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ONE-METHYLENE INCORPORATED DIMERIZATION REACTION OF KETONE ENOLATES. 1. A NEW ROUTE TO 1,5-DIKETONES FROM KETONES HAVING α-ACTIVE HYDROGEN ON ONE SIDE

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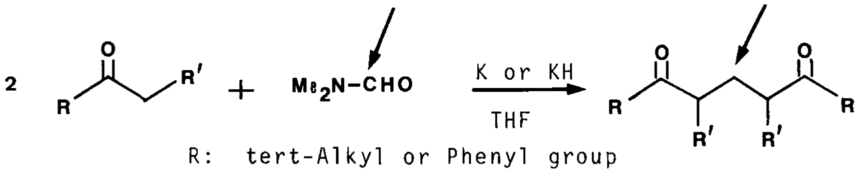
Abstract: A novel reaction of ketone enolate with dimethylformamide (DMF) to give 1,5-diketone has been found. It is a dimerization of ketone enolates accompanying the incorporation of one-methylene from DMF.

Dimethylformamide (DMF) is well known to be an effective aprotic dipolar solvent for the alkylation reaction of enolate anions and a superior reagent as reported by Vilsmeier and Haack.[2] We report here a new dimerization reaction of enolate anions induced by DMF. As shown in eq. 1, the product is 1,5-diketone which has a dimerized ketone structure interposing one methylene at α-position of each carbonyl group. Though oxidative couplings of ketone enolates to 1,4-diketones are known,[3] this type of DMF participating dimerization reaction of ketone enolates has not been reported up till now.



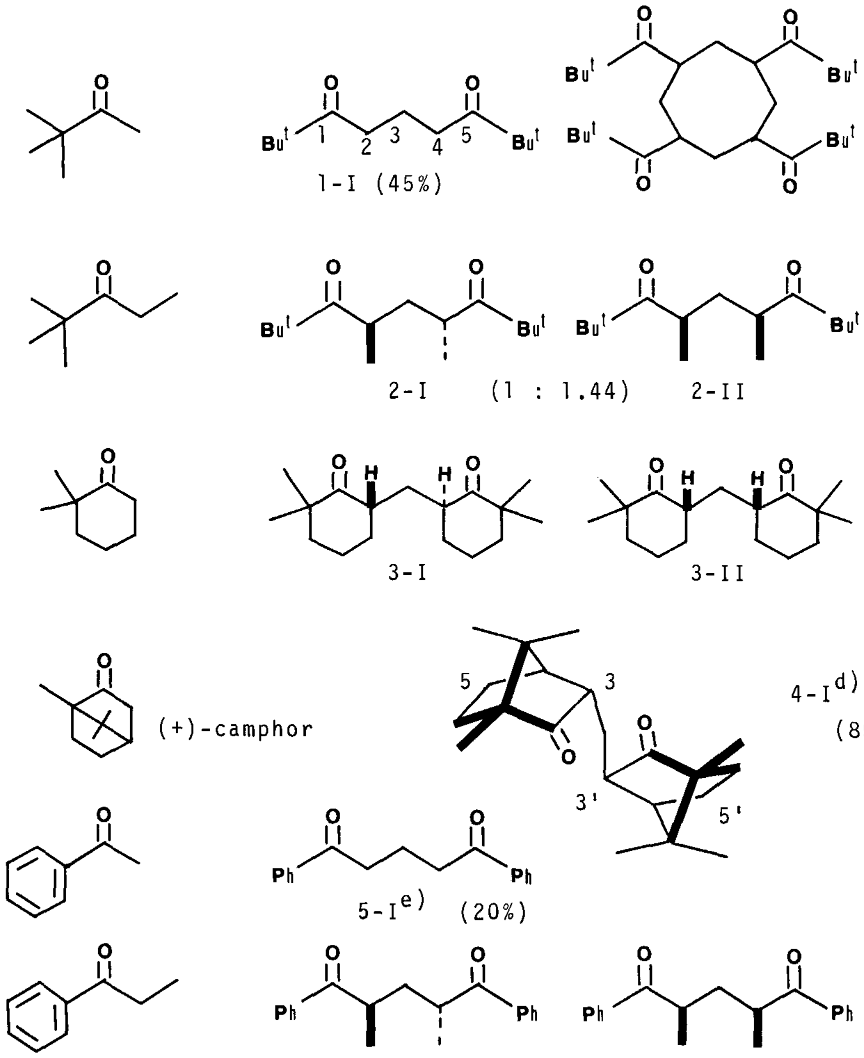
(1)

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

Typical procedure is as follows: Onto potassium metal (508 mg, 13 mmol) were added THF (30 mL) and DMF (3.04 mL, 39 mmol) under argon atmosphere. After stirring at room temperature until the metal was completely dissolved, ketone (13 mmol) in THF (5 mL) was added to the mixture. The resulting solution was immediately heated and refluxed for 5 - 20 h, and then was quenched with 5% HCl at room temperature. After normal work up procedure, the product was purified by flash chromatography.

