THE JOURNAL OF Organic Chemistry®

VOLUME 46, NUMBER 19

SEPTEMBER 11, 1981

Acylation of Ketone Silyl Enol Ethers with Acetyl Tetrafluoroborate. A Synthesis of 1,3-Diketones

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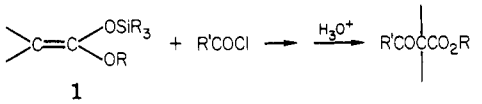
Received March 10, 1981

Silyl enol ethers, obtained by silylation of ketones, are acylated with acetyl tetrafluoroborate to give 1,3-diketones in reasonable yields. The *tert*-butyldimethylsilyl enol ether of cyclohexanone gives a nearly quantitative yield of acetylcyclohexanone, while the trimethylsilyl enol ethers of cyclohexanone and other ketones give moderate yields of the corresponding 1,3-diketones. The regiospecificity of the reaction was studied with the isomeric silyl enol ethers of 2-methylcyclohexanone.

The trialkylsilyl derivatives of esters (silyl ketene acetals, **1**) are readily C-acylated with acid chlorides to furnish a simple synthesis of β-keto esters (eq 1).[1,2] In contrast, the



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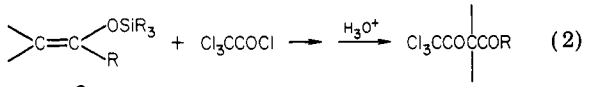
less reactive trialkylsilyl derivatives of ketones (silyl enol ethers, **2**) are C-acylated only by polyhalogenated acid chlorides (eq 2).[3] Simple acid chlorides either do not react



(2)

2

or, in the presence of catalysts such as mercury(II) chloride, react to give exclusively O-acylated products, **3** (eq 3).[4]

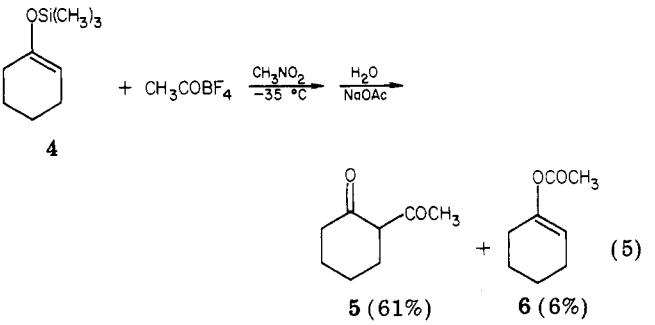
$$\mathbf{2} + CH_3COCl \xrightarrow{HgCl_2} \xrightarrow{H_3O^+} \underset{\mathbf{3}}{CH_3CO_2CR{=}C<} \quad (3)$$

We find that a variety of trialkylsilyl enol ethers are readily C-acylated with acetyl tetrafluoroborate to give the corresponding 1,3-diketones in reasonable yields (eq 4). We report here some of the initial results of our study of this reaction.

$$\mathbf{2} + CH_3COBF_4 \xrightarrow[-35\ °C]{CH_3NO_2} \xrightarrow{NaOAc} RCOCCOCH_3 \quad (4)$$

Results and Discussion

Reaction of 0.5 M nitromethane solution of the trimethylsilyl enol ether of cyclohexanone, **4**, with an equivalent amount of acetyl tetrafluoroborate followed by hydrolysis with aqueous sodium acetate gave a 61% yield of the C-acylated product, **5**, together with 6% of the O-acylated isomer, **6**, and 30% recovered cyclohexanone (eq 5). The same sequence conducted at 0.25 M concentration in nitromethane gave slightly more of the C-acylated product (65% yield of **5**) and none of the O-acylated product. Prior to the hydrolysis step, the major component in the reaction mixture is the boron fluoride complex **7**. Since **7** is known[5] to be readily formed by reaction of **5** with boron trifluoride, the stoichiometry of the acylation reaction is most probably as shown in eq 6 and 7.



