

Condensation of Unsymmetrical Aliphatic Ketones with Formaldehyde in Trifluoroacetic Acid

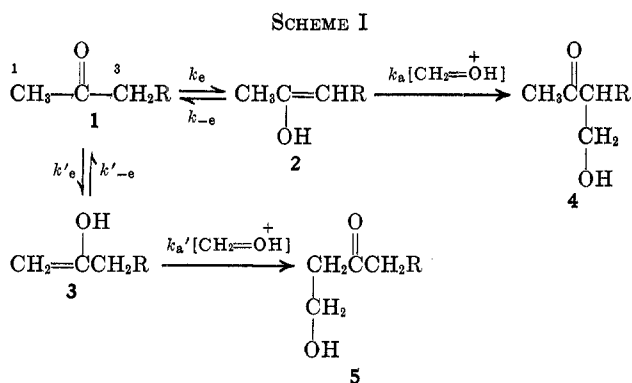
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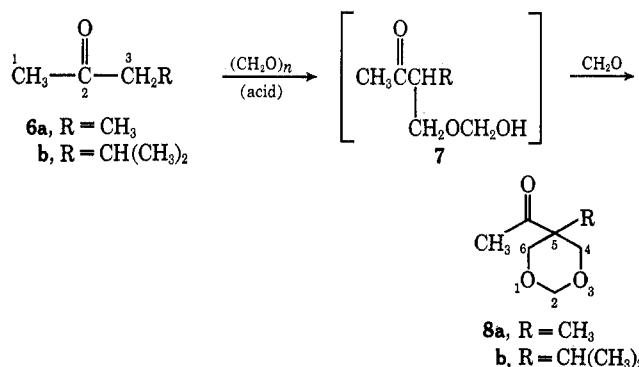
Received November 7, 1969

It is shown that methyl ethyl, methyl isopropyl, and methyl isobutyl ketones and 2-methylcyclohexanone condense with paraformaldehyde in trifluoroacetic acid predominantly at the more substituted α -carbon atom. Methylene positions condense with 3 mol of formaldehyde forming 1,3-dioxanes whereas methine positions condense with 1 mol irreversibly, forming β -ketols which trifluoroacetylate faster than they are formed.

Several generalizations regarding the mechanism and scope of the acid-catalyzed condensation of nonenolizable aldehydes with ketones are to be found in a recent review of the aldol reaction.¹ Important steps in the acid-catalyzed condensation of formaldehyde with unsymmetrical aliphatic ketones (1) are summarized in Scheme I.

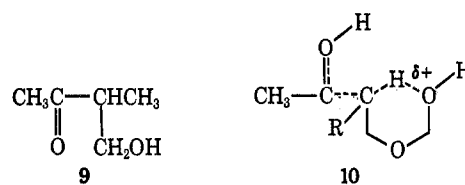


Recently three very important studies of the acid-catalyzed condensation of trioxane with aldehydes and ketones have appeared.² No α -disubstituted ketones were studied but methyl ethyl (6a) and methyl isobutyl ketones (6b) were found to condense with 3 mol of formaldehyde predominantly at the methylene position forming 1,3-dioxanes (8) with selectivity that varied with the choice of catalyst.^{2a} Aluminum chloride and



boron trifluoride etherate gave nearly equal amounts of 1 and 3 condensation with 6b whereas sulfuric acid led to a 6:1 preference for the 3 position. Selectivity was not due to preferential enolization of ketol 9 in the 3 position but was attributed to intramolecular catalysis of enolization in hemiformal 7 via a six-membered-ring transition state 10. Dioxane 8a is also formed selectively in acetic acid with sulfuric acid catalyst, conditions under which the condensation step is rate limiting.^{2c}

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Prior to the reports of Wesslen and coworkers,² we had begun a study of the aldol reaction in trifluoroacetic acid, primarily because of its high solvent power, volatility, and suitability as an nmr solvent. The results of part of this study are reported in the next section.

Results and Discussion

Condensation at a Methylene Position.—In the present study condensation of 0.1 mol of methyl ethyl (6a) and methyl isobutyl ketones (6b) with paraformaldehyde (0.4 mol of CH₂O) in trifluoroacetic acid at 60–75° gave dioxanes 8a and 8b in yields of 23.2 and 47.7%, respectively (Table I; see Experimental Section).

