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A NEW SIMPLE CONVERSION OF α,ß-UNSATURATED CARBONYL COMPOUNDS INTO THEIR CORRESPONDING CYCLOPROPYL KETONES AND ESTERS

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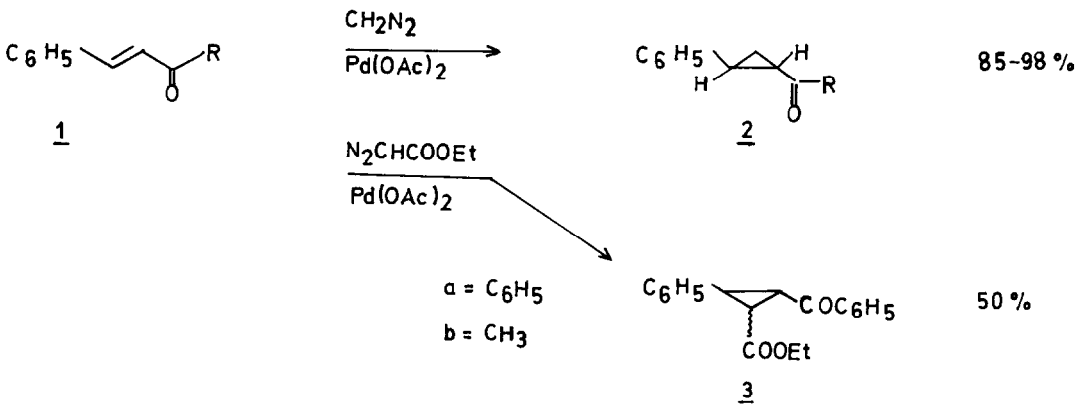
Attempts to prepare 13,14-methylene prostaglandin analogues[1] using conventional methods[2], e.g. the Corey-method[3] and the Simmons-Smith reaction[4], resulted in failure. Since Paulissen,et al.[5] had recently converted styrene with diazomethane as well as ethyl diazoacetate in the presence of $Pd(OAc)_2$ in high yields into the corresponding cyclopropanes, we treated a number of α,ß-unsaturated carbonyl compounds under analogous conditions to determine the scope of this reaction.

We found that these reagents add stereospecifically cis to α,α- or α,ß-disubstituted α,ß-unsaturated ketones or esters in excellent yields whereas trisubstituted α,ß-unsaturated carbonyl compounds did not react in contrast to the Corey-method[3,6]. The formation of cyclopropyl epoxides as by-products (less than 5%) was observed in a few cases[7] whereas allylic alcohols reacted only when a large excess of reagent was used[1].

Thus 1a and 1b gave with $Pd(OAc)_2/CH_2N_2$ 2a and 2b in high yields, whereas 1a afforded with ethyl diazoacetate a 50% yield of 3[8]. $PdCl_2$ as a catalyst was less effective and Pd(II) acetylacetonate gave beside 2a also the pyrazoline 5.



As expected from carben-metal-olefin complexes[9] as probable intermediates the formation of cyclopropyl ketones occurs directly and does not proceed via the corresponding pyrazolines, since 4[10] is readily isomerized by $Pd(OAc)_2$ to the stable 5

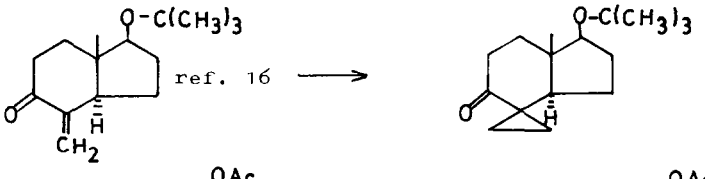
Standard Procedure: To benzalacetophenone 1a (1 g) and $Pd(OAc)_2$ (10 mg) in ether (15 ml) an ethereal CH_2N_2-solution (20 ml, prepared from 2 g N-nitroso-N-methyl urea) was added dropwise at 0°C with continuous stirring during 10 min. After evaporation the residue was chromatographed on silica gel (5 g) with n-hexane Yield 1.05 g (98%) 2a, mp 43-45°C[3].

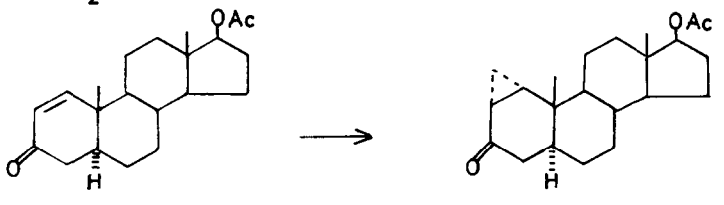
In the following Table I our reactions of α,ß-unsaturated carbonyl compounds with $CH_2N_2/Pd(OAc)_2$ under standard conditions are summarized[11], whereas the following α,ß-unsaturated steroidal ketones did not react in agreement with our substitution-rule: 17ß-acetoxy-1-methyl-5α-androst-1-en-3-one, 17ß-acetoxy-2-methyl-5α-androst-1-en-3-one, 17ß-acetoxy-4-androsten-3-one, 17ß-acetoxy-androsta 1,4-dien-3-one, 17ß-acetoxy-androsta-4,6-dien-3-one, 21-acetoxy-4,16-pregnadien-3,20-dione

Furthermore symmetrical unsaturated carbonyl compounds like diethyl fumarate as well as maleic anhydride gave only polar pyrazolines whereas coumarin as well as 1,3-dimethyluracil failed to react.