(5)

4 **5** (61%) **6** (6%)

$$\mathbf{4} + CH_3COBF_4 \rightarrow \mathbf{5} + (CH_3)_3SiF + BF_3 \quad (6)$$

Hydrogen fluoride generated in the formation of complex **7** may then react with **4** to generate cyclohexanone, and this protonolysis of starting materials is probably a

(1) Kramarova, E. N.; Baukov, Y. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1973**, *43*, 1857.
(2) Rathke, M. W.; Sullivan, D. F. *Tetrahedron Lett.* **1973**, 1297.
(3) (a) Jarvie, A. W. P. *Organomet. Chem. Rev. Sect. A* **1970**, *6*, 153. (b) Murai, S.; Kuroki, Y.; Hasegawa, K.; Tsutumi, S. *J. Chem. Soc., Chem. Commun.* **1972**, 946. (c) For reaction with oxaloyl chloride see: Murai, S.; Hasegawa, K.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 636.
(4) Rasmussen, J. K. *Synthesis* **1977**, 98.
(5) Wang, C. B.; Chang, C. K. *Synthesis* **1979**, 549.

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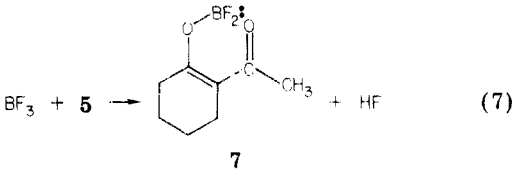
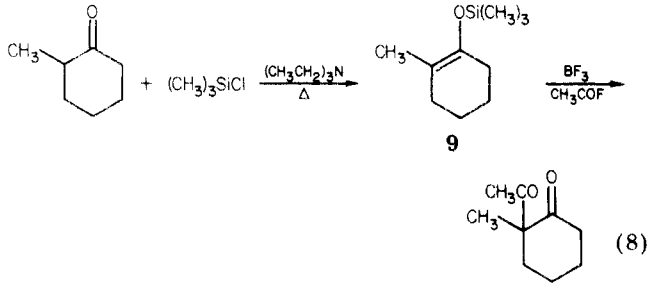


7

major factor limiting the yield of acylation product. In accord with this, the *tert*-butyldimethylsilyl enol ether of cyclohexanone, **8**, which is presumably less reactive to hydrogen fluoride[6] cleavage, was acylated in nearly quantitative yield (90% C-acylated product **5**, no O-acylated product **6**).

Results obtained for the acylation of a variety of trimethylsilyl enol ethers with acetyl tetrafluoroborate (procedure A) are presented in Table I. Since boron trifluoride is formed in the initial acylation step (eq 6), we examined an alternative procedure (procedure B, Table I) in which acetyl tetrafluoroborate is generated in situ from acetyl fluoride and catalytic amounts of boron trifluoride. This latter procedure seems to be especially useful when the C-acylated products are incapable of forming boron complexes analogous to **7** (Table I, entry III).

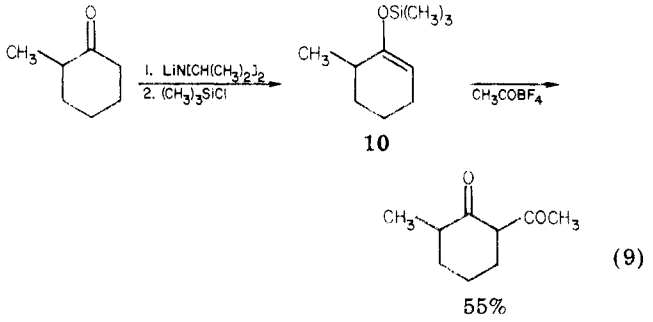
The regiochemistry of the acylation reaction was examined with the two isomeric silyl enol ethers (**9** and **10**) obtained from 2-methylcyclohexanone. In both cases, only a single C-acylation product was obtained with no detectable contamination (GLC and NMR analysis) of the regioisomeric product (eq 8 and 9).