TABLE I
OPTIMAL CONDENSATION EXPERIMENTS

Ketone,	(H ₂ CO) _n ,	Time,	Temp, ^a	Product,
mol	mol	hr	°C	(% yield)
6a	0.1 0.4	24	60	8a (23.2) ^a
6b	0.1 0.4	24	75	8b (47.7) ^a
12a	0.1 0.13	24	25	14a (72.8) ^a
12b	0.1 0.13	24	60	14b (77.8) ^a

^a These yields are minimal since the dioxanes proved to be quite water soluble and difficult to extract.

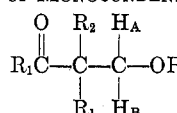
The reactions were followed by nmr³ for a decrease in the signal for the CH₃C(=O)– group at δ 2.30 for 6a and 2.32 for 6b. It was thus observed qualitatively that the former ketone was much more reactive than the latter. In the case of 6a, the signals for starting material were replaced by AB quartets centered at δ 5.30 (2 H, J = 6.5 Hz, $\Delta\nu$ = 32 Hz) and 4.19 (4 H, J = 12 Hz, $\Delta\nu$ = 76 Hz) expected^{2a} for the 1,3-dioxane ring positions 2, 4, and 6, respectively, in addition to signals for the 5-methyl and CH₃C(=O)– substituents (δ 1.07 and 2.44, respectively).

(1) A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968).

(2) (a) B. Wesslen and L. O. Ryrfors, *Acta Chem. Scand.*, **22**, 2071 (1968); (b) B. Wesslen, *ibid.*, **22**, 2085 (1968); (c) B. Wesslen, *ibid.*, **23**, 1017 (1969).

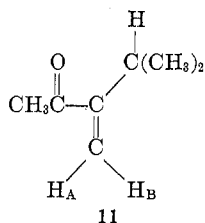
(3) Determined at 100 MHz in TFA at room temperature unless otherwise noted. Support for the 100 MHz nmr spectrometer from National Science Foundation Grant No. GP-8510 is gratefully acknowledged.

TABLE II
 PHYSICAL DATA OF MONOCONDENSATION PRODUCTS

Compd (R)	Bp (mm) or mp, °C	$\nu_{\text{C=O}}^{\text{CHCl}_3}$ cm ⁻¹			J_{AB} , Hz	δ_{R_2}	δ_{R_1}
			COCF ₃	δ_{AB} ($\Delta\nu$) ^a			
13a (H)	50-55 (0.004)	1690		3.51 (~0) ^b		1.18	
13b (H)		1685		3.57 (~0)		1.16 ^b	2.17 ^b
14a (COCF ₃)	58-62 (0.01)	1700	1775	4.44 (22) ^c	11	1.34 ^c	
14b (COCF ₃)	28-30 (0.01)	1700	1780	4.46 (~0) ^c		1.33 ^c (R ₁)	2.35
16a (Ts)		1710		3.92 (~0) ^d		1.10 ^d	
16b (Ts)	54.5-55.5	1705		3.90 (~0) ^d		1.11 ^d (R ₁ ')	2.05

^a Separation in hertz between an inner and outer line of the AB quartet. ^b In CDCl₃. ^c In TFA. ^d In CCl₄.

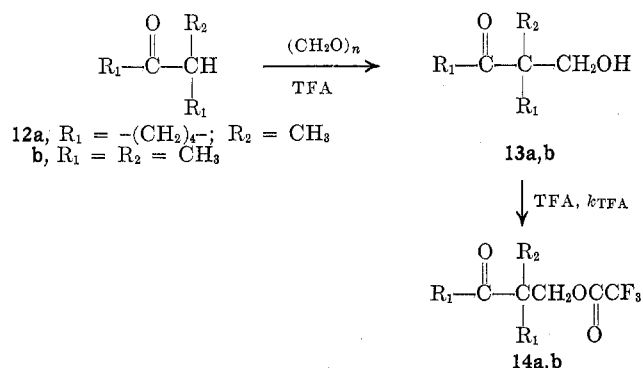
Condensation of **6b** could not be carried to completion since prolonged heating resulted in elimination to form the α,β -unsaturated ketone **11**,⁴ as evidenced by the



appearance of a singlet at δ 6.26 and doublet at δ 5.99 for H_A and H_B, respectively. Condensation with more than 3 mol of formaldehyde per mol of **6b** seemed to be more prevalent than competing dioxane formation at the 1 position, since consumption of the starting ketone (singlet at δ 2.30) was incomplete after 4 equiv of CH₂O [singlet at δ 5.3 for (CH₂O)₃] had been consumed. The formation of an isomeric dioxane at the 1 position is unlikely also in view of the fact that dioxane **8b** could be isolated in greater than 95% purity (by vpc) by partial fractional distillation of the crude product.

