Reactions of 2-Fluorotropone with Grignard Reagents

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On the addition of ethylmagnesium bromide to 2-fluorotropone in tetrahydrofuran, direct substitution of fluorine occurs to give 2-ethyltropone which, under the reaction conditions, undergoes, to some extent, Grignard addition at C-7 to give an intermediate enolate. The latter either acts as an *O*- and *C*-nucleophile, competing in the replacement of fluorine from unchanged 2-fluorotropone, or undergoes *C*-protonation during work-up to give a mixture of *cis*- and *trans*-2,7-diethylcyclohepta-3,5-dien-1-one. All the products have been separated by chromatography. A similar reaction scheme applies to other alkyl and aryl Grignard reagents.

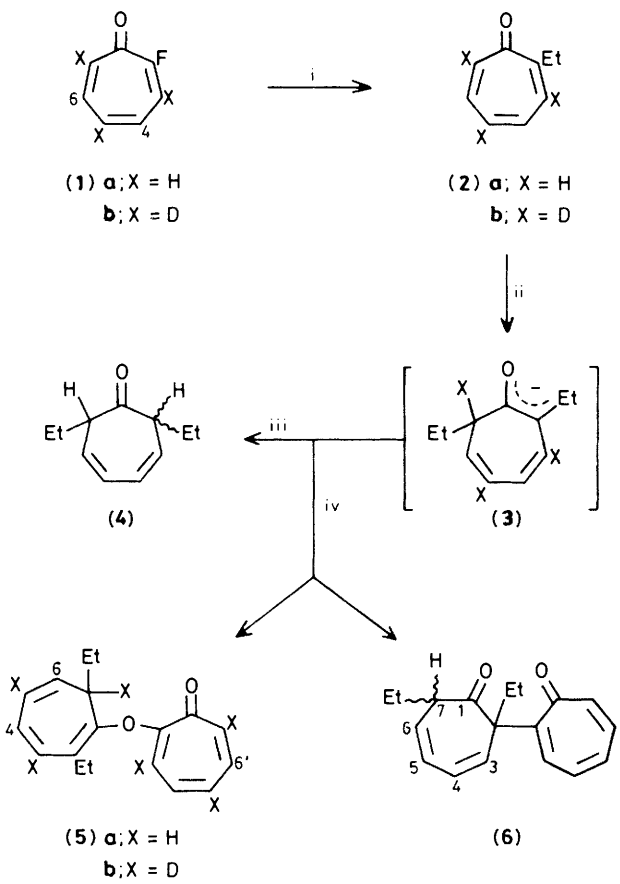
Although the reactions of tropone (cyclohepta-2,4,6-trien-1-one) derivatives with nucleophiles have been studied in depth,[1] the behaviour of fluorotropones towards carbon nucleophiles has not been investigated previously. Fluorine is the most easily replaced nucleofugic substituent with either oxygen or nitrogen nucleophiles.[1],† This contrasts with the generally poorer nucleofugic aptitude of chlorine, which also activates other tropone ring carbons leading to either telesubstitution[2a] or ring contraction[2b] with certain nucleophiles. Besides oxygen and nitrogen nucleophiles, other important such nucleophiles are the Grignard reagents which, in the case of 2-chlorotropone, are known to lead often to ring-contraction products[3] or to the products of C-7 addition.[4]

We have now examined the reactions of 2-fluorotropone with Grignard reagents, in particular ethylmagnesium bromide, and found the reaction to be quite complex. Thus, ethylmagnesium bromide was added to 2-fluorotropone (slightly more than 1 mol equiv.) in tetrahydrofuran (THF) at 0 °C and the mixture was then neutralized, the organic layer evaporated, and the residue subjected to repeated layer chromatography to afford 2-ethyltropone (**2a**) (40%), a diastereoisomeric mixture of the ketone (**4**) (10%), the tropone ether (**5a**) (6.6%), and a diastereoisomeric mixture of (**6**) (1.7%) (Scheme). The structural assignments of these compounds mainly rest on the ^{1}H n.m.r. spectra (Experimental section).

The process was repeated with 2-fluoro[3,5,7-$^2H_3$]tropone (**1b**) in place of (**1a**) resulting in the isolation of the deuterio compounds (**2b**) and (**5b**) (the other products were not investigated) (Scheme). This proves that the formation of 2-ethyltropone (**2a**) occurs by direct substitution of the halogen by the organometallic reagent. The competing pathways are shown in the Scheme. Similar results, though with lower yields of the products of type (**2**), were obtained with either n-butyl- or phenyl-magnesium bromide.

Although the yields of the products of type (**2**) were not optimized, the above reactions are best carried out in THF. For example, in diethyl ether as a solvent, enolates of type (**3**) were found to precipitate out. Acidification of the mixture led, in this case, to products of type (**2**) in only 10% yield, as well as products of type (**4**) (15%). Also, lithium organometallic reagents proved to be unsuitable. In fact, the reaction of (**1a**) with phenyl-lithium in THF at 0 °C gave 2-phenyltropone in only 7% yield, as well as the product of type (**4**) (24%).