9

20%

(8)



10

55%

(9)

Conclusions

A wide variety of methods have been described in the literature for the C-acylation of ketones including the reaction of metal enolates with acid chlorides[7] and acyl cyanides,[8] the acylation of enamines,[9] and the direct acid-catalyzed acylation of ketones with acid anhydrides.[10]

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(7) Beck, A. K.; Hoekstra, M. S.; Seebach, D. *Tetrahedron Lett.* **1977**, 1187.
(8) Howard, H. S.; Meerholz, C. A.; Michael, J. P. *Tetrahedron Lett.* **1979**, 1339.
(9) See: House, H. O. "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin: New York, 1972; Chaper 11.
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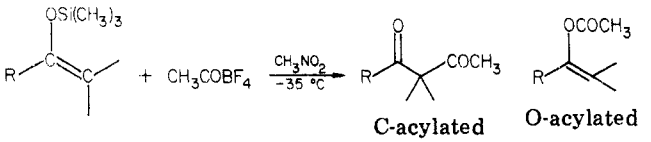
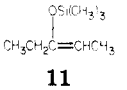
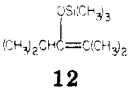
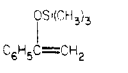
Table I. Reaction of Trimethylsilyl Enol Ethers with Acetyl Tetrafluoroborate



C-acylated O-acylated

entry	silyl enol ether	procedure[a]	% C-acylated[b]	% O-acylated[b]
I	 **4**	A	67	6
		B	68	32
II	 **11**	A	92	1
III	 **12**	A	49	25
		B	84	7
IV	 **13**	A	40	0
		B	56	0
V	 **14**	A	23	0
		B	43	0

[a] Procedure A is treatment with 1 equiv of preformed acetyl tetrafluoroborate. Procedure B is in situ formation of acetyl tetrafluoroborate from BF_3 gas (10%) and acetyl fluoride. [b] Yields determined by GLC analysis.

The procedure described here utilizing silyl enol ethers appears to offer some significant advantages in convenience, control of regiochemistry, and application to the acylation of tertiary centers.

Experimental Section

Reagent grade nitromethane was dried over 5A molecular sieves. Infrared spectra were obtained with a Perkin-Elmer 237-B spectrophotometer. ^1H NMR spectra were recorded on a Varian T-60 spectrometer, and shifts are reported in parts per million relative to Me_4Si. Mass spectral data were obtained with a Finnigan Model 4000 gas chromatograph–mass spectrometer equipped with a 6 ft × 0.25 in. column packed with 10% SE-30 on Chromosorb W. All analytical GLC was performed on a Varian 920 gas chromatograph equipped with a stainless steel 6 ft × 0.25 in. column packed with 20% SE-30 on Chromosorb W. Product yields were determined by GLC analysis using *n*-alkanes as internal standards.

Silyl Enol Ethers. Silyl enol ethers were generally prepared by reaction of the ketone with trimethylchlorosilane and triethylamine in dimethylformamide by the procedure of House[10] followed by distillation through a short Vigreux column.

Cyclohexanone trimethylsilyl enol ether (4) was prepared as above: ^1H NMR ($CDCl_3$) δ 0.2 (9 H, s), 1.57 (4 H, m), 1.93 (4 H, M), 4.75 (1 H, m).

3-Pentanone trimethylsilyl enol ether (11) was prepared as above: ^1H NMR ($CDCl_3$) δ 0.2 (9 H, s), 1.0 (3 H, t, J = 7 Hz), 1.45 (3 H, d, J = 6 Hz), 1.95 (2 H, m), 4.45 (1 H, p, J = 5 Hz).

2,4-Dimethyl-3-pentanone trimethylsilyl enol ether (12) was prepared as above: ^1H NMR ($CDCl_3$) δ 0.2 (9 H, s), 0.95 (6 H, d, J = 7 Hz), 1.55 (3 H, s), 1.6 (3 H, s), 2.73 (1 H, septet, J = 7 Hz).

Cyclopentanone trimethylsilyl enol ether (13) was prepared as above: ^1H NMR ($CDCl_3$) δ 0.2 (9 H, s), 1.6–2.4 (6 H, m), 4.5 (1 H, br s).

Acetophenone trimethylsilyl enol ether (14) was prepared as above: ^1H NMR ($CDCl_3$) δ 0.2 (9 H, s), 4.35 (1 H, d, J = 2 Hz),

4.75 (1 H, d, J = 2 Hz), 7.0-7.5 (5 H, m).

2-Methylcyclohexanone trimethylsilyl enol ether (9) was prepared as above followed by distillation through a spinning-band column to separate the 79:21 mixture of **9** and **10**: ^{1}H NMR ($CDCl_3$) δ 0.2 (9 H, s), 1.53 (3 H, s, and 4 H br m), 1.9 (4 H, br m).