In contrast, methyl ethyl ketone (**6a**) reacted completely to give a crude product containing only minor impurities by nmr, even when 1 equiv of CH₂O in excess was used. No unreacted starting material could be detected.

Condensation at Methine Positions.—Condensation of 2-methylcyclohexanone (**12a**) with formaldehyde has apparently not been previously studied under acidic conditions (excepting, of course, the Mannich reaction⁵). Reaction of this ketone with paraformaldehyde in

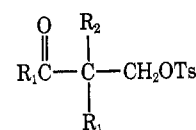
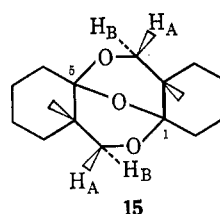


(4) T. A. Spencer, D. S. Watt, and R. J. Friary, *J. Org. Chem.*, **32**, 1234 (1967).

(5) H. O. House and B. M. Trost, *ibid.*, **29**, 1339 (1964).

TFA under a variety of conditions (Table I summarizes optimal conditions) produced moderate yields of 2-trifluoroacetoxymethyl-2-methylcyclohexanone (**14a**) which was characterized by its nmr spectrum (Table II, Experimental Section) and infrared carbonyl bands at 1700 and 1775 cm⁻¹.

Hydrolysis of **14a** with aqueous methanolic 2 N sodium hydroxide gave ketol **13a**⁶ which underwent dehydrative dimerization (see Experimental Section) forming **15**. The structure of **15** followed readily from elemental analysis and lack of hydroxyl and carbonyl absorption in the infrared. Moreover, the nmr spectrum of **15** was uniquely simple, showing, besides methylene absorption, a 6 H singlet at δ 0.91 (in CDCl₃) and 4 H AB quartet centered at δ 3.79 (J = 11.5 Hz, $\Delta\nu$ = 89 Hz). Structure **15** has a C₂ axis of symmetry through the bridge oxygen and perpendicular to the



16a, R₁ = (CH₂)₄; R₂ = CH₃
b, R₁ = R₂ = CH₃

plane of atoms 2,4,6, and 8 in the chair-chair or boat-boat conformation of the 2,6,9-trioxabicyclo[3.3.1]-octane ring system, as required for equivalence of the methyl groups and methylene hydrogens H_A and H_B in pairs. Because of dimerization it was preferable to characterize ketol **13a** as the previously reported tosylate **16a**.⁷

Analysis of the condensation of ketone **12a** after low conversion at room temperature revealed the presence of singlets at δ 1.34, 1.29, and 1.24. After complete conversion additional weak singlets appeared at δ 1.38 and 0.90 (\pm 0.01). The origin of the δ 1.24 singlet is undetermined, but singlets at δ 1.34 and 1.29 are assigned to trifluoroacetate **14a** and dimer **15**, respectively, on the following basis.

Nmr spectra of crystalline **15** and freshly distilled ketol **13a** in TFA were essentially identical after ca. 0.5 hr at room temperature (6 H singlet at δ 1.29 and 2 H AB, $\Delta\nu$ = 0, at δ 3.77) indicating rapid conversion of

(6) J. Colonge, J. Dreux, and H. Delplace, *Bull. Soc. Chim. Fr.*, 1635 (1956).

(7) E. Wenkert and P. D. Strike, *J. Org. Chem.*, **27**, 1883 (1962).

the latter to the former. The spectra of these same solutions showed trace amounts of trifluoroacetate **14a** after 30 min, but the spectra became identical with one another and to that of freshly distilled **14a** after ca. 18 hr at room temperature. The absence of doublet at δ 1.09 for starting ketone **12a** indicates that no reverse aldol reaction takes place. Furthermore, the absence of methyl doublets other than for **12a** during the course of the condensation requires that positional selectivity for the methine position be >95%.

In summary, the condensation of ketone **12a** appears to be irreversible in TFA and the initial ketol **13a** is trifluoroacetylated far faster than it is formed. This method offers an opportunity for further study of the aldol reaction under what should be completely kinetically controlled conditions. The convenient synthesis of tosylate **16a**, compared with the previous method,⁷ requiring several lengthy steps, attests to the synthetic utility of the method.

