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A NEW GENERAL SYNTHESIS OF α-OXODIMETHYLKETALS[1] AND α-DIKETONES : AN IMPROVED BISSULFENYLATION OF α-OXOMETHYLENES

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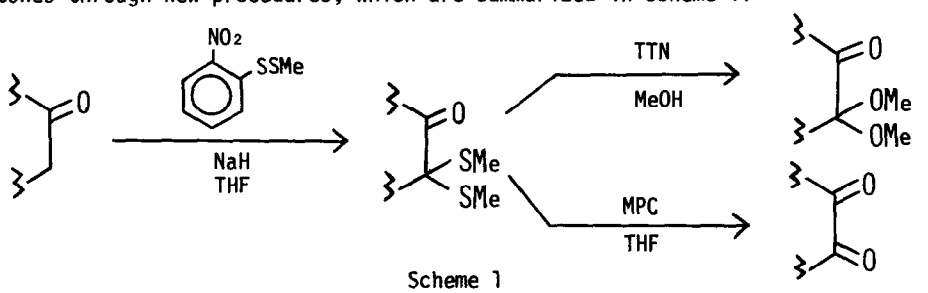
Recently, synthetic utility of the alkylthio group has been increased, because its conversion into alkoxyl and hydroxyl groups has been exploited.[2] We also have reported new methods using thallium trinitrate (TTN), $Tl(ONO_2)_3 \cdot 3H_2O$, or mercuric perchlorate (MPC), $Hg(OClO_3)_2 \cdot 3H_2O$, for conversions of thioethers into ethers[3], of thioacetals and thioketals into carbonyl compounds[4], and of β-oxosulfides into α-oxodimethylacetals[5] or α-oxodimethylketals.[6]

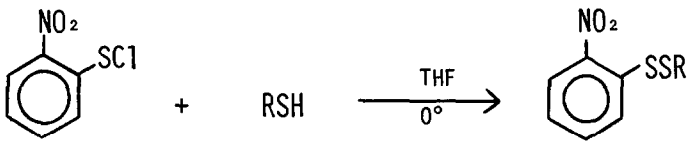
We wish to report here the selective conversion of α-oxomethylenes into α-oxodimethylketals or α-diketones through new procedures, which are summarized in Scheme 1.



Scheme 1

Sulfenylation at the α-carbon atom of a carbonyl group by symmetrical disulfide has generally been done using a strong base like n-BuLi.[7] Our attention had been directed toward exploitation of a useful agent for bissulfenylation of the active methylene group. Parker and Kharash's study[8] gave us a suggestion for the potential application of such unsymmetrical disulfide as alkyl 2-nitrophenyl disulfide. We expected for this reagent the following merits : 1) 2-Nitrophenylthio group probably activates not only the S-S bond but also the sodium enolate. This "double activation" in the transition state may be illustrated as formula 5 ; 2) Various kinds of alkyl groups are available (see the synthetic procedure of this reagent described below) ; 3) At the end of reaction, the resulting sodium 2-nitrobenzenethiolate can significantly be removed by water.

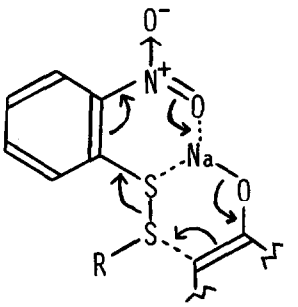
Thus we synthesized four kinds of unsymmetrical disulfides 1-4 by treatment of the corresponding alkanethiol with one mol equiv. of 2-nitrophenylsulfenyl chloride in THF under ice-cooling (See Scheme 2). Compound 1 was used in the following reactions.



