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ANNULATION OF 2-FORMYL-2-CYCLOHEXENONES BY REACTION WITH ENAMINES

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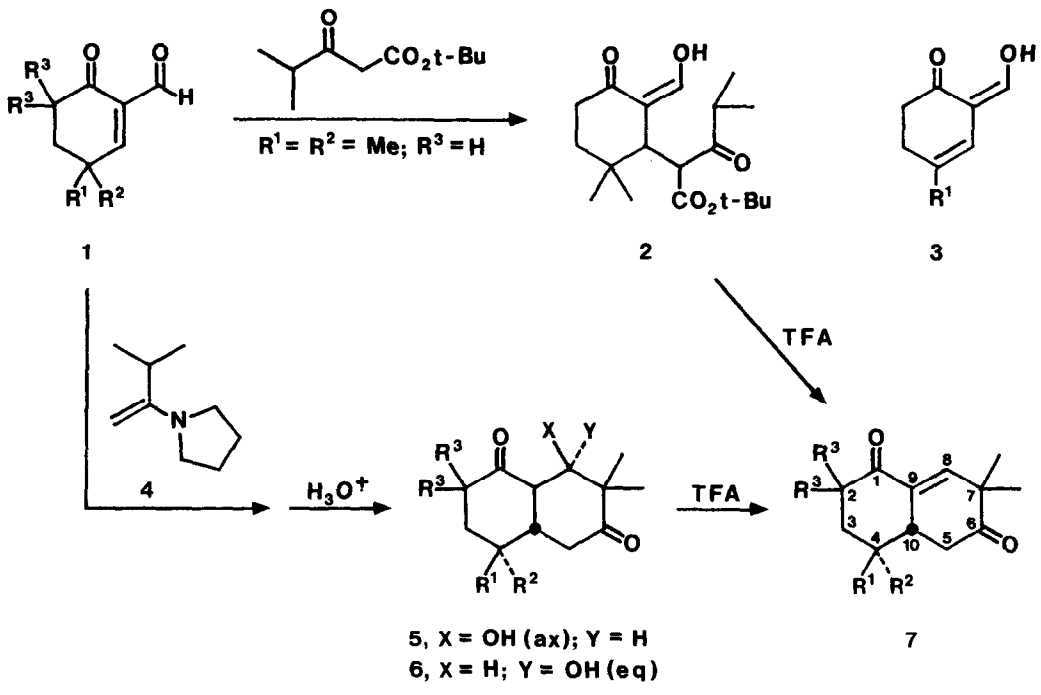
Abstract: 3-Methyl-2-pyrrolidino-1-butene reacts with a series of 2-formyl-2-cyclohexenones to give mixtures of 7,7-dimethyl-Δ^8-octalin-1,6-diones and 7,7-dimethyl-8-hydroxy-*trans*-decalin-1,6-diones which are dehydrated by TFA to afford the octalindiones in overall yields of 80% or better; annulation is >95% diastereoselective with 4-monosubstituted formyl enones.

We recently described details of a new method for annulation of cyclohexanones, through conversion of the ketone to its 2-formyl-2,3-dehydro derivative **1**, Michael addition of the enolate of a β-keto ester, and cyclodehydration (**1** → **2** → **7**).[2] A distinctive feature of this sequence is that it attaches the new ring to the α and β carbons of the cyclohexanone rather than the α and carbonyl carbons as in most other annulation procedures. It also offers considerable structural versatility; substituents may be included on the γ-carbon of the keto ester as well as on the starting ketone. It is limited, however, by the requirement that the cyclohexanone be fully substituted at its 4-position. A 4-protio enalone (**1**, R^2 = H) suffers abstraction of that proton by the keto ester enolate (**1** → **3**) rather than undergoing Michael addition, so the annulation fails in such cases.

We now report that enamines can replace keto ester enolates in this annulation (**1** → **5**/**6** → **7**). Furthermore, with enamines as Michael nucleophiles deprotonation of enalones **1** (R^2 = H) is not a competitive problem, so annulation of 4-monosubstituted or even 4-unsubstituted ketones is feasible. Also, reaction of the enamine with a 4-monosubstituted enalone is highly diastereoselective.

