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A FACILE METHOD FOR THE PREPARATION OF 5-ALKOXY-1,4-DIKETONES

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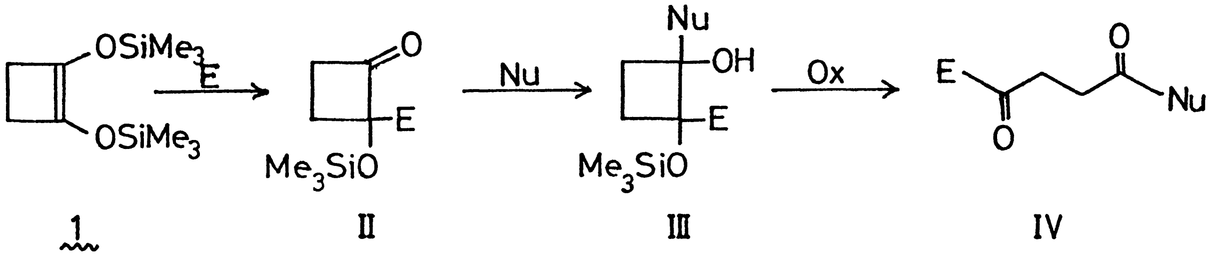
The title compounds were prepared efficiently by Lewis acid catalyzed reaction of 1,2-bis(trimethylsiloxy)-1-cyclobutene with acetals, followed by addition of the Grignard reagent and ring cleavage of the resulting vis-diols with $Pb(OAc)_4$.

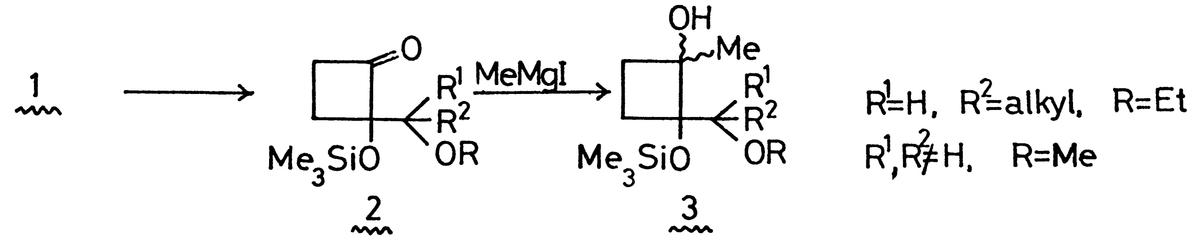
Since 1,4-diketones have been recognized as excellent precursors for naturally occuring cyclopentenone systems, various methods have hitherto been devised for their preparation.[1] Recently, we have shown synthetic utilities of 1,2-bis(trimethylsiloxy)-1-cyclobutene 1, easily available from reductive silylation of succinic ester,[2] and described highly efficient methods for cyclopentane-1,3-dione[3] and 4-ketoester.[4] By using the same starting material 1, we wish to describe here a new methodology for 5-alkoxy-1,4-diketones, which consists of succesive introduction of both of electrophile (E) and nucleophile (Nu) as the terminal groups as shown in the following equation.



As reported in the previous paper,[3] 1-alkoxyalkyl group can easily be introduced on the cyclobutene 1 as electrophile (E) by Lewis acid catalyzed reaction with the corresponding acetals to give II (E = $C(OR)R^1R^2$) over 90% yield.

Addition reaction of methylmagnesium iodide on the carbonyl group of 2 has initially been examined. The corresponding addition product 3 was obtained almost quantitatively when 2 (R^1 = H, R^2 = alkyl or aryl) derived from the acetal was treated with 1.2 eq of methylmagnesium iodide at 0°C. However, with 2 (R^1, $R^2 \neq$ H) derived from the ketal, the addition reaction was found to be quite sensitive to the steric factor of the alkoxy substituent, OR. When the alkoxy group of 2 (R^1, $R^2 \neq$ H) was the smallest methoxy group, 3 could be isolated in good yield, sometimes accompanying recovery of the starting material in substantial amount (see the Table). Surprisingly, with 2 (R^1, $R^2 \neq$ H) possessing ethoxy substituent, the reaction was usually very sluggish, giving the adduct 3 in only very low yield. For example, methoxy derivative 2 (R^1, R^2 = $-(CH_2)_5-$, R = CH_3) afforded the corresponding adduct 3 in 88% yield, while the adduct was obtained in only 20% yield from the ethoxy one 2 (R^1, R^2 = $-(CH_2)_5-$, R = C_2H_5) under similar reaction conditions (1.5 eq of CH_3MgI, 0 °C, 30 min in ether).

The adducts were usually obtained as a mixture of cis- and trans-isomer of monosilylated cyclobutane-1,2-diols. Although stereochemistry of the isomeric diols is not precisely assigned yet,[5] trans-diol appears to be formed as a predominant one because of sterically hindered effect of alkoxyalkyl group of 2. This assumption is also supported by the fact that a minor component of 2 (R^1 = H, R^2 = C_6H_5, R = C_2H_5)[6] reacted to yield the corresponding 5-alkoxy-1,4-diketone 4 (R^1 = H, R^2 = C_6H_5, R = C_2H_5) through oxidative ring cleavage on treating with KIO_4 and dil. H_2SO_4, while the major component of 2 (R^1 = H, R^2 = C_6H_5, R = C_2H_5)[6] survived under such reaction conditions.[7] Under more severe reaction conditions complex mixtures were formed.



