

Synthesis of 1,4-Diketones by Fluoride-catalysed Michael Addition and Supported Permanganate Oxidation

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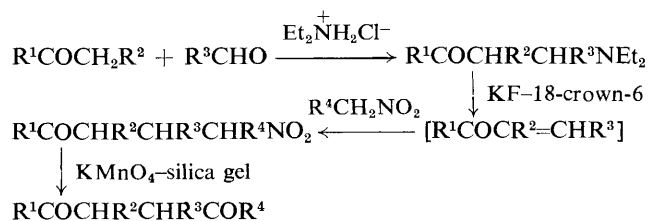
A wide variety of 1,4-diketones may be prepared from simple starting materials by using fluoride ion-catalysed Michael additions and silica gel-supported permanganate-promoted Nef transformations.

A variety of synthetic methods for the preparation of 1,4-diketones have been developed,¹ since 1,4-diketones are valuable intermediates for further elaboration into natural products and related compounds involving furan or cyclo-

pentenone ring systems. Certainly the most straightforward route is one which employs the 1,4-addition of an appropriate nucleophile to a suitable unsaturated acceptor² and it is recognised that nitroalkanes are among the better nucleophiles

for such reactions.³ The utility of this route has been hampered, however, by the fact that the only direct methods for transforming a nitro-group into a carbonyl require harsh conditions and often proceed in poor yield.⁴ Furthermore, traditional methods for effecting the preliminary Michael addition are often of low efficiency.⁵ These problems have led many workers to develop alternative routes to 1,4-diketones although none has matched the inherent simplicity, economy, and potential versatility of the 1,4-addition route.

We report that the employment of two recently developed synthetic reagents for the addition and transformation stages enables the nitroalkane-enone reaction for the preparation of a wide variety of 1,4-diketones to be used with impunity. The fluoride ion is now recognised as one of the most efficient catalysts for the Michael reaction⁶ and we have found that it consistently gave excellent yields in short reaction times for the addition of nitroalkanes to enones. We have used KF-18-crown-6 as the source of F⁻ in our reactions⁷ although we have no reason to suppose that other sources of F⁻ such as CsF and tetra-alkylammonium fluorides would not be as efficient.⁸ For the nitro-transformation stage we have found that the recently reported silica gel-supported KMnO₄ reagent⁸ is capable of efficiently converting γ -nitroketones into the corresponding 1,4-diketones with none of the disadvantages that accompany other nitro-transformation reactions. Our route to 1,4-diketones is summarised in the equation. As indicated in the equation it is possible to start with a ketone and an alde-



hyde rather than the corresponding enone.⁹ We have found that KF-18-crown-6 rapidly converts the resulting amine into the enone *in situ*, thus eliminating the need to isolate the enone.

The versatility of our scheme is demonstrated by the wide range of 1,4-diketones that we have prepared (Table 1). The product-controlling groups are in the enone (or the ketone and the aldehyde) and the nitroalkane and we have found that it is possible to vary any of these groups within the general reaction scheme thus providing excellent flexibility in product design. We believe that this flexibility along with the ease of the overall reaction and the use of simple starting materials at last fulfils the promise of this route to 1,4-diketones.

In a typical reaction, the enone (or the product from the reaction of equimolar quantities of the ketone, aldehyde, and diethylammonium chloride in MeOH or *N,N*-dimethyl-

Table 1. Yields of 1,4-diketones R¹COCHR²CHR³COR⁴.

R ¹	R ²	R ³	R ⁴	Yield % (by ¹ H n.m.r. spectroscopy)
Me	H	H	Me	82
Me	H	H	Et	80
Me	H	Me	Et	78
Me	H	Me	Me	80
Me	H	Ph	Et	72
Ph	Ph	H	Me	91
Ph	Me	H	Me	71
Ph	H	Ph	Me	86
Ph	H	Ph	Et	83
Ph	H	Ph	Me	87
Et	H	H	Me	73

formamide) is allowed to react with a 10–20 fold excess of the nitroalkane in the presence of a catalytic amount of KF-18-crown-6⁷ in refluxing MeCN. ¹H N.m.r. analysis showed the reactions to be complete in less than 3 h. Evaporation of the solvent and the excess of nitroalkane followed by extraction into CH₂Cl₂ and washing with aqueous HCl generally gives the pure nitroketone (>80% isolated yield). The nitroketone is then treated with a stoichiometric amount† of KMnO₄-silica gel in benzene at 70 °C for *ca.* 2 h (we have observed that some of the reactions appear to occur rapidly at room temperature in the absence of solvent) after which time ¹H n.m.r. analysis generally shows total conversion into the 1,4-diketone. Multiple washings of the filtered adduct with ether result in an overall recovered yield of up to 70%.

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† Recent calculations (A. Al Jazaa, J. H. Clark, and M. S. Robertson, *Chem. Lett.*, 1982, 405) have shown that the optimum loading for this reagent is *ca.* 0.5 mmol KMnO₄/g silica gel using a high surface area mesoporous silica.