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SYNTHESIS OF UNSYMMETRICAL 1,4-DIKETONES BY THE CERIC AMMONIUM NITRATE PROMOTED CROSS-COUPLING OF TRIMETHYLSILYL ENOL ETHERS

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Summary: Unsymmetrical 1,4-diketones are prepared in good yields (60-80%) by cerium (IV) ammonium nitrate oxidative cross-coupling between 1,2-disubstituted and 1-substituted trimethylsilyl enol ethers.

There is continuing interest in the synthesis of 1,4-diketones[1] since these compounds are extensively used as key intermediates in the synthesis of furans and many natural and biologically active products possessing the cyclopentanone ring, such as prostaglandins and jasmonoids.

The oxidative addition of carbonyl compounds to systems with an enolic double bond (e.g. isopropenyl acetate) is a useful approach to 1,4-diketones,[3] and following this line, we have recently described an efficient synthetic procedure based on the reaction of ketones with isopropenyl acetate promoted by cerium (IV) ammonium nitrate (CAN).[4]

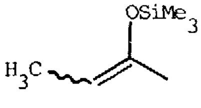
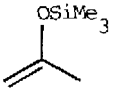
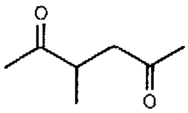
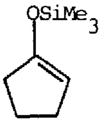
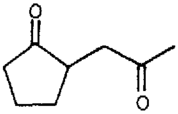
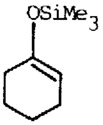
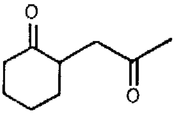
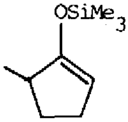
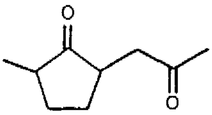
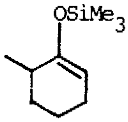
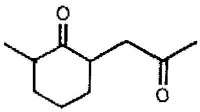
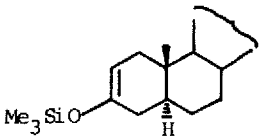
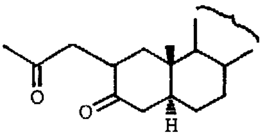
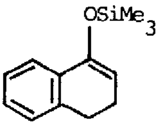
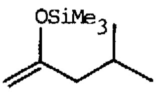
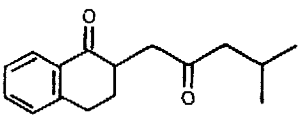
However, the oxidation of ketones by CAN is slow and requires the use of the carbonyl compound as the reaction solvent, which does not allow the method to be applied to solid ketones or to ketones of high molecular weight.

We wish now to report that a substantial improvement in this approach can be obtained by using trimethylsilyl enol ethers, which are much more easily oxidized than the parent ketones. Thus, we have found that CAN induces a very efficient cross-coupling between 1,2-disubstituted and 1-substituted trimethylsilyl enol ethers to give 1,4-dicarbonyl compounds in good yields.[5] The 1,2-disubstituted silyl enol ether is used in stoichiometric amount (1:2) with respect to CAN, which allows the procedure to be successfully applied to a solid ketone such as cholestanone. The results are reported in the table, where it can also be seen that with unsymmetrical ketones the reaction always takes place regiospecifically at the β-carbon involved in the enolic double bond.

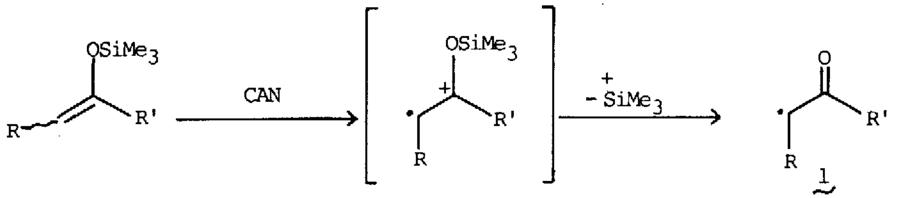
The success of the method probably rests on the easier oxidizability of a 1,2-disubstituted silyl enol ether with respect to a 1-substituted.[8] CAN should preferentially react with the former to give the β-oxo carbon radical **1**, presumably through a radical cation intermediate (eq. 1).

