SYNTHESIS OF 3-CARBOMETHOXY-3,4-DIALKYLCYCLOHEXANONES Werner M. Grootaert<sup>la</sup>, Roelant Mijngheer and Pierre J. De Clercq<sup>lb<sup>\*</sup></sup> Department of Organic Chemistry, State University of Ghent, Laboratory for Organic Synthesis, Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

## ABSTRACT

The uncatalyzed 1,4-addition of phenylmagnesium bromide and furylmagnesium iodide to methyl 5-methoxy-1,5-cyclohexadienylcarboxylate (1), directly followed by alkylation and hydrolysis leads to the corresponding cyclohexanones of type 2 (R, and R, trans) in moderate to high yield.

Short sequences to variously substituted cyclohexanones are of continuous synthetic interest. In connection with a novel entry into gibberellins<sup>2</sup> we investigated the potential use of methyl 5-methoxy-1,5-cyclohexadienylcarboxylate (1) for the synthesis of some 3-carbomethoxy-3,4-dialkylcyclohexanones (2) and wish to report now on the obtained results. In the proposed scheme, a one-step 1,4-addition (nucleophile  $R_1$ )/alkylation (electrophile  $R_2$ ) sequence leads, after hydrolysis, to cyclohexanones of type  $\underline{2}$ .



Ester 1<sup>3</sup> is obtained via Birch reduction of m-methoxybenzoic acid (under careful controlled conditions of reaction and work-up)<sup>4</sup>, directly followed by esterification  $(CH_2N_2)$  : 82 % isolated yield after rapid chromatography on silica gel (EtOAc:isooctane, 5:95)<sup>5</sup>.

From <u>1</u> high yields of cyclohexanones <u>5a</u> and <u>5b</u> are obtained in essentially one step when using phenylmagnesiumbromide/2,3-dibromopropene or propargylbromide in the 1,4-addition/alkylation sequence. In a typical experiment 1 is added to 1.5 eq of phenylmagnesium bromide in diethylether at -20 °C and, after reaction for 1-2 h at -20°C, treated successively with 15 eq of HMPA and 2.6 eq of the bromide; after 2 h at r.t., the mixture is worked-up with saturated  $NH_ACl$ /ether and the ether phase stirred with 2 N hydrochloric acid.

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Reaction products are isolated by rapid filtration over silica gel (EtOAc: isooctane, 3:7) and purified by recrystallization : 75 % isolated  $\underline{5a}^6$  (m.p. 89°C) and 81 %  $\underline{5b}^6$  (m.p. 117-118°C). Attempts at isolating the intermediate enolether (cf. <u>4</u>) by chromatography (silica gel, EtOAc:isooctane, 1:9) resulted in a moderate yield (45 %) of a mixture of  $\Delta^{1,2}$  (cf. <u>4</u>) and  $\Delta^{1,6}$ isomers<sup>7</sup>. The use of HMPA was found crucial for successful alkylation.

In a similar way the 1,4-addition of furyImagnesium iodide in ether and subsequent alkylation with 2,3-dibromopropene/HMPA gave  $\underline{6a}^6$  in 46 % isolated yield. Whereas 2-iodofuran is available from 2-furoic acid via Hunsdiecker reaction<sup>8</sup>, a more convenient preparation involved the addition of iodine to furyllithium in THF or ether at -40°C and subsequent purification by distillation (70 %) : the thus obtained 2-iodofuran is reasonably stable, either neat or in solution (few days at r.t., several months at -20°C). For the purpose of preparing the Grignard derivative for subsequent 1,4-addition to  $\underline{1}$ , the crude solution of 2-iodofuran <u>in ether</u> can be used directly : thus, there was obtained from  $\underline{1}$ , after 1,4-addition and hydrolysis, a 40 % yield of  $\underline{2}$  (R<sub>1</sub> = C<sub>4</sub>H<sub>3</sub>O; R<sub>2</sub> = H). In contrast, the same procedure in THF only led to trace amounts of conjugate adduct<sup>9,10</sup>.

In contrast to the above results, no conjugate adduct could be isolated from the reaction of <u>1</u> with methylmagnesium iodide in ether<sup>9</sup>; lithium dime-thylcuprate addition (1.5 eq, ether), however, followed by alkylation with 2,3-dibromopropene and hydrolysis, gave  $\underline{7a}^{6}$  (47 % isolated yield; m.p. 44-47°C).

