

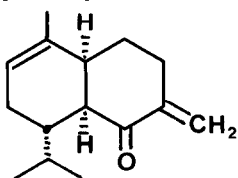
A DIRECT SYNTHESIS OF α -METHYLENE KETONES

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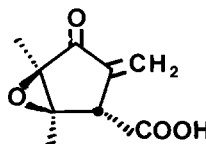
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The α -methylene structural unit is found in many naturally occurring sesquiterpenes or in antibiotics :



chiloscophone (1)



methylenomycin A (2)

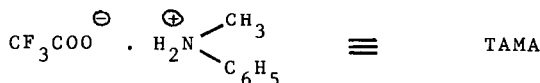
Moreover, the potential utility of the highly reactive system $O=C-C=CH_2$ has been demonstrated repeatedly throughout literature. α -Methylene ketones are widely used in organic synthesis, especially for their ability to function as excellent Michael acceptors (3).

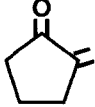
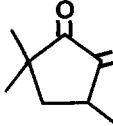
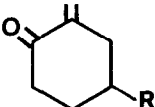
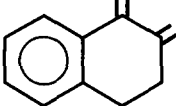
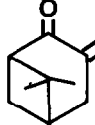

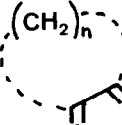
The introduction of a methylene group α to a ketone can be achieved in general via : - the base catalyzed condensation of formaldehyde (3b, 4)
- the initial Mannich α -aminoalkylation of C-H acidic compounds (5) followed by 'quaternization and β -elimination of the dialkylamino group (5a, 6)
- several indirect solutions recently developed to thwart the serious synthetic restrictions which accompany attempts of α -methylenation of ketones (7).

None of these valuable methods affords a simple, direct solution to this problem. We report here the successful direct α -methylenation of ketones, a method which promises to be of considerable importance.

The approach is entirely analogous to the classical Mannich reaction but, by suitable choice of substrates, the α -methylene ketone is the direct product isolated from the process.

The reagents are s-trioxane and N-methylanilinium trifluoroacetate (in french *trifluoroacetate de N-méthylanilinium* : TAMA) a nicely colorless crystalline salt easily available on large scale.



KETONE	REACTION TIME / SOLVENT	PRODUCT* / YIELD
<u>1</u>	48 hr , dioxanne	no reaction
<u>2</u>	30 min , THF	 > 90%
<u>3</u>	10 hr , THF	 90%
<u>4a,b</u>	R = H 15 min , THF	 > 90%
	R = tBu 25 min , THF	> 90%
<u>5</u>	4 hr , dioxanne	 96%
<u>6a,b</u>	R = H , CH ₃ 24 hr , dioxanne	no reaction
<u>7**</u>	3 days, dioxanne	 89%
<u>8**</u>	25 min , THF	 87%
<u>9abc</u>	n = 5 2 hr , dioxanne	 94%
	6 15 min , dioxanne	92%
	10 3 hr , dioxanne	92%
<u>10a,b</u>	R = CH ₃ 48 hr , dioxanne	85%
	R = C ₆ H ₅ 6 hr, dioxanne	96%

* all compounds exhibited satisfactory spectral and analytical data.

**courtesy of Drs H.HEUMANN, J.HATEM, Lab. Stéréochimie, Marseille Univ. III

Reaction of trifluoro acetic acid with 1 eq. of N-methylaniline at 0°C for 1.5 hr afforded the crystalline TAMA which was obtained pure (mp = 66.5°C) in *circa* 90% yield (221 g scale) simply by filtration, washing with anhydrous Et₂O and drying *in vacuo*. The compound is not deliquescent, can be weighed in the air and stored for months under inert atmosphere.

Refluxing the keto-derivative with s-trioxane (1.5 to 3 eq) and TAMA (1.1 to 2.5 eq) in aprotic dry solvent, led to an equivalent controlled aldol condensation of formaldehyde :



The reaction is monitored by tlc or vpc analysis, then diluted with pentane or ether. The organic layer is washed with H₂O, half-saturated aqueous NaHCO₃ and dried over MgSO₄. The crude material is often analytically pure. Filtration through a short column of silica gel or bulb-to-bulb distillation, is sufficient to get the pure α -methylene ketone in high yield.

A representative summary of some of our results is given in the table.

