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Enaminone Intermediate in the One-Methylene Incorporated Dimerization Reaction of Ketone Enolate.[1)]
Cross Reaction to Unsymmetrical 1,5-Diketones

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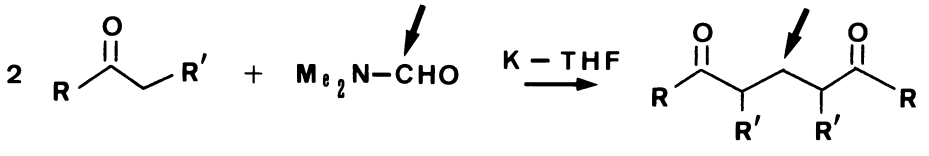
An enaminone has been isolated as an intermediate from the one-methylene incorporated dimerization reaction of ketone enolate using N-phenyl-N-methylformamide. The reaction of the enaminone with the other ketone enolates gives unsymmetrical 1,5-diketones in good yields.

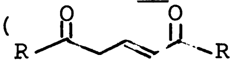
Recently we have found a novel one-methylene incorporated dimerization reaction of ketone enolate; N,N-dimethylformamide (DMF) and ketones with potassium metal or potassium hydride in tetrahydrofuran (THF) give symmetric 1,5-diketones, according to Eq. 1.[1)] This reaction is particularly of interest in view of the reaction mechanism although restricting to some ketones. We describe here an enaminone is a significant intermediate in the dimerization reaction and in addition the reaction of the enaminones with the other ketone enolates make possible to undergo a cross coupling to unsymmetrical 1,5-diketones (Eq. 2).

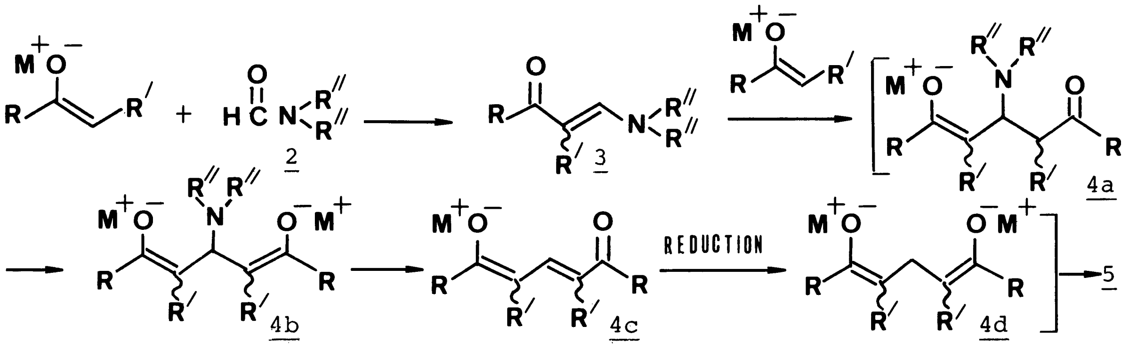


(1)

R : tert-Alkyl or Phenyl group
R': Alkyl group or Hydrogen

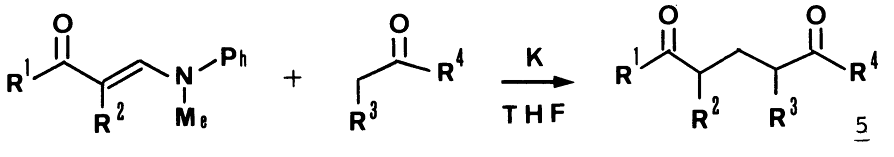
By changing DMF to N-phenyl-N-methylformamide (4a), we obtained E-1-(N-phenyl-N-methylamino)-4,4-dimethyl-1-penten-3-one (3a) (54% yield) together with 1,5-diketone (11% yield) in the reaction [pinacolone (1 equiv.), 4a (3 equiv.), and potassium metal (2 equiv.)]. The isolated enaminone 3a with potassium metal and pinacolone under similar conditions gave 1,5-diketone in a good yield so that the enaminone has proved to be an effective intermediate.