Potassium metal and potassium hydride are effective to rapidly convert a hindered ketone to its enolate;[4] sodium metal and sodium hydride in this reaction result in low yield. The reaction of camphor with DMF-d_7 (d > 99.5%) reveals the origin of the methylene group in 4-I; as deuterium is found in the product, it originated from the formyl group of DMF via some reductive processes.[5]

Table 1. 1,5-Diketone Products from the New Dimerization of Ketone Enolates



Entry	Ketone	Products (Isolated yields)[a]
1		1-I (45%) 1-II[b] (20%)
2		2-I (1 : 1.44) 2-II (76%)
3		3-I 3-II (83%)[c]
4	(+)-camphor	4-I[d] (85%)
5		5-I[e] (20%)
6		6-I (1 : 1.54) 6-II (68%)

a) Products were isolated by silica-gel column chromatography and their spectral data are shown in reference 6.
b) 1-I was easily converted to 1-II under similar conditions.
c) Major isomer (46%) and minor isomer (37%).
d) Camphor was recovered (10%).
e) 5-I was obtained with nitrogen containing by-products.

As shown in Table 1, 1,5-diketones are formed only from the ketones which bear tert-alkyl or phenyl group on one side of carbonyl group. The reactions with ketones having α' hydrogen, e.g., 2-butanone and 2-methylcyclohexanone, proceed to aldol and the related reactions and give a complex mixture of products. A by-product (1-II) can be obtained as major product (80% yield) when two equivalents of potassium were used. The ketone enolates having alkyl substituents at the α-carbon show higher yields (entries 2,3,4,6).

As for the stereochemistry of the products, syn isomers are formed in preference to anti isomers (1 : 1.5) (entries 2,6); the structural assignment is based on symmetry arguments. Though the isomers produced from 2,2-dimethylcyclohexanone (entry 3) were easily separated by chromatography, the stereochemistry of them has not been assigned. (+)-Camphor gave the endo - endo isomer (4-I) as a single product presumably because of its steric reason.

The 1,5-diketone (5-I) was obtained from the reaction with acetophenone in lower yield (20%) which was accompanied with a large amount of nitrogen containing by-products. Though pinacolone does not give products at low temperature, propiophenone gives products in 17% yield in the reaction at -10°C for 3 h.

Studies on the reaction mechanism are currently in progress.

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References and Notes

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5) EI/MS (70 eV): 318 (M^+, $-CD_2-$, 20.7), 317 (M^+, -CDH-, 30.5), 316 (M^+, $-CH_2-$, 2.2), 290 (63.9), 289 (base), 288 (4.7). The details on the mechanism for the new reaction will be mentioned in a subsequent paper.
6) 1-I: mp 32.5-33.5°C, bp 127°C/4 mmHg. IR (neat): 1700 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.09 (18H, s), 1.78 (2H, t, J= 7.0 Hz), 2.49 (4H, t, J= 7.0 Hz). ^{13}C-NMR ($CDCl_3$): δ 18.2 (t), 26.4 (q), 35.3 (t), 44.0 (s), 215.7 (s). EI/MS (70 eV): 213 ($M^+ + 1$, 1.6), 212 (M^+, 1.4), 197 (0.7), 115 (36.4), 137 (9.7), 127 (23.8), 109 (base). Anal calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.32; H, 11.40.
   1-II: mp >200°C (sublimation). IR (nujol): 1695 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.14 (36H, s), 1.50-1.78 (8H, m), 2.83-3.06 (4H, m). ^{13}C-NMR ($CDCl_3$): δ 25.8 (q), 32.0 (t), 42.9 (d), 44.6 (s), 215.6 (s). Anol calcd for $C_{28}H_{48}O_4$: C, 74.95; H, 10.78. Found: C, 74.86; H, 10.65. The ^{13}C-NMR spectra show a single isomer but the stereochemistry has not been determined yet.