Although major isomers of 3 were almost inert to the periodate oxidation, oxidative ring cleavage was easily effected with lead tetra-acetate in the presence of pyridine.[8] Both of the isomeric alcohols underwent facile ring opening to yield the corresponding 5-alkoxy-1,4-diketone 4 in good yield. Typical example is as follows. Cyclobutanone 2 (R^1 = H, R^2 = C_5H_{11}, R = C_2H_5)

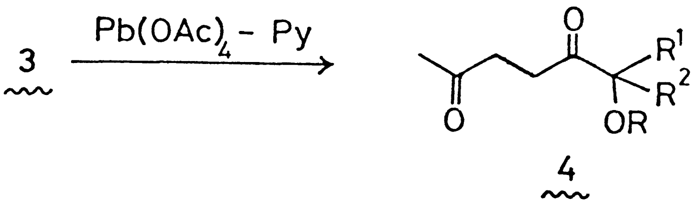
(286 mg, 1 mmol) was treated with 1.2 eq of methylmagnesium iodide in ether for 30 min at 0 °C and the reaction mixture was quenched with aq NH_4Cl. The aqueous layer was saturated with NaCl and organic materials were extracted four times with 10 ml of ethyl acetate. After drying and removal of the solvent, 3[9] (R^1 = H, R^2 = C_5H_{11}, R = C_2H_5) was obtained as the crude product almost quantitatively. The crude 3 was dissolved in pyridine (15 ml) and lead tetra-acetate (1.44 g, 3 mmol) was added all at once. After stirring for 15 min at room temperature, oxalic acid (4.0 g) was added and the reaction mixture was diluted with hexane. Solid precipitate was removed by filtration and the filtrate was washed with dil. HCl saturated with NaCl. The aqueous layer was extracted four times with ethyl acetate (10 ml). The filtrate and extracts were combined and dried over anhydrous $MgSO_4$. After removal of the solvent, the remaining oil was purified by silica gel chromatography, giving the corresponding 5-alkoxy-1,4-diketone 4 (R^1 = H, R^2 = C_5H_{11}, R = C_2H_5)[10] (175 mg, 75%).

Table Preparation of 4[a)] via 3[b)].

2			Yield, %		
R^1	R^2	R	3	4	(b.p. °C/Torr)
H	CH_3	C_2H_5	--	73[c)]	(142-145/28)
H	C_5H_{11}	C_2H_5	--	75[c)]	(100-102/0.07)
H	C_6H_5	C_2H_5	--	80[c)]	(127-130/0.17)
CH_3	CH_3	CH_3	82[e)]	75[d)]	(66-69/1.3)
CH_3	C_6H_{13}	CH_3	76[f)]	83[d)]	(78-81/0.07)
$-(CH_2)_5-$		CH_3	88[g)]	70[d)]	(78-80/0.06)
$-(CH_2)_{11}-$		CH_3	70[h)]	75[d)]	(128-131/0.04)

a) Satisfactory analytical and spectral data were obtained for assigned structures. b) Satisfactory spectral data were obtained for assigned structures. c) Overall yield based on 2. d) Yield based on 3. e) 5% of 2 was recovered. f) 11% of 2 was recovered. g) 3% of 2 was recovered. h) 20% of 2 was recovered.

Thus, for the preparation of 4, formation of diastereomeric mixtures 3 did not offer any difficulty and 5-alkoxy-1,4-diketone 4 could usually be prepared efficiently by employing lead tetra-acetate—pyridine as an oxidation reagent.



We are currently studying the generality of this type of reaction for the preparation of 1,n-dicarbonyl compounds.

References and Notes

1) See, for example; R. A. Ellison, Synthesis, 397 (1973); T. L. Ho, Syn. Commun., 265 (1974).

2) K. Ruhlmann, Synthesis, 236 (1971); J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, Org. React., **23**, 259 (1976).

3) E. Nakamura and I. Kuwajima, J. Am. Chem. Soc., **99**, 961 (1977).

4) E. Nakamura, K. Hashimoto, and I. Kuwajima, J. Org. Chem., **42**, 4166 (1977).

5) Because of four possible diastereomeric pairs of diols, it has been difficult to assign the correct structures.

6) 3 (R^1 = H, R^2 = C_6H_5, R = C_2H_5) was separable into two components (5:1) by silica gel chromatography. On treatment of the minor component with KIO_4—K_2SO_4 (1 N) in ethanol for 1 hr at 40°C, the corresponding 4 was obtained in 53% yield along with the recovered 3 (23%).

7) For the synthesis of cis-Jasmone, Weinreb et al. also realized ring cleavage of cyclobutane-1,2-diol derivative with periodic acid. Low efficacy (ca. 35%) reported there might also be attributable to inert character of the trans-diol to the oxidizing agent. S. M. Weinreb and R. J. Cvetovich, Tetrahedron Lett., 1233 (1972).

8) H. R. Goldschmid and A. S. Perlin, Can. J. Chem., **38**, 2280 (1960).

9) Since the diols 3 are usually unstable on heating, it failed to isolate them by distillation. Purification of 3 was carried out by chromatography.

10) The product exhibited following spectral data. IR (neat); 1715, 1460, and 1100 cm^{-1}. NMR (CCl_4); δ 0.7∿1.8 (m, 14H), 1.17 (t, J = 6.6 Hz, 3H), 2.31 (s, 3H), 2.63 (s, 4H), 3.42 (q, J = 6.6 Hz, 2H), and 3.53 (t, J = 6 Hz, 1H).

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