As shown in Scheme 1, the enaminone 3 is first produced from formamide 2 and enolate anion and then another enolate anion attacks the enaminone to give the condensed enolate anions 4a and/or 4b. The amino moiety in 4a and 4b may be feasibly eliminated to give 4c under such highly basic conditions. Actually, unsaturated compounds ( -type) were occasionally obtained from the reaction. The following reduction processes have not been sure yet; but some intermediates (4c etc.) should be reduced by potassium amide produced in the reaction or enolate anion itself via a single-electron-transfer mechanism.2)



Scheme 1.

The enaminone substantiating the above mechanism prompted us to develop a new method of unsymmetrical 1,5-diketone synthesis. The starting enaminones were prepared from the condensation of α-formyl ketones (ketones with NaH/HCOOEt) and amines.3) Although 1,5-diketones can generally be synthesized by Michael addition of enolate anion to α,β-unsaturated ketone (i.e. Robinson annelation of 1,3-diketone with unsaturated ketones in KOH-MeOH and the condensation of the enaminone derived from 1,3-diketone with unsaturated ketones in acidic media to give unsaturated 1,5-diketones),4) this reaction indicated in Eq. 2 is especially effective as a method for the synthesis of unsymmetrical 1,5-diketone from ketone. The results are summerized in Table 1. Unsymmetrical 1,5-diketones 5 were obtained in good yields.

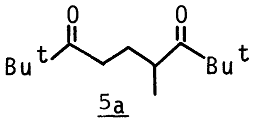
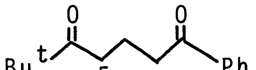
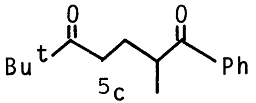
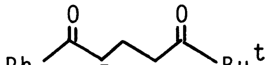
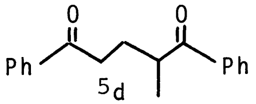
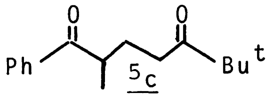
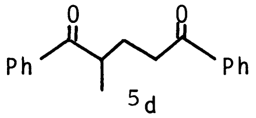
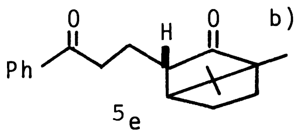


(2)

Typical procedure is as follows: Onto potassium metal (3 equiv.) in THF (0.1 M solution) were added enaminone (1 equiv.) and ketone (1 equiv.) under argon atmosphere. The solution was stirred at room temperature until the metal was completely dissolved to give a reddish solution. The resulting solution was further stirred and/or refluxed for 10 - 20 h and then was quenched with 5% HCl at room temperature. After usual work-up procedure, the product was purified by flash chromatography. Potassium hydride can also be used successfully. As the combinations in entries 3 and 6 and in entries 5 and 7 are respectively in opposite sense to each other, the reactions give the same 1,5-diketones. When enolates derived from pinacolone is used, the reaction proceeds even at room temperature.

To our knowledge, this is the first example of using enaminones as Michael acceptors (not as nucleophiles) to give 1,5-diketones. Further extentions on the scope and the study on the mechamism of this reaction are in progress.

Table 1. Unsymmetrical 1,5-diketones from the cross reaction with enaminone and ketone enolate

Entry	R^1	R^2	R^3	R^4	Conditions Temp	Time/h	Products[a)]	Yield/%
1	t-Bu	H	Me	t-Bu	reflux	20	 5a	61
2	t-Bu	H	H	Ph	reflux	10	 5b	78
3	t-Bu	H	Me	Ph	reflux	10	 5c	72
4	Ph	H	H	t-Bu	rt	20	 5b	68
5	Ph	H	Me	Ph	reflux	10	 5d	61
6	Ph	Me	H	t-Bu	rt	20	 5c	48
7	Ph	Me	H	Ph	reflux	20	 5d	55
8	Ph	H	Camphor		reflux	10	 5e	75

a) Isolated by silica-gel column chromatography: for the spectral data, see Ref. 5.

b) Stereochemistry determined on the basis of the ^{13}C-NMR spectra.