2-I and 2-II: a mixture of isomers, oil. IR (neat): 1705 cm^{-1}. Anal calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.87; H, 11.70. 2-I: ^1H-NMR ($CDCl_3$): δ 1.04 (6H, d, J= 6.8 Hz), 1.15 (18H, s), 1.50 (2H, dd, J= 6.8 and 7.7 Hz), 3.07 (2H, sext, J= 6.8 Hz). ^{13}C-NMR ($CDCl_3$): δ 16.6 (q), 25.8 (q), 36.0 (d), 36.9 (t), 37.7 (s), 217.3 (s). 2-II: ^1H-NMR ($CDCl_3$): δ 1.03 (6H, d, J= 6.8 Hz), 1.15 (18H, s), 1.23 (1H, m), 1.94 (1H, m), 2.89 (2H, sext, J= 6.8 Hz). ^{13}C-NMR ($CDCl_3$): δ 19.9 (q), 25.7 (q), 36.7 (d), 43.9 (t), 44.1 (s), 217.6 (s).

3-I and 3-II: minor isomer: mp 57.5-59.0°C. IR (nujol): 1685 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.03 (6H, s), 1.19 (6H, s), 1.28-2.33 (14H, m), 2.74 (2H, m). ^{13}C-NMR ($CDCl_3$): δ 21.6 (t), 25.1 (q), 25.6 (q), 29.8 (t), 34.9 (t), 41.9 (t), 42.9 (d), 45.4 (s), 216.2 (s). Anal calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.16; H, 10.54. major isomer: oil. IR (neat): 1685 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.02 (6H, s), 1.11 (6H, s), 1.20-2.25 (14H, m), 2.68 (2H, m). ^{13}C-NMR ($CDCl_3$): δ 21.4 (t), 24.6 (q), 25.2 (q), 30.5 (t), 35.6 (t), 41.7 (t), 44.4 (d), 45.1 (s), 217.0 (s). Anal calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.19; H, 10.49.

4-I: mp 198.5-199.5°C. $[\alpha]^{18}{}_D$ + 82.40° (c= 1.068, $CHCl_3$). IR (nujol): 1740 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.88 (12H, s), 2.01 (6H, s), 2.25-2.85 (10H, m), 2.04 (2H, m), 2.41 (2H, m). ^{13}C-NMR ($CDCl_3$): δ 9.5 (q), 19.3 (q), 19.5 (q), 20.1 (t), 24.7 (t), 31.1 (t), 45.8 (s), 46.0 (d), 47.5 (d), 58.7 (s), 220.8 (s). EI/MS (70 eV): 316 (M^+, 19.4), 301 (2.8), 288 (base), 273 (8.9), 260 (2.7), 255 (2.4), 245 (2.0), 165 (6.2), 152 (43.7), 137 (13.6), 124 (24.5), 109 (20.0). Anal calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.82; H, 10.26. The stereochemistry on the cross-linkage of 4-I has been elucidated to be endo - endo from the observed γ-shift in the ^{13}C-NMR spectrum; 6.9 ppm high-field shift at C-5 (and C-5') from that of camphor: J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, J. Am. Chem. Soc., 92, 7107 (1970); The ^{13}C-NMR chemical shift of C-5 of 2-norbornanone is 27.3 ppm while that of C-5 of endo-3-methyl-2-norbornanone is 20.9 ppm.

5-I: mp 63.5-64.5°C. IR (nujol): 1675 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 2.17 (2H, q, J= 7.0 Hz), 3.02 (4H, t, J= 7.0 Hz), 7.06-7.40 (6H, m), 7.78 (4H, m). Anal calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.01; H, 6.40.

6-I and 6-II: a mixture of isomers, oil. IR (neat): 1690 cm^{-1}. Anal calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.42; H, 7.18. 6-I: ^1H-NMR ($CDCl_3$): δ 1.21 (6H, d, J= 6.8 Hz), 2.01 (2H, t, J= 7.1 Hz), 3.51 (2H, tq, J= 7.1 and 6.8 Hz), 7.29-7.46 (6H, m), 7.71-7.84 (4H, m). ^{13}C-NMR ($CDCl_3$): δ 18.1 (q), 36.9 (t), 38.0 (d), 127.5 (d), 128 (d), 132.2 (d), 135.9 (s), 203.2 (s). 6-II: ^1H-NMR ($CDCl_3$): δ 1.17 (6H, d, J= 6.8 Hz), 1.49 (1H, dt, J= 13.7 and 6.8 Hz), 2.45 (1H, dt, J= 13.7 and 7.0 Hz), 3.61 (2H, tq, J= 7.0 and 6.8 Hz), 7.45-7.62 (6H, m), 7.98-8.12 (4H, m). ^{13}C-NMR ($CDCl_3$): δ 17.1 (q), 36.6 (t), 37.6 (d), 127.8 (d), 128.1 (d), 132.4 (d), 135.7 (s), 202.8 (s).

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