† To our knowledge, there is only one report to date of the nucleophilic replacement of fluorine with rearrangement. This concerns C-7 telesubstitution of the fluorine in 2-fluorotropone by phosphorus nucleophiles (M. Cavazza, G. Morganti, C. A. Veracini, A. Guerriero, and F. Pietra, *Tetrahedron Lett.*, 1982, **23**, 4115).



Scheme. *Reagents:* i, EtMgBr, THF; ii, EtMgBr; iii, H_3O^+; iv, (**1a**)

In conclusion, fluorine is easily replaced without rearrangement by carbon nucleophiles from the tropone α-carbon, as expected, in the case of Grignard reagents. However, competing reactions, which could only be minimized, by adding the reagents in a particular order at low temperature, caused the product of direct substitution of fluorine to occur in only low yield; moreover, the isolation of the reaction products requires difficult chromatographic procedures. Therefore, these reactions have little synthetic value. However, it must be recalled that the general synthetic methods for 2-alkyltropones are based either on the solvolysis of *endo*-alkyl-*exo*-chloro isomers of alkyl chloroketene–cyclopentadiene adducts,[5] or on the

reactions of tropones carrying a nucleofugic group at C-2 with magnesium,[3,4] lithium,[6] or copper organometallic compounds,[7] and all these methods suffer from significant limitations. Thus, the ketene route proved unsuccessful for 2-aryltropones,[5] while the methods utilizing organometallic reagents were unsatisfactory in terms of the yield[3] and the regioselectivity.[7] In fact, the reactions of Grignard reagents with 2-chlorotropone usually lead only to ring-contraction products,[3] and the problem of the regioselectivity (C-2 *vs.* C-7 attack) does not appear to have been solved. Also, with alkyl (aryl) cuprates in place of the Grignard reagents, there is little regioselectivity, as shown by the fact that C-2 attack is preferred over C-7 attack by a factor of only two.[7] Finally, hydroxy replacement by organolithium compounds[6] is affected by the carbonyl–hydroxy tautomerism in tropolones,[1] leading, *per se*, to isomeric mixtures. Thus, in certain cases, the synthesis of 2-alkyl- and, particularly 2-aryltropones, is best carried out with 2-fluorotropone–Grignard reagents.*

Experimental

Electron impact mass spectra were obtained on a Hewlett-Packard 5995 A instrument. ^{1}H N.m.r. spectra were recorded on a Varian 360 spectrometer, chemical shifts being given in δ(p.p.m.) with respect to internal Me_4Si. U.v. spectra were recorded on a Unicam SP8-150 instrument, and i.r. spectra on a Perkin-Elmer 337 spectrometer. Merck Kieselgel 60 P_{254} was used for the 2-mm thick silica-gel plates. Ether refers to diethyl ether. Light petroleum refers to the fraction with b.p. 40—70 °C.

Reaction of 2-*Fluorotropone* (**1a**) *with Ethylmagnesium Bromide.*—To a stirred solution of freshly sublimed 2-fluorotropone (**1a**) (0.3 g, 2.4 mmol) in tetrahydrofuran (4 ml) was slowly added, under nitrogen at 0 °C, ethylmagnesium bromide (1.8 ml, slightly less than 1 mol equiv.; 1.3M in ether). After 40 min the mixture was neutralized with dilute sulphuric acid and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4), and evaporated to leave a residue which was subjected to repeated t.l.c. as follows. With ether–light petroleum (8:2) as eluant we obtained 2,7-*diethylcyclohexa*-3,5-*dien*-1-*one* (**4**) (0.40 g, 10%), as a diastereoisomeric oily mixture, R_F 0.8 (Found: C, 80.2; H, 9.7. $C_{11}H_{16}O$ requires C, 80.5; H, 9.8%); $\lambda_{max.}$(MeOH) 280 and 230 nm; $\nu_{max.}$(neat) 1 710 cm^{-1}; *m/z* 164 (4.7%, *M*), 163 (4.7, *M* − H), 149 (100, *M* − CH_3), and 136 (16, *M* − C_2H_4), δ($CDCl_3$) 6.3 and 5.7 (two m, each 2 H, diene H), 3.1 and 2.8 (two m, each 1 H, methine H of each diastereoisomer), 1.8 (4 H, m, CH_2), 0.9 (6 H, m, CH_3).