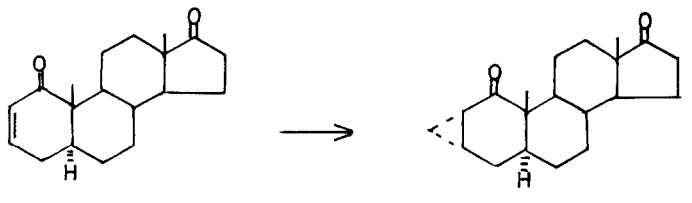
Table I

R_1	R_2	R_3	R_4	mp	Yields[11]	References
Ph	H	H	Ph		98%	3
Ph	H	H	CH_3		85%	12,13
CH_3	CH_3	H	CH_3	no reaction		
Ph	H	H	CO_2Et	33-34°	90%	14
H	Ph	H	CO_2Et		85%[15]	14
CH_3	H	H	CO_2Me		89%	6
H	H	CH_3	CO_2Me		88%	6
CH_3	CH_3	H	CO_2Me	no reaction		

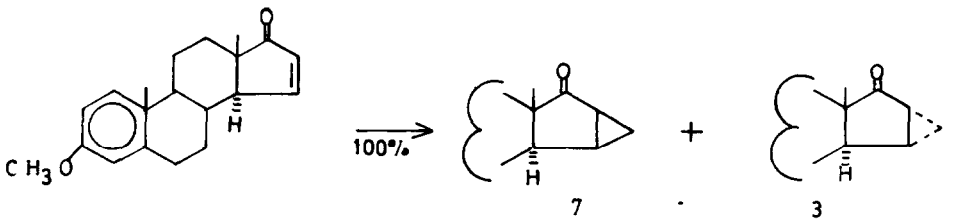




80% ref 17



mp 153-155° ref 18
75%



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REFERENCES

1) B. Raduchel, U. Mende, G. Cleve, G.-A. Hoyer and H. Vorbruggen, Tetrahedron Lett. subsequent paper.

2) H. Laurent and R. Wiechert in "Organic Reactions in Steroid Chemistry", Vol. II p. 53, Edit. J. Fried and J.A. Edwards; Van Nostrand, Reinhold Co., N.Y. (1972).

3) E.J. Corey and M. Chaykovsky, J. Amer. Chem. Soc. 87, 1353 (1965).

4) H.E. Simmons, T.L. Cairns, S.A. Vladuchic and S.M. Hoiness, Org. Reactions Vol. 20, 1 (1973).

5) R. Paulissen, A.J. Hubert and Ph. Teyssie, Tetrahedron Lett. 1465 (1972).

6) S.R. Landor and N. Punja, J. Chem. Soc. (C) 2495 (1967)

7) For the formation of epoxides in the reaction of ketones with CH_2N_2 see G.W. Cowell and A. Ledwith, Quart. Rev., 24, 119 (1970).

8) H. Nozaki, D. Tunemoto, S. Matubara and K. Kondŏ, Tetrahedron 23, 545 (1967).

9) W.R. Moser, J. Amer. Chem. Soc., 91, 1135 (1969).

10) L.I. Smith and W.B. Pings, J. Org. Chem., 2, 23 (1937).

11) All products were characterized either by comparison with authentic samples or by their physical and analytical data which will be reported in the full paper.

12) A mixture of olefinic and cyclopropyl epoxides was obtained as by-product (4%)

13) R. Huisgen, R. Sustmann and K. Bung, Chem. Ber., 105, 1324 (1972).

14) J.M. Conia and J. C. Limasset, Tetrahedron Lett. 3151 (1965).

15) Since the starting material was always contaminated with some trans-cinnamic-ester, the resulting cyclopropane contained corresponding amounts of trans product.

16) Z.G. Hajos and D.R. Parrish, J. Org. Chem., 38, 3244 (1973)

17) R. Wiechert and E. Kaspar, Chem. Ber., 93, 1710 (1960).

18) As by-product 3% of (1R)-1,1-methylenoxy-5α-androst-2-en-17-one [mp 123-126°, nmr ($CDCl_3$) H-18 s. δ 0.88, H-19 s. δ 1.03 ppm] was obtained.

19) R. Wiechert, R. Nickolson and D. Bittler, private communication.