the 3β-hydroxy function in gibberellins. The poor nucleophilicity of the 3β-hydroxy groups is probably due to a combination of steric and electronic factors [see: L. Lombardo, L.N. Mander and J.V. Turner, *Aust. J. Chem.*, 34, 745 (1981)].
9. Selected data as follows: (**5**) mp 152-153°, IR 1760, 1715, 1640 cm^{-1}; ^1H NMR δ 1.22 (s, 3H), 2.82 [d, J = 11 Hz, H(6)], 3.49 [d, J = 11 Hz, H(5)], 3.72 (s, 3H), 4.86 (br s, 1H), 4.98 (br s, 1H), 5.56 [d, J = 4 Hz, H(3)], 5.98 (dd, J = 4,8 Hz, H(2)], 6.40 (d, J = 8 Hz, H(1)]; 7.44 and 8.04 (m, 5H); HRMS 448.1878, calcd for $C_{27}H_{28}O_6$ 448.1886.
(**7**) mp 96°C; $[\alpha]_D^{18}$ +150° (c. 0.5, $CHCl_3$); IR 1770, 1732, 1240, 1130, 1055, 875, 830 cm^{-1}; ^1H NMR δ 0.12 [s, 9H, C(13) OTMS], 0.16 [s, 9H, C(3) OTMS], 1.14 (s, 3H), 2.16 (br s, 2H), 2.76 [d, J = 10 Hz, H(6)], 3.32 [d, J = 10 Hz, H(5)], 3.72 (s, 3H), 4.10 [d, J = 4 Hz, H(3)], 4.92 (br s, 1H), 5.22 (br s, 1H), 5.72 [dd, J = 4 Hz, 10 Hz, H(2)], 6.20 [d, J = 10 Hz, H(1)]; MS *m/z* (relative intensity) 504 (100); HRMS 504.2350, calcd for $C_{26}H_{40}O_6Si_2$: 504.2363.
(**8**) ^1H NMR δ 0.12 (s, 9H), 0.13 (s, 9H), 1.17 (s, 3H), 2.14 (br s, 2H), 2.76 [d, J = 10 Hz, H(6)], 2.94 [d, J = 10 Hz, H(5)], 3.72 (s, 3H), 4.24 [br s, H(3)], 4.92 (br s, 1H), 5.20 (br s, 1H), 5.70 [dd, J = 3,10 Hz, H(2)], 6.16 [d, J = 10 Hz, H(1)]; MS *m/z* 504 (M^+, base peak).
(**9**) ^1H NMR as for (7) but devoid of resonances δ 0.12, 0.16; MS *m/z* 522 (M^+).
(**16**) ^1H NMR δ 0.12 (s, 9H), 1.30 (s, 3H), 2.66 [d, J = 9 Hz, H(6)], 3.08 [d, J = 9 Hz, H(5)], 3.14 [br s, H(2,3)], 3.68 (s, 3H), 4.90 (br s, 1H), 5.20 (br s, 1H); MS *m/z* 432 (M^+), ≡ MS authentic sample.[12]
(**17**) ^1H NMR δ 1.28 (s, 3H), 2.66 [d, J = 9 Hz, H(6)], 3.08 [d, J = 9 Hz, H(5)], 3.14 [br s, H(2,3)], 3.68 (s, 3H), 4.92 (br s, 1H), 5.20 (br s, 1H); IR, MS ≡ IR, MS authentic sample;[12] HRMS 360.1576 calcd for $C_{20}H_{24}O_6$ 360.1573.
10. Phosphoranes can be generated from phosphonium salts and ethylene oxide, so the latter was not expected to interfere with methylenation, see: J. Buddrus, *Chem. Ber.*, 107, 2050 (1974); J. Buddrus and W. Kimpenhaus, *Chem. Ber.*, 107, 2062 (1974).
11. Full details for the preparation of this ketone will be described in a future publication.
12. J. MacMillan, J.C. Seaton and P.J. Suter, *Tetrahedron*, 18, 349 (1962); we are grateful to Professor MacMillan for providing authentic spectra of GA_6-derivatives.
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