Table

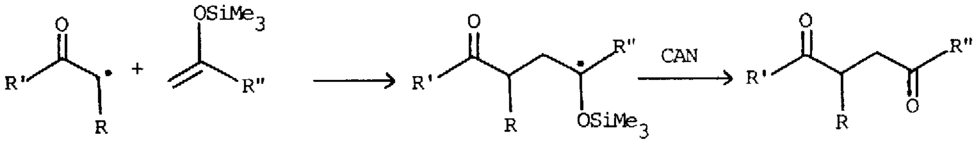
CAN-Promoted Cross-Coupling of Trimethylsilyl Enol Ethers

	1,2-Disubstituted trimethylsilyl enol ether	1-Substituted trimethylsilyl enol ether	1,4-Diketone	Isolated yield, %
1.			 [a]	74
2.			 [a]	75
3.			 [a]	80
4.			 [a,b]	69
5.			 [a,b]	75
6.	 [c]		 [d]	55
7.				78

[a] Ref. 4d. [b] 1:1 mixture of cis and trans isomer. [c] 3-Trimethylsilyloxy-5α-cholest-2-ene; the product was contaminated by ca. 20% of the 3-ene isomer. [d] The product was contaminated by ca. 20% of 4-substituted isomer.



(1)



(2)

The β-oxo radical (an electrophilic species) can easily add to the terminal double bond of the electron rich 1-substituted silyl enol ether to give a new radical which is oxidized by CAN to form eventually the 1,4-dicarbonyl compound (eq. 2).

Unless a significant excess (from 5 to 10:1) of the 1-substituted silyl enol ether is used, some homocoupling, which however exclusively involves the 1,2-disubstituted silyl enol ether, is observed.[10] This finding supports the mechanistic hypothesis reported in eqs. 1 and 2. If instead the 1-substituted silyl enol ether had been oxidized by CAN, substantial homocoupling of this species should have occurred, expecially since it is used in large excess; this was not observed.

In a typical experiment a mixture of disubstituted trimethylsilyl enol ether (4.5 mmol) and 1-substituted trimethylsilyl enol ether (45 mmol) was added dropwise to a vigorously stirred suspension of CAN (9.0 mmol) and anhydrous sodium hydrogen carbonate (18 mmol) in dry acetonitrile (50 mL) at room temperature. The mixture was allowed to react until the orange colour of CAN disappeared and a thick white precipitate formed (2-5 min). The reaction mixture was poured into water and extracted with four 100 mL portions of chloroform. The combined organic extracts were dried with sodium sulphate and the solvent evaporated. The residual brown oil was finally distilled under vacuum (0.5 mmHg) to give pure 1,4-diketone in 60-80% yield. Solid reaction products were recrystallized from a mixture of petroleum ether and diethyl ether 95:5. All the known compounds had NMR and mass spectra in agreement with literature data. The unknown compounds (entries 6 and 7 in the table) had the expected spectra and correct C,H analyses

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5. Some oxidative cross-coupling of silyl enol ethers (by Ag_2O in DMSO) has been reported.[6] However, the reaction requires relatively high temperatures, between 65-100°C. Several examples of oxidative homocoupling of silyl enol ethers are available in the literature.[7]

6. Y. Ito, T. Konoike, T. Saegusa, J.Am.Chem.Soc., 97, 649 (1975).

7. S. Inaba, I. Ojima, Tetrahedron Lett., 2009 (1977); R.M. Moriarty, R. Penmasta, I. Prokash, Tetrahedron Lett., 28, 873 (1987).

8. Alkyl substitution significantly decreases the oxidation potential of an alkene. For example the $E_{1/2}$ value (vs. SCE) is 2.8 V for 1-octene and 2.3 V for cis-2-octene.[9]

9. T. Shono, "Electroorganic Chemistry as a New Tool in Organic Synthesis"; Springer-Verlag: New York, 1984, p. 9.

10. With 1,2,2-trialkyl substituted silyl enol ethers homocoupling is the main reaction observed even in the presence of an excess of the 1-substituted silyl enol ether. Thus, this method cannot be applied to the former substrate.

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