Similar condensation of ketone **12b** gave ketol trifluoroacetate **14b** as the only detectable product in the nmr spectra of crude condensation mixtures. The trifluoroacetate was characterized as a crystalline ketol tosylate **16b** following basic hydrolysis. Analysis of the mixture after low conversion by nmr revealed only two singlets at δ 2.35 and 2.30 in the region for methyl groups next to a carbonyl group. This fact and the absence of CH₃ doublets, except for starting ketone **12b** at δ 1.17 ($J = 7$ Hz), require >95% positional selectivity for the methine position.

Experimental Section

Melting points and boiling points are uncorrected and the former were measured in an electrically heated Thiele-Dennis tube. Infrared spectra were recorded on a Beckman IR-5A or Perkin-Elmer 457 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian HA 100 spectrometer in the frequency sweep mode, and chemical shifts were reported in δ units in either CDCl₃ or trifluoroacetic acid. Vpc analyses and purifications were performed on a Varian Aerograph Model A 90-P3 or 700 instrument using helium carrier gas at 80-100 ml/min and a thermal conductivity detector. Analyses were performed by Galbraith Laboratories, Inc.

Materials.—Trifluoroacetic acid was redistilled Eastman highest purity grade. Paraformaldehyde was Fisher Certified grade. Toluenesulfonyl chloride was Eastman practical grade, recrystallized according to Pelletier.⁸ Ketones were commercially available materials used without redistillation.

Condensations in TFA.—Typically the ketone (0.100 mol) and paraformaldehyde (0.130 equiv for methine condensation, 0.400 equiv for methylene condensation) were dissolved in five times the weight of ketone of TFA and stirred in a preheated bath. Aliquots were withdrawn periodically and the reaction was followed by nmr to maximum ketone consumption. Identical reaction mixtures were obtained whether the paraformaldehyde was added all at once or 1 equiv at a time.

Excess TFA was removed with an aspirator vacuum at 25° and the crude product was freed of residual TFA by dissolving in ether and washing with saturated sodium bicarbonate solution until neutral. Drying of the ether layer with anhydrous magnesium sulfate, filtration, and evaporation of solvent *in vacuo*,

followed by vacuum distillation, gave liquid trifluoroacetates **14a,b** (Table I) and 1,3-dioxanes **8a,b** (purified by fractional distillation⁹ followed by preparative vpc; 8 ft \times 0.25 in. column of 20% SE-30 on Chromosorb P).

2-Methyl-2-trifluoroacetoxymethylcyclohexanone (14a) (Table II).—*Anal.* Calcd for C₁₀H₁₃O₃F₃: C, 50.42; H, 5.50; F, 23.93. Found: C, 50.39; H, 5.59; F, 23.87.

3,3-Dimethyl-4-trifluoroacetoxy-2-butanone (14b) (Table II).—*Anal.* Calcd for C₈H₁₁O₃F₃: C, 45.28; H, 5.23; F, 26.86. Found: C, 45.44; H, 5.29; F, 27.11.

5-Methyl-5-acetyl-1,3-dioxane (8a): bp 32-27° (0.007 mm); lit.^{2a} bp 74-76° (2.4 mm); $\nu_{\text{max}}^{\text{CHCl}_3}$ 2850, 1700, 1350, 1155, 1085, 1025, 930 cm⁻¹; nmr (CDCl₃) 4.81 (2 H, q, $J = 6$ Hz, $\Delta\nu = 20$ Hz), 3.92 (4 H, q, $J = 11$ Hz, $\Delta\nu = 78$ Hz), 2.27 (3 H, s), 0.98 (3 H, s).

5-Isopropyl-5-acetyl-1,3-dioxane (8b): bp 50-54° (0.007 mm); lit.^{2a} bp 66-67° (0.9 mm); $\nu_{\text{max}}^{\text{CHCl}_3}$ 2840, 1695, 1346, 1158, 1028, 922 cm⁻¹; nmr (CDCl₃) 4.79 (2 H, q, $J = 6$ Hz, $\Delta\nu = 34$ Hz), 4.06 (4 H, q, $J = 11$ Hz, $\Delta\nu = 89$ Hz), 2.32 (3 H, s), 1.74 (1 H, $J = 7$ Hz), 0.88 (6 H, $J = 7$ Hz).

