Tetrahedron Letters No. 31, pp 2709 - 2710, 1976. Pergamon Press. Printed in Great Britain.

A NEW SPIROCYCLISATION REACTION

Ae.de Groot and B.J.M.Jansen

Laboratory of Organic Chemistry, Agricultural University, Wageningen, The Netherlands

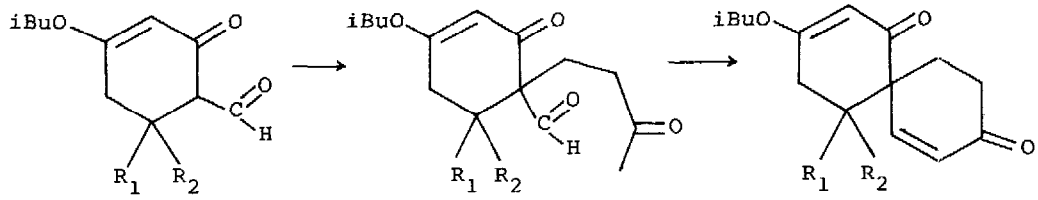
(Received in UK 1 June 1976; accepted for publication 14 June 1976)

The adducts of 2-formylcycloalkanones and methyl vinyl ketone give mixtures of several cyclised products when treated with acid or base[1,2]. For instance 2-formyl-2-(3-oxobutyl)cyclohexanone (1), when distilled from potassium hydroxide, gave a mixture of 1, deformylated products such as 2-(3-oxobutyl)-cyclohexanone and 4,4a,5,6,7,8-hexahydro-2 (3H)-naphthalenone, and as major product cyclohex-2-enespirocyclohexane-2',4-dione in 35% yield.

A second general synthesis of spiro compounds, starting with sodium enolates of 2-formylcycloalkanones and carboethoxycyclopropyltriphenylphosphonium tetrafluoroborate also produces spirocycles in moderate (30-44%) yields[3,4].

We now present a new, high yield synthesis of spiro compounds by cyclisation of the 6-(3-oxobutyl) or 6-(2-oxopropyl) substituted 6-formyl-3-isobutoxy-2-cyclohexenones (compounds of type 3 or 5).

The 6-formyl-3-isobutoxy-2-cyclohexenones (2a-c) were easily obtained by condensation of ethyl formate with the corresponding 3-isobutoxy-2-cyclohexenones, using sodium hydride in ether[3,5]. The addition of 2a to methyl vinyl ketone could be achieved in 77% yield by the action of triethylamine in ethyl acetate solution. A few additional potassium hydroxide pellets however were necessary to effect a fast reaction of 2b and 2c to give the adducts 3b and 3c in 87% and 85% yield respectively. To avoid deformylation during the cyclisation reaction



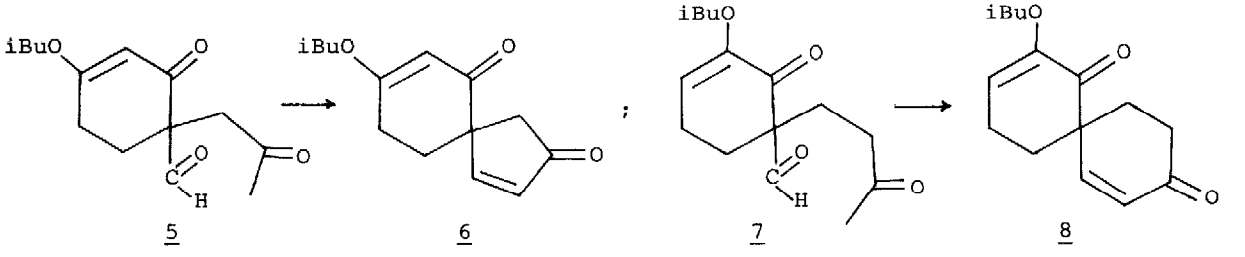
2 3 4

a, $R_1=R_2=H$; b, $R_1=H$, $R_2=CH_3$; c, $R_1=R_2=CH_3$

a careful choice of basic catalyst proved necessary and we finally found that pyrrolidine and acetic acid in methanolic solution, when refluxed for 3 hours, gave high yields (80-90%) of the compounds 4a-c. The nmr spectra all showed doublets around δ6.1 and δ6.8 (J=10.5 Hz) and singlets at δ5.3 of the vinylic protons and were in agreement with the proposed structures[6].

The ring carbonyl function, being part of a vinologous ester, is not sufficiently reactive to give rise to a condensation reaction which explains the high yields of spirocyclised compounds. This is in contrast to the aforementioned 2-formyl-2-(3-oxobutyl)cyclohexanone (1).

Analogous to the 6-(3-oxobutyl) substituted compounds 3a-c, the 6-(2-oxopropyl) substituted compound 5[7], on refluxing for 32 hours with pyrrolidine and acetic acid in methanolic solution, also cyclised to the spirocompound 6 in 50% yield.



5 6 7 8

The difference in reactivity between the ring carbonyl function and the aldehyde function also proved to be large enough in compound 7[8] and a 72% yield of spirocyclised product 8 was obtained.

In connection with synthetic efforts directed towards the rapidly expanding class of spirosesquiterpenes this spirocyclisation reaction may be a valuable extension of the available methods. Compounds of type 4c and 6 especially can be used as suitable starting compounds for a general synthesis of chamigrenes and spirovetivanes.

References

1. V.Dave and J.S.Whitehurst, J.Chem.Soc. C, 1973, 393, and references cited therein.
2. V.Dave and J.S.Whitehurst, Tetrahedron, 30, 745 (1974).
3. W.G.Dauben and D.J.Hart, J.Am.Chem.Soc., 97, 1622 (1975).
4. P.L.Fuchs, J.Am.Chem.Soc., 96, 1607 (1974).
5. Ae.de Groot and B.J.M.Jansen, Rec.Trav.Chim. (Pays-Bas), 95, 81 (1976).
6. Correct elemental analyses or mass spectra were obtained for all the spiro compounds.
7. Obtained from 2a and iodoacetone in 54% yield, together with 26% O-alkylated product.
8. Obtained in 62% yield by formylation of 2-isobutoxy-2-cyclohexenone followed by condensation with methyl vinyl ketone.