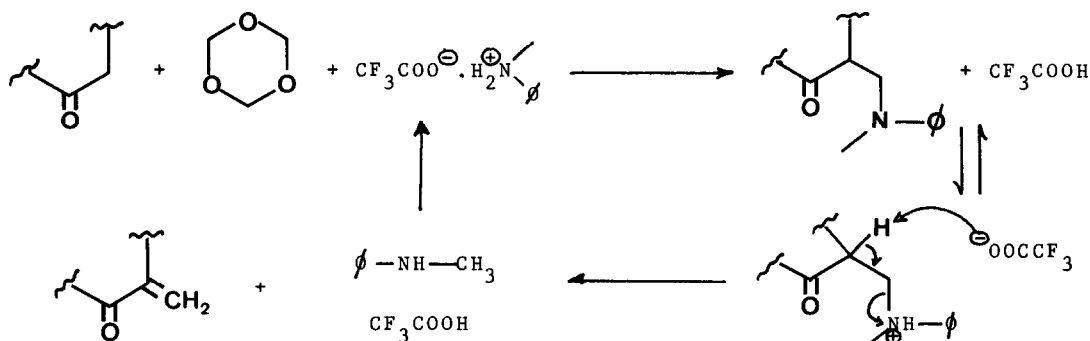
As can be seen from the results presented, the reaction described here is capable of serving as a general synthesis of α -methylene ketones, although there exists some restrictions.

The crude yields of 2, 4a,b are nearly quantitative, but isolation in pure form is complicated by minor processes involving dimerization, or polymerization (8). Introduction of substituent(s) at the α position of the initial carbonyl (e.g. 3, 5, 7, 8) proved to stabilize the α -methylene ketone.

The nearly neutral and aprotic conditions contribute to the stability of the product during the course of the reaction, and preclude subsequent migration of the double bond. The reaction time is very dependent on the reactivity of each substrate. In relatively long time cases (3, 7, 10) the reaction appeared to reach a state of 'quasiequilibrium', and the extent of evolution needed further addition of reagents. This can be circumvented by a periodic portion-wise addition of the reagents.

The postulated mechanism of this addition involves the classical formation of the Mannich base, first formed by the TAMA induced condensation of the ketone and formaldehyde. This derivative undergoes spontaneously a β -deamination after protonation and base catalyzed reaction type by way of the anion derived from the acid. The last step in the reaction sequence is essentially irreversible, and the process directly leaves the α -methylene ketone as sole product of the reaction.

We have controlled that TAMA can be used in catalytic amount (0.1 eq.), the reaction only becoming slower.



Thus TAMA can be considered responsible for this direct methylene transfer.

The requirements we put on the amine are that it would present enough nucleophilicity to insure the first step of the condensation, and that it be readily eliminated to yield the desired enone. The same kind of speculations on pKa determined the choice of trifluoroacetic acid.

The easy availability of TAMA, the simplicity of the procedure, and the high yields make this reaction particularly attractive. Where applicable, this one-step synthesis constitutes the easiest and most straightforward route available to α -methylene ketones. Potential advantages are relatively mild, neutral, aprotic conditions leading to no dialkylation, polymerization and greater product stability. The yields of α -methylene ketones are very good and, because of its mildness and simplicity the present reaction procedure would seem to compete very favorably with other methods of synthesis.

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Bibliography :

- 1) S.HAYASHI, A.MATSUO, Tetrahedron Letters, 1289, (1970).
- 2) T.HANEISHI, N.KITAHARA, Y.TAKIGUCHI, M.ARAI, S.SUGAWARA, J.Antibiot., 27, 386, (1974).
For a total synthesis of methylenomycin A see : R.M.SCARBOROUGH Jr, A.B.SMITH III, J.Amer.Chem.Soc., 99, 7085 (1977).
- 3) a- J.HOOZ, R.B.LAYTON, J.Amer.Chem.Soc., 93, 7320 (1971) and ref. therein
b- G.SBORK, J.D'ANGELO, J.Amer.Chem.Soc., 96, 7114 (1974)
- 4) A.T.NIELSEN, W.J.HOULIHAN, Org.react., 16, 1 (1968)
E.J.COREY, D.E.CANE, J.Org.Chem., 36, 3070 (1971)
- 5) a- for a recent review, see M.TRAMONTINI, Synthesis, 703 (1973)
b- Y.JASOR, M.GAUDRY, M.J.LUCHE, A.MARQUET, TETRAHEDRON 33, 295 (1977)
- 6) M.I.FARBENOV, G.S.MIRONOV, Chem.Abstr., 59, 5062 (1963) - A.AHOND, A.CAVE, C.KAN FAN, P.POTIER, Bull.Soc.Chim.Fr., 2707 (1970) - S.DANISHEFSKY, T.KITAHARA, R.Mc KEE, P.F.SCHUDA J.Amer.Chem.Soc., 98, 6715 (1976) - N.L.HOLY, YU FANG WANG, ibid 99, 944 (1977) - J.L.ROBERTS, P.S.BORRAMEO, C.D.POULTER, Tetrahedron Letters, 1621 (1977).
- 7) A.J.MANSON, D.WOOD, J.Org.Chem., 32, 3434 (1967) - R.B.MILLER, B.F.SMITH, Tetrahedron Letters, 5039 (1973) - G.M.KSANDER, J.E.Mc MURRY, M.JOHNSON, J.Org.Chem., 42, 1180 (1977) - F.HUET, M.PELLET, J-M.CONIA, Tetrahedron Letters, 3505 (1977).
- 8) H.J.ROTH, CH.SCHWENKE, G.DVORAK, Arch.Pharm., 298, 326 (1965).