2-Methylcyclohexanone trimethylsilyl enol ether (10) was prepared by reaction of 2-methylcyclohexanone with lithium diisopropylamide at -78 °C in THF followed by addition of trimethylchlorosilane. Distillation of the product through a spinning-band column gave material of 99% purity by GLC: ^{1}H NMR ($CDCl_3$) δ 0.2 (9 H, s), 1.0 (3 H, d, J = 7 Hz), 1.5 (4 H, m), 1.95 (4 H, m), 4.66 (1 H, t, J = 4 Hz).

Cyclohexanone *tert*-butyldimethylsilyl enol ether (8) was prepared by reaction of cyclohexanone (18.6 g, 200 mmol) with lithium diisopropylamine (200 mmol) at 0 °C in THF (200 mL) followed by addition of *tert*-butyldimethylchlorosilane (32.9 g, 210 mmol). Short-path distillation of the product gave a 75% yield of the enol ether: ^{1}H NMR ($CDCl_3$) δ 0.1 (6 H, s), 0.9 (9 H, s), 1.4-1.7 (4 H, m), 1.8-2.2 (4 H, m), 4.8 (1 H, m).

Preparation of Acetyl Fluoride. Acetyl fluoride was prepared by reaction of acetyl chloride with anhydrous KF in acetic acid solution as previously described.[11] Greater than 98% yields of distilled material [bp 20 °C (745 mm)] were routinely obtained.

Acylation of Ketone Silyl Enol Ethers (Procedure A). Acetyl tetrafluoroborate was prepared by reaction of boron trifluoride with acetyl fluoride at 0 °C in the absence of solvent as previously described.[12] A 50-mL flask with a septum inlet and magnetic stirring bar was flushed with argon and charged with 1.49 g (11.5 mmol) acetyl tetrafluoroborate. The flask was immersed in a nitromethane-dry ice slush bath at -35 °C, and 23 mL nitromethane was injected. The silyl enol ether (11.5 mmol) was added dropwise to the solution, and the mixture was stirred for 1 h at -35 °C and then allowed to reach room temperature. The solution was quenched with 5 mL of saturated aqueous sodium acetate and refluxed for 2 h. The cooled aqueous layer was then extracted twice with ether. The combined organic extract was dried over sodium sulfate and analyzed by GLC for C-acylated ketone. Samples for spectral examination were obtained by preparative GLC.

Acylation of Ketone Silyl Enol Ethers (Procedure B). A 50-mL flask with septum inlet and mercury bubbler was flushed with argon and charged with 23 mL nitromethane and 11.5 mmol (0.714 g) acetyl fluoride. The flask was immersed in a cooling bath maintained at -35 °C. After the mixture was stirred for 10 min, BF_3 gas (1.15 mmol, 27 mL was added by means of a gas-tight syringe. The silyl enol ether (11.5 mmol) was then injected into the reaction solution all at once. The solution was allowed to stir for 1 h and then worked up as described for procedure A above.

2-Acetylcyclohexanone was prepared from cyclohexanone trimethylsilyl enol ether by procedure A: ^{1}H NMR ($CDCl_3$) δ 1.70 (4 H, m), 2.05 (3 H, s), 2.31 (4 H, m), 15.2 (1 H, s); mass spectrum, m/e (relative intensity) 140 (M^+, 30) 125 (49), 97 (26), 69 (29), 55 (31), 43 (100).

3-Methyl-2,4-hexanedione was prepared from 3-pentanone trimethylsilyl enol ether by procedure A: ^{1}H NMR ($CDCl_3$) δ 1.0 (3 H, t, J = 7 Hz), 1.21 (3 H, d, J = 8 Hz), 2.15 (3 H, s), 2.45 (2 H, q, J = 7 Hz), 3.75 (1 H, q, J = 8 Hz), 16.3 (1 H, s).

3,3,5-Trimethyl-2,4-hexanedione was prepared from 2,4 dimethyl-3-pentanone trimethylsilyl enol ether by procedure B: ^{1}H NMR ($CDCl_3$) δ 1.03 (6 H, d, J = 7 Hz), 1.33 (6 H, s), 2.06 (3 H, s), 2.86 (1 H, septet, J = 7 Hz).