Hydrolysis of Ketol Trifluoroacetates 14a,b.—The trifluoroacetates were stirred at 0° with a 10% excess of 2 N sodium hydroxide and sufficient methanol to provide a homogeneous mixture for 2 hr. The ketols were isolated in nearly quantitative yield by ether extraction and distillation.

3,3-Dimethyl-4-hydroxy-2-butanone (13b): bp 83-85° (15 mm); lit.¹⁰ bp 85-86° (14 mm); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3400, 2900, 1685, 1355, 1110, 1030 cm⁻¹; nmr (CDCl₃) 3.57 (2 H, d, $J = 6$ Hz), 2.80 (1 H, broad t, $J = 6$ Hz), 2.17 (3 H, s), 1.16 (6 H, s).

2-Methyl-2-hydroxymethylcyclohexanone (13a): bp 50-55° (0.004 mm); lit.⁶ bp 107-108° (11 mm); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3450, 2586, 1690, 1432, 1310, 1035 cm⁻¹; nmr (CDCl₃) 3.51 (2 H, s), 2.66 (1 H, broad s), 2.38 (1 H, m), 1.79 (7 H, m), 1.18 (3 H, s).

exo-4,7-Dimethyl-2,6,9-trioxatetracyclo[3.3.1.4^{1,8}.4^{4,5}]heptadecane (Dimer 15).—Addition of water to a methanol solution of ketol **13a** and a trace of *p*-toluenesulfonic acid which had been standing for 1 week at room temperature gave white crystals: mp 95-96° (after recrystallization from ether); $\nu_{\text{max}}^{\text{CHCl}_3}$ 2940, 1450, 1166, 1080, 967 cm⁻¹; nmr (CDCl₃) 3.78 (4 H, q, $J = 11$ Hz, $\Delta\nu = 98$ Hz), 1.56 (16 H, m), 0.91 (6 H, s). *Anal.* Calcd for C₁₆H₂₆O₃: C, 72.14; H, 9.84. Found: C, 72.07; H, 9.56.

Preparation of Ketol Tosylates 16a,b.—The tosylates were prepared from 1.5 to 2 equiv of tosyl chloride in pyridine and crude or short-path distilled ketols, according to the procedure given by Fieser.¹¹ Crude tosylates **16a** and **16b** were obtained in yields of 76.5 and 100%, respectively.

3,3-Dimethyl-4-hydroxy-2-butanone tosylate (16b): $\nu_{\text{max}}^{\text{CHCl}_3}$ 1705, 1354, 1172, 972 cm⁻¹; nmr (CCl₄) 7.52 (4 H, q, $J = 8$ Hz, $\Delta\nu = 42$ Hz), 3.90 (2 H, s), 2.45 (3 H, s), 2.05 (3 H, s), 1.11 (6 H, s). *Anal.* Calcd for C₁₂H₁₈O₄S: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.76; H, 6.66; S, 12.01.

2-Methyl-2-hydroxymethylcyclohexanone Tosylate (16a).—The crude tosylate **16a** could not be crystallized even after repeated column chromatograph on silicic acid using benzene-ethyl acetate and ether-hexane eluents. This compound tends to form an oil after initial crystallization:¹² $\nu_{\text{max}}^{\text{CHCl}_3}$ 2940, 1710, 1360, 1170, 970 cm⁻¹ (lit.⁹ ir 1710, 1360, 1175 cm⁻¹); nmr (CCl₄) 7.50 (4 H, q, $J = 8$ Hz), 3.92 (2 H, s), 2.44 (3 H, s), 2.24 (1 H, m), 1.74 (7 H, m), 1.10 (3 H, s).

Registry No.—Formaldehyde, 50-00-0; **13a**, 10316-61-7; **13b**, 1823-90-1; **14a**, 24706-86-3; **14b**, 24706-87-4; **16a**, 13756-93-9; **16b**, 24706-89-6; **15**, 24694-65-3.

(9) Trifluoroacetylated materials contaminated **8a,b** after fractionation; these were not investigated.

(10) J. Decombe, *Compt. Rend. H.*, **203**, 1077 (1936).

(11) L. F. Fieser, and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 1179.

(12) Private communication from Professor E. Wenkert whom we thank for a helpful discussion.

(8) S. W. Pelletier, *Chem. Ind.* (London), 1034 (1953).