In all cases only one diastereoisomeric alkylated adduct was isolated. The anticipated trans-orientation of  $R_1$  and  $R_2$  was proven by <sup>1</sup>H NMR and chemical correlation.

Reduction of 5a with sodium borohydride (CH<sub>3</sub>OH, -40°C) gave alcohols  $8a^6$  and  $9a^6$  (ratio 35/65, quantitative). The equatorial (in 8a) and axial (in 9a) orientation of the alcohol group is clearly indicated by the H-l vicinal J-values (sum of 16 and 31 Hz, respectively); in both products, the equatorial position of the phenyl group is inferred from the J-values of H-4 (13.0 and 3.0 Hz for 8a; 11.2 and 3.0 Hz for 9a).



Finally, only <u>9a</u> gave rise to the corresponding lactone  $(10a^6; m.p. 105^\circ C;$ benzene, p-TsOH, r.t., quantitative), hereby proving the stereochemistry of <u>5a</u>, <u>8a</u> and <u>9a</u>. Reduction of <u>6a</u> with K-selectride (THF, -78°C) led to lactone <u>10b</u> (m.p. 58°C, 15 % isolated) and alcohol <u>8b</u> (54 %) : analogous J-values for H-1 and H-4 again confirm the proposed structures.

Since conjugate additions to  $\alpha,\beta$ -dialkylated unsaturated esters are known to proceed poorly in general<sup>11</sup>, the  $\alpha$ -vinylogous situation of the methoxy group in <u>1</u> must play a crucial role in the present reaction. With this respect it is interesting to note that upon reaction of phenylmagnesium bromide with the methyl ester of  $\alpha$ -bromocrotonic acid only conjugate addition was observed<sup>12</sup>. Furthermore, although no systematic study was undertaken so far with <u>1</u>, it seems likely that for a satisfactory conjugate addition in the absence of copper reagents an sp<sup>2</sup> nucleophile should be involved. Some applications of this short entry to cyclohexanes <u>2</u> (3 steps from m-methoxybenzoic acid) in natural product synthesis will be reported in due course.

## Acknowledgments

We are indebted to the Nationaal Fonds voor Wetenschappelijk Onderzoek and the Ministerie voor Wetenschapsbeleid for financial support to the laboratory.

## References and Notes

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- 2. See following paper in this issue.
- 3. A.J. Birch, A.J. Pearson, J. Chem. Soc., Perkin 1, 638 (1978).
- 4. M.E.C. Biffin, A.G. Moritz and D.B. Paul, Austr. J. Chem., <u>25</u>, 1329 (1972). The addition of Na to the reaction mixture should be performed rapidly in order to prevent overreduction to 3-methoxycyclohex-2-ene-1-carboxylic acid. On larger scales (e.g., 50 g acid), where rapid addition at -33°C becomes hazardous, Na is added to the liq NH<sub>3</sub> sln. at -78°C and, after addition, the sln. is stirred for 3 h at -33°C.
- 5. The ester obtained in this way is crystalline (m.p. 7°C) at low temperature : unless purified by chromatography no crystalline material is obtained and rapid decomposition takes place even at  $-20^{\circ}$ C.