2-Acetylcyclopentanone was prepared from cyclopentanone trimethylsilyl enol ether by procedure A: ^{1}H NMR ($CDCl_3$) δ 1.96 (3 H, s), 1.64-2.72 (6 H, m), 2.20 (s), 3.3 (m), 13.8 (br s).

4-Phenyl-2,4-hexanedione was prepared from acetophenone trimethylsilyl enol ether by procedure A: ^{1}H NMR ($CDCl_3$) δ 2.1 (3 H, s), 4.0 (s), 6.07 (s), 7.2-7.9 (5 H, m).

2-Acetyl-6-methylcyclohexanone was prepared by 2-methylcyclohexanone trimethylsilyl enol ether **9** by procedure A: ^{1}H NMR ($CDCl_3$) δ 1.17 (3 H, s), 1.5-1.8 (4 H, m), 2.08 (3 H, s) 2.0-2.5 (3 H, m), 12.5 (1 H, s).

2-Acetyl-2-methylcyclohexanone was prepared from 2-methylcyclohexanone trimethylsilyl enol ether **10** by procedure B: ^{1}H NMR ($CDCl_3$) δ 1.23 (3 H, s), 1.45-1.9 (6 H, m), 2.08 (3 H, s), 2.2-2.6 (2 H, m).

Acknowledgement is made to the National Science Foundation for partial support of this work.

Registry No. **4**, 6651-36-1; **5**, 874-23-7; **6**, 1424-22-2; **8**, 62791-22-4; **9**, 19980-35-9; **10**, 19980-33-7; **11**, 17510-47-3; **12**, 55339-64-5; **13**, 19980-43-9; **14**, 13735-81-4; trimethylchlorosilane, 75-77-4; cyclohexanone, 108-94-1; 3-pentanone, 96-22-0; 2,4-dimethyl-3-pentanone, 565-80-0; cyclopentanone, 120-92-3; acetophenone, 98-86-2; 2-methylcyclohexanone, 583-60-8; *tert*-butyldimethylchlorosilane, 18162-48-6; acetyl fluoride, 557-99-3; acetyl chloride, 75-36-5; acetyl tetrafluoroborate, 2261-02-1; 3-methyl-2,4-hexanedione, 4220-52-4; 3,3,5-trimethyl-2,4-hexanedione, 42412-60-2; 2-acetylcyclopentanone, 1670-46-8; 1-phenyl-1,3-butanedione, 93-91-4; 2-acetyl-6-methylcyclohexanone, 78456-49-2; 2-acetyl-2-methylcyclohexanone, 1195-75-1; 3-acetoxy-2,4-dimethyl-2-pentene, 4007-46-9.

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(12) Seed, F. *Z. Anorg. Allg. Chem.* **1943**, *250*, 343.

Reactions of Allylic Grignard Reagents and Unsaturated Amines[1]

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Received July 3, 1980

Reactions were studied of allylic Grignard reagents with allylic and propargylic amines. Additions were observed to *N*-allylaniline (**1**), cinnamylamine (**6**), *N,N*-dimethylcinnamylamine (**10**), and 3-(dimethylamino)-1-phenyl-1-propyne (**12**) but not to allylamine, diallylamine, *N*-allyl-*N*-methylaniline, *N,N*-dimethylallylamine, or *N,N*-diethylallylamine. Reactions of 3-amino-1-phenyl-1-propyne (**8**) furnished phenylacetylene rather than an addition product. By comparing reactivities of the amines and comparable hydrocarbons, it is concluded that tertiary amino functions and metalated primary and secondary amino functions can assist Grignard reagent additions to alkene and alkyne functions. Comparisons of reactivities of the unsaturated amines and comparable alcohols suggest that assistance by a metalated amino function is less effective than by a metalated hydroxyl function but more effective than by a tertiary amino function. Another comparison suggests that a metalated phenylamino group is more effective than a metalated primary amino group.

Eisch[5] and Felkin[6] observed that allylic organomagnesium compounds (in excess) add to alkenols. For example, allylmagnesium bromide and allyl alcohol form a good yield of an addition product[6] (eq 1). The hydroxyl

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