3-Methyl-2-pyrrolidino-1-butene (**4**)[4] was used as a model enamine to test this reaction, for several reasons: (a) the corresponding enolate has already been examined with several enalones,[2] (b) geminate C-7 substitution[3] of the resulting octalindione forces it into the Δ^8 structure **7**, which is easier to characterize than the tautomeric $\Delta^7 \rightleftharpoons \Delta^8$ mixtures that are expected from less substituted systems,[2] and (c) the absence of chiral centers at C-5 and C-7 of the bicyclic products **5** - **7** simplifies analysis of the stereochemical course of the annulation with respect to the enalone ring. Enalones **1a** - **1f** were used as acceptors. Enalone **1e** has been used successfully with enolates;[2] it simply tests the ability of the enamine to react as a similar Michael addend. The others are of the type that undergo



1, 5, 6, 7: a, $R^1 - R^3 = H$ d, $R^1 = t\text{-Bu}$; $R^2 = R^3 = H$
b, $R^1 = Me$; $R^2 = R^3 = H$ e, $R^1 = R^2 = Me$; $R^3 = H$
c, $R^1 = i\text{-Pr}$; $R^2 = R^3 = H$ f, $R^1 = R^2 = H$; $R^3 = Me$

exclusive 4-deprotonation by enolates; thus they critically address the question of whether the enamine can overcome this problem. The enalones were all synthesized by DDQ dehydrogenation of the corresponding 2-hydroxymethylenecyclohexanones.[2]

Reactions of **4** with the enalones were conducted in benzene for 24 h at ca 25 °C. A 2:1 molar ratio of enamine:enalone is necessary for optimum results. Hydrolysis affords mixtures of one or two bicyclic ketols (**5** and **6**) and/or the enedione (**7**) in combined yields of ca. 90% or better, with the sole exception of **1d** which gives enol **3** and no annulation products whatsoever (see Table). The ketols in these crude mixtures are completely dehydrated by exposure to trifluoroacetic acid (TFA) for 4 h at reflux, so the octalindiones **7** can be obtained from the formyl enones **1** in overall yields of better than 80% in most cases.[5]

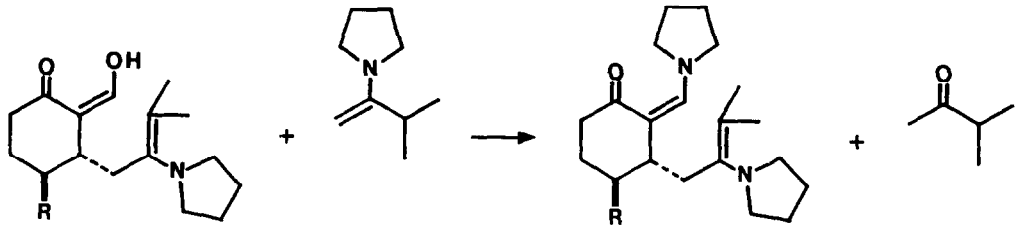
Annulation products from 4-monosubstituted enalones **1b** and **1c** contain only one C-8 diastereomeric pair of ketols, and only one diastereomeric enedione is present in the crude products from their TFA dehydration, within the limits we can detect by ^{13}C NMR (ca 20:1). The annulation is clearly highly diastereoselective in those cases. We assign the trans R^1:C-5 configurations[3] to those products (equatorial 4-alkyl group), on the basis of ^{13}C NMR chemical shift correlations which are too extensive to detail here. Thus the enamine bonds to the face of the enalone which is remote from the 4-alkyl group.

Table. Yields and Product Distributions

Enalone	Annulation Product: Total %	Annulation Product: Distribution, % of Total[a] 5	6	7	Enedione 7, % from TFA Treatment of Annulation Mixture
1a	90	65	11	24	92
1b	91	42	5	53	92
1c	85	33	33	34	76
1d	0	--	--	--	--
1e	92	77[b]	5[b]	9[b]	91
1f	94	50	50	0	99

(a) By ^{13}C NMR integration, ± ca. 5%; (b) The remaining 9% was unchanged 1e.

The requirement for two molar equivalents of enamine results from the fact that 4 undergoes exchange with a hydroxymethylene ketone to form the corresponding pyrrolidinomethylene ketone and 3-methyl-2-butanone. Thus, the initial Michael adduct (8 or its enamino double bond isomer[6]) consumes a second molecule of 4.[7] Both of these steps are very fast; resonances of the enalone completely disappear and those of the liberated 3-methyl-2-butanone appear in the ^1H NMR spectrum as soon as 1b and 4 are mixed. Cyclization appears to be much slower, and may even partly occur during the hydrolysis step.