In addition, a mixture, R_F 0.5, was obtained composed of compounds (**6**), (**5a**), and (**2a**) (0.18 g), and traces of unchanged (**1a**), R_F 0.26. Using benzene–ether (85:15) as eluant† this mixture gave 2-ethyltropone (**2a**) as an oil (0.13 g, 40%), R_F 0.26, whose analytical and spectral data exactly matched those in the literature,[5] while compounds (**6**) and (**5a**) were collected together, R_F 0.4. Finally, using ether–light petroleum (7:3) as eluant, (**6**) and (**5a**) were separated to give a diastereoisomeric mixture of 2-(7-*oxocyclohexa*-1,3,5-*trienyl*)-2,7-*diethylcyclohexa*-3,5-*dien*-1-*one* (**6**) as an oil (0.011 g, 1.7%), R_F 0.40 (Found: C, 80.6; H, 7.5. $C_{18}H_{20}O_2$ requires C, 80.3; H, 7.2%); $\nu_{max.}$(neat) 1 709 cm^{-1}; *m/z* 269 (1%, *M* + 1), 268 (5, *M*), 240 (5, *M* − C_2H_4), 239 (16, *M* − C_2H_5), 211 (46), and 159 (100); δ($CDCl_3$) 7.1 (5 H, m, tropone H), 6.2 and 5.5 (4 H, 2 m, diene H), 3.6 (1 H, m, methine H of the two diastereoisomers), 2.1 (2 H, q, *J* 9.0 Hz, 2-H_2), 1.7 (2 H, m, 7-H_2), and 0.9 and 0.8 (6 H, 2 superimposed t, *J* 9.0 Hz); and 2-(2,7-*diethylcyclohexa*-1,3,5-*trienyloxy*)*tropone* (**5a**) as an oil (0.43 g, 6.6%), R_F 0.36 (Found: C, 80.1; H, 7.9. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%); $\nu_{max.}$(neat) 1 625, 1 600, 1 400, 1 260, 1 216, 1 178, 1 060, 773, 750, and 700 cm^{-1}; *m/z* 268 (3%, *M*), 239 (4, *M* − C_2H_5), and 117 (100); δ($CDCl_3$) 7.5—7.0 (5 H, m, tropone H), 6.7 (3 H, m, 3-, 4-, 5-H), 5.4 (1 H, dd, *J* 16 and 8 Hz, 6-H), 2.2 (3 H, m, 7-H and 2-H_2), 1.7 (2 H, m, 7-H_2), and 0.8 (3 H, m, Me).

Reaction of 2-*Fluoro*[3,5,7-$^2H_3$]*tropone* (**1b**) *with Ethylmagnesium Bromide.*—Starting from (**1b**),[2a] under identical conditions with those used above for (**1a**), we obtained the product (**2b**) as an oil (38%); δ($CDCl_3$) 7.22 (1 H, br s, 4- or 6-H), 7.12 (1 H, br s, 6- or 4-H), 2.73 (2 H, q, *J* 9.0 Hz, CH_2), 1.20 (3 H, t, *J* 9.0 Hz, CH_3); compound (**5b**) was also obtained as an oil (6%); δ($CDCl_3$) 7.40 (1 H, br s, 4′- or 6′-H), 7.05 (1 H, br s, 6′- or 4′-H), 6.7 (1 H, br s, 4-H), 5.4 (1 H, br s, 6-H), 2.2 (2 H, q, *J* 9.0 Hz, 2-H_2), 1.7 (2 H, m, 7-H_2), and 0.8 (3 H, m, Me). The other products were not isolated.

Reaction of 2-*Fluorotropone* (**1a**) *with either n-Butylmagnesium Bromide or Phenylmagnesium Bromide.*—Using the same method as in the above case of ethylmagnesium bromide, we isolated 2-n-butyltropone[4] (25%) or 2-phenyltropone[6] (15%) from the reaction of 2-fluorotropone (**1a**) with, respectively, n-butylmagnesium bromide or phenylmagnesium bromide. Both compounds were identical with those from independent synthesis.[7] The other products were not isolated.

Acknowledgements

We thank both the C.N.R. and the M.P.I., Roma, for financial support.

References

1 F. Pietra, *Chem. Rev.*, 1973, **73**, 293, and references therein to previous reviews; F. Pietra, *Acc. Chem. Res.*, 1979, **12**, 132.
2 (*a*) G. Biggi, F. Del Cima, and F. Pietra, *J. Am. Chem. Soc.*, 1973, **95**, 7101; (*b*) G. Biggi, A. J. de Hoog, F. Del Cima, and F. Pietra, *ibid.*, 1973, **95**, 7108.
3 H. Tsuruta and T. Mukai, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2489.
4 A. P. ter Borg, R. van Helden, and A. F. Bickle, *Recl. Trav. Chim.*, 1962, **81**, 591.
5 W. T. Brady and J. P. Hieble, *J. Am. Chem. Soc.*, 1972, **94**, 4278.
6 W. von E. Doering and C. F. Hiskey, *J. Am. Chem. Soc.*, 1952, **74**, 5688.
7 M. Cavazza and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 1974, 501.

* *Note added in proof.* In continuance of this work, we are now exploring a route to 2-alkyl- and 2-aryl-tropones *via* flash thermolysis of bicyclo-[3.2.0]hepta-3,6-dien-2-ones.[1] We are generating the latter compounds from the photocycloadducts of suitable cyclopentenones with alkynes.

† Clearly, the stepwise t.l.c. separation described here could be better carried out by quicker gradient-elution column chromatography on silica gel with the indicated eluants.

Received 13*th June* 1983; *Paper* 3/978