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References

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3a: IR (nujol) 1680 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.19 (9H, s), 3.28 (3H, s), 5.63 (1H, d, J=13 Hz), 7.10-7.34 (5H, m), 8.05 (1H, d, J=13 Hz); ^{13}C-NMR (CDCl$_3$) δ 27.2 (q), 36.7 (q), 42.2 (s), 95.2 (d), 119.7 (d), 124.1 (d), 129.1 (d), 146.3 (s), 148.1 (d), 203.5 (s).

3b: IR (neat) 1650 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 3.26 (3H, s), 6.16 (1H, d, J=17 Hz), 7.09-7.49 (6H, m), 7.84-8.01 (4H, m), 8.19 (1H, d, J=17 Hz).

3c: IR (neat) 1655 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.83 (3H, s), 3.21 (3H, s), 6.86-7.06 (6H, m).

4) R. M. Coates and J. E. Shaw, J. Am. Chem. Soc., 92, 5657 (1970); J. E. Telschow and W. Reusch, J. Org. Chem., 40, 862 (1975).

5) For all new compounds the elemental analyses were satisfactorily done.

5a: IR (neat) 1700 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.03 (3H, d, J=6.8 Hz), 1.12 (9H, s), 1.50-2.05 (2H, m), 2.40 (1H, dd, J=7.3, 1.7 Hz), 2.47 (1H, dd, J=7.3, 3.5 Hz), 3.08 (1H, sext, J=6.8 Hz); ^{13}C-NMR (CDCl$_3$) δ 17.8 (q), 25.9 (q),26.3 (q), 27.8 (t), 33.4 (t), 38.2 (d), 43.8 (s), 44.3 (s), 214.5 (s), 218.5 (s).

5b: IR (neat) 1700, 1685 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.13 (9H, s), 2.00 (2H, quint, J=6.8 Hz), 2.62 (2H, t, J=6.8 Hz), 2.99 (2H, t, J=6.4 Hz), 7.42-7.53 (3H, m), 7.88-8.02 (2H, m); ^{13}C-NMR (CDCl$_3$) δ 18.6 (t), 26.3 (q), 35.3 (t), 37.5 (t), 43.9 (s), 127.8 (d), 128.3 (d), 132.7 (d), 136.7 (s), 199.6 (s), 215.1 (s).

5c: IR (neat) 1690 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.09 (9H, s), 1.19 (3H, d, J=6.6 Hz), 1.44-2.31 (2H, m), 2.37-2.63 (2H, m), 3.50 (1H, sext, J=6.6 Hz), 7.26-8.03 (5H, m); ^{13}C-NMR (CDCl$_3$) δ 17.5 (q), 26.4 (q), 27.5 (t), 33.6 (t), 39.5 (d), 44.1 (s), 128.2 (d), 128.5 (d), 132.8 (d), 136.4 (s), 203.7 (s), 215.2 (s).

5d: IR (neat) 1690, 1675 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.25 (3H, d, J=7.0 Hz), 1.73-2.50 (2H, m), 2.70-3.31 (2H, m), 3.67 (1H, sext, J=6.6 Hz), 7.30-7.60 (3H, m), 7.83-8.06 (2H, m); ^{13}C-NMR (CDCl$_3$) δ 17.4 (q), 27.7 (t), 35.7 (t), 39.6 (d), 127.7 (d), 128.1 (d), 128.3 (d), 128.4 (d), 132.7 (d, 2C), 136.2 (s), 136.6 (s), 199.4 (s), 203.4 (s).

5e: IR (nujol) 1740, 1685 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0.87 (3H, s), 0.89 (3H, s), 1.00 (3H, s), 1.45-2.25 (7H, m), 2.40 (1H, m), 3.14 (2H, m), 7.35-7.57 (3H, m), 7.86-8.01 (2H, m); ^{13}C-NMR (CDCl$_3$) δ 9.4 (q), 19.1 (q), 19.4 (q), 20.1 (t), 22.3 (t), 31.0 (t), 36.8 (t), 45.7 (s), 46.7 (d), 48.5 (d), 58.6 (s), 127.9 (d), 128.4 (d), 132.8 (d), 136.8 (s), 199.5 (s), 220.8 (s).

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