8 9

This process joins the small but growing number of reactions in which a six-membered ring is created by fusion of two C_3 components.[8] Its efficiency and simplicity, coupled with its very high diastereoselectivity, suggest that it may be widely useful. Further investigation into its scope is in progress.

Typical Procedure: A solution of 2.08 mmol of 95% pure 1b in 12 mL of PhH was treated with 4.35 mmol of 4 in 2 mL of PhH. After 24 h at ca 23 °C solvent was removed and the residue was refluxed for 1.5 h in a mixture of 20 mL of CH_2Cl_2 and 20 mL of 1 N HCl. The aqueous layer was extracted with CH_2Cl_2 and the CH_2Cl_2 solutions were washed with HCl, $NaHCO_3$, and brine, dried, and taken to dryness to afford 1.80 mmol (91%) of a mixture of 5b, 6b, and 7b (see Table). These can be separated by chromatography on Florisil if desired. The crude mixture was refluxed for 4 h in 50 mL of TFA, cooled, diluted with H_2O, extracted with Et_2O, and washed with $NaHCO_3$ and brine. Evaporation left 1.65 mmol (84% based on 1b) of crude 7b

which had ^{1}H and ^{13}C NMR spectra identical with a sample purified by chromatography on Florisil (88% recovery) and recrystallization.

REFERENCES AND NOTES

(1) (a) Fayetteville. (b) Academic guest, 1983, at ETH Zürich while on leave from the University of Arkansas. (c) Abstracted from the Ph.D. dissertation of M.J.B., University of Arkansas, 1985, and in part from the M.Sc. thesis of A.M., Imperial College, London, U.K., 1983; work of A.M. done at ETH Zürich as part of the exchange program between the two universities. (d) Zürich.

(2) Meyer, W.L.; Burgos, C.G.; Brannon, M.J.; Goodwin, T.E.; Howard, R.W. J. Org. Chem. **1985**, 50, 438.

(3) The decalin-tetralin numbering convention shown in structure 7 is used for all decalin and octalin derivatives herein. All compounds were examined only as racemates, although the prefix (±) is omitted and only one enantiomer is depicted.

(4) Carlson, R.; Nilsson, A.; Stromquist, M. Acta Chem. Scand. **1973**, B37, 7. Carlson, R.; Nilsson, A.; Rappe, L.; Babadzamian, A.; Metzner, J. Ibid. **1978**, B32, 85.

(5) All new compounds listed in the Table except **6a**, **6b**, and **6c** have been obtained in pure form. They gave satisfactory microanalytical results and have IR, ^{1}H NMR, and ^{13}C NMR spectra in accord with the assigned structures. **6a**, **6b**, and **6c** have been characterized only spectrally, in enriched mixtures which still contain the other isomeric ketol.

(6) We refer to the initial reaction as a Michael addition of **4** to **1**, but have no evidence to exclude the possibility that it may be of the hetero Diels Alder type with the dihydropyran adduct being in mobile equilibrium with open hydroxymethylene ketones such as 8. Cf. Snider, B.B. Tetrahedron Lett. **1980**, 21, 1133. Desimoni, G.; Tacconi, G. Chem. Rev. **1975**, 75, 651.

(7) We have not isolated intermediates such as 8 or 9 from these reactions, but only infer their presence from NMR spectra of reaction mixtures. However, in our Laboratory Mr. Dennis Scott has confirmed that **4** reacts very rapidly with 3-unsubstituted 2-hydroxymethylenecyclohexanones in the sense shown by 8 → 9. Structures 8 and 9 are shown as (Z) about the CO-C=CHN double bond only for pictorial convenience; we have no evidence regarding that configuration.

(8) Seebach, D.; Calderari, G.; Meyer, W.L.; Merritt, A. Chimia **1985**, 39, 183. Nelson, R.P.; Lawton, R.G. J. Am. Chem. Soc. **1966**, 88, 3884. Büchi, G.; Wüest, H. Helv. Chim. Acta **1971**, 54, 1767. Kende, A.S.; Constantinides, D.; Lee, S.J.; Liebeskind, L. Tetrahedron Lett. **1975**, 405. Chan, T.H.; Brownbridge, P. J. Am. Chem. Soc. **1980**, 102, 3534. Anzeveno, P.B.; Matthews, D.P.; Barney, C.L.; Barbuch, R.J. J. Org. Chem. **1984**, 49, 3134.

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