1 R = Me 83 %
2 R = Et 86 %
3 R = i-Pr 74 %
4 R = t-Bu 83 %

Scheme 2

Estrone 3-methyl ether (6) on treatment with 2.2-2.4 mol equivs. of NaH in THF then with methyl 2-nitrophenyl disulfide (1) (MNPDS) gave α-oxodimethylthioketal 7. Epiandrosterone (10) and dihydrolanosterone (14) on the same treatment afforded the corresponding dimethylthioketals, 11 and 15, respectively. These thioketals (7, 11, and 15) were treated with 2.2 mol equivs. of TTN in MeOH at room temperature for 5 minutes to give the corresponding α-oxodimethylketals 8, 12, and 16. On the other hand, these thioketals on treatment with 2.2 mol equivs. of MPC in THF at room temperature for 5 minutes gave the corresponding α-diketones, 9 and 13, and diosphenol 17.



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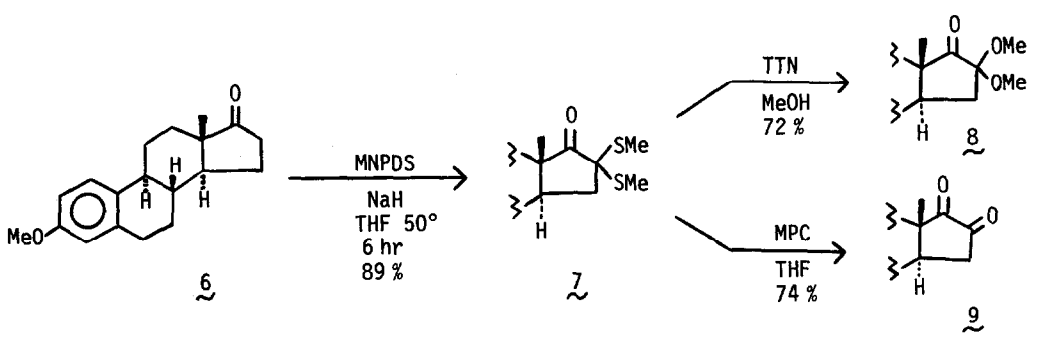
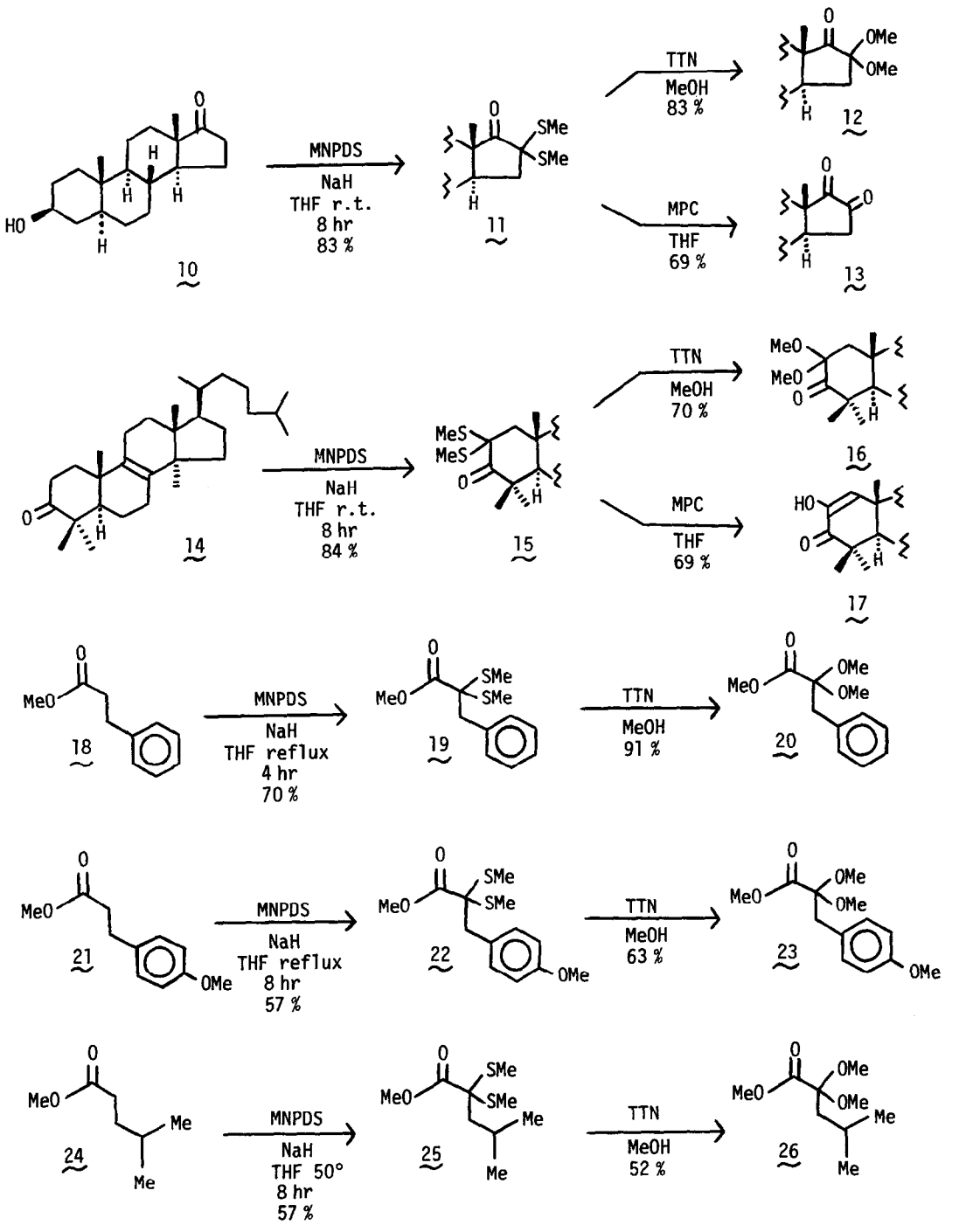
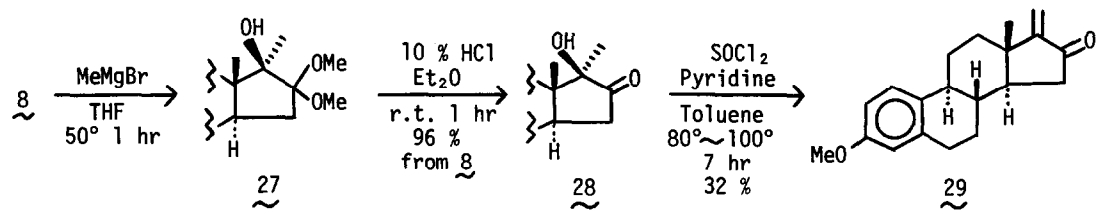
Treatment with 2.4 mol equivs. of NaH and 2.2-2.4 mol equivs. of MNPDS in THF under reflux converted methyl esters 18, 21, and 24 into the corresponding bis-sulfenylated products 19, 22, and 25, respectively. These compounds were subsequently allowed to react with 2.2 mol equivs. of TTN in MeOH to give dimethylketals 20, 23, and 26, respectively.





Thus, the simple and useful synthetic methods for α-oxodimethylthioketals, α-diketones,[9] and α-oxodimethylketals[9] have been systematically established.

As one of the applications of our methods to the synthesis of SH-alkylating tumor-inhibitors[10], we tried the conversion of α-oxodimethylketal 8 into α-methylenecyclopentanone 29. The compound 8 on warming at 50° with 3 mol equivs. of methylmagnesium bromide gave the methylated product 27, whose treatment with acid afforded α-hydroxyketone 28 in quantitative yield. Compound 28 on treatment with thionyl chloride and pyridine in hot toluene gave the desirable product 29.



Thus, α-oxodimethylketal has been effectively utilized as a regiospecifically protected α-diketone.

References and Notes

1 The IUPAC's nomenclature rule has rejected the word "ketal" and unified it as "acetal". In this communication, however, we dare to use "ketal", because of convenience of distinction between them.

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9 *Cf.* B. M. Trost and G. Massiot, *J. Am. Chem. Soc.*, 99, 4405 (1977).

10 *Cf.* E. Fujita and Y. Nagao, *Bioorg. Chem.*, 6, 287 (1977).

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