- 6. Satisfactory elementary analyses and spectral data were obtained. Relevant NMR data (CDC1, 360 MHz); 5a : 7.31, 7.09 (5H,m), 5.58 (1H,m), 5.53 (1H,m), 3.67 (3H,s), 3.08 (1H,dd; 12.5, 3.5 Hz), 3.02 (1H,d; 14.5 Hz), 2.96 (1H,dd; 15.5, 2.0 Hz), 2.65 (1H,ddt; 15.5, 4.5, 2.0 Hz), 2.55 (1H,d; 14.5 Hz) ppm. 5b : 7.30, 7.17 (5H,m), 3.65 (3H,s), 3.41 (1H,dd; 3.8, 12.5 Hz), 2.81 (1H,d; 15.0 Hz), 2.57 (1H,dd; 15.0, 2.0 Hz), 2.40 (1H, dd; 17.0, 2.5 Hz), 2.27 (1H,dd; 17.0, 2.5 Hz), 2.22 (1H,t; 2.5 Hz) ppm. 6a : 7.36 (1H, dd; 1.75, 0.75 Hz), 6.35 (1H,dd; 3.25, 2.0 Hz), 6.12 (1H,bd; 3.25 Hz), 5.66 (1H;bs), 5.60 (1H,d; 1.75 Hz), 3.63 (3H,s), 3.33 (1H,dd; 4.75, 9.0 Hz), 3.14 (1H,dd; 14.75, 1.0 Hz), 2.92 (1H,dd; 15.5, 2.0 Hz), 2.76 (1H,d; 14.75 Hz), 2.68 (1H,dtd; 15.5, 5.75, 1.75 Hz), 2.50 (1H,dd; 15.25, 1.0 Hz) ppm. 7a : 5.63, 5.57 (2H,m), 3.72 (3H,s), 3.26 (1H,dd; 14.5, 1.0 Hz), 2.77 (1H,dd; 15.5, 1.7 Hz), 2.62 (1H,d; 14.5 Hz), 2.07 (1H,ddq; 3.5, 10.5, 6.75 Hz), 1.09 (3H,d; 6.75 Hz) ppm. 8a : 7.27, 7.04 (5H,m), 5.56, 5.51 (2H,m), 4.57 (1H, vtt; Σ 31.0 Hz), 3.51 (3H,s), 3.12, 2.49 (2H, AB; 14.5 Hz), 2.60 (1H,dd; 13.0, 3.0 Hz), 2.55 (1H,ddd; 13.25, 4.75, 1.75 Hz), 1.32 (1H,dd; 13.25, 10.5 Hz) ppm. 8b : 7.31 (1H, dd; 0.6, 1.75 Hz), 6.30 (1H,dd; 3.25, 1.75 Hz), 6.04 (1H,bd; 3.25 Hz), 5.63 (1H,bs), 5.55 (1H,bs), 4.39 (1H,tt; 4.5, 10.0 Hz), 3.53 (3H,s), 3.33 and 2.72 (2H, AB; 14.75 Hz), 2.78 (1H,dd; 11.0, 4.5 Hz). 9a : 7.27, 7.09 (5H,m), 5.56, 5.53 (2H,m), 4.08 (1H,m; Σ 24 Hz), 5.34 (OH, bd; 8.0 Hz), 3.44 (3H,s), 3.22, 2.51 (2H, AB; 14.8 Hz), 2.67 (1H,dd; 11.2, 3.0 Hz), 2.45 (1H,ddd; 15.2, 4.0, 2.0 Hz), 1.82 (1H,dd; 15.2, 4.4 Hz) ppm. 10a: 7.28 (5H,m), 5.44, 5.38 (2H), 4.87 (1H,t; ~4.6 Hz), 2.89 (1H,dd; 10.5, 8.5 Hz), 2.63, 2.51 (2H, AB; 15.0 Hz), 2.77 (1H,ddd; 12.0, 6.25, 1.5 Hz), 2.09 (1H,d; 12.0 Hz) ppm. 10b : 7.31 (1H,dd; 1.75, 0.75 Hz), 6.33 (1H,dd; 3.5, 1.75 Hz), 6.21 (1H,bd; 3.5 Hz), 5.50 (2H,bs), 4.84 (1H,bt; 5.0 Hz), 3.08 (1H,dd; 13.0, 5.8 Hz), 2.72 and 2.64 (2H, AB; 14.5 Hz).
- 7. Even on prolonged standing at -20°C the  $\Delta^{1,2}$  olefin isomerizes; ca 1/1 ratio after 2 weeks, as indicated by <sup>1</sup>H NMR (90 MHz) :  $\delta$  (CDCl<sub>3</sub>) 5.06 (bs) and 4.72 (m) for the  $\Delta^{1,2}$  and  $\Delta^{1,6}$  isomer, respectively.
- 8. H. Gilman, H.E. Mallory and G.F. Wright, J. Am. Chem. Soc., <u>54</u>, 733 (1932). 2-Iodofuran thus obtained ( $\sim$  20 % yield in our hands) decomposes in a matter of minutes; solutions of the corresponding Grignard derivative, however, are stable for a few weeks.
- 9. A complex mixture was obtained, presumably originating from 1,2-reaction.
- Reports on 1,4-additions involving the 2-furan nucleus are scarce; for the successful reaction of 2-furylmagnesium bromide (catalyzed by CuCl) on 1-acetylcyclopentene in THF (15 % yield), see : A. Takeda, K. Shinhama and S. Tsuboi, J. Org. Chem., <u>45</u>, 3125 (1980).
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(Received in UK 26 April 1982)