Tetrahedron Vol 45, No 14, pp 4619 to 4626, 1989
Printed in Great Britain

0040-4020/89 $3 00+.00

NEW ROUTES TO SUBSTITUTED TROPONES

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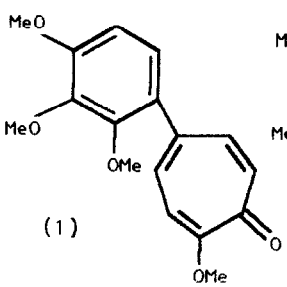
(*Received in UK* 2 *May* 1989)

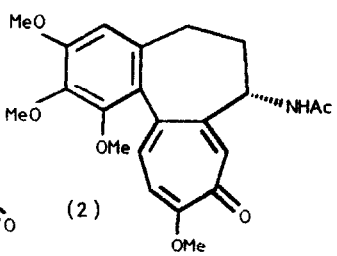
Abstract: We describe the synthesis of various mono- and di-substituted tropones from 8-oxabicyclo[3.2.1]octenones, and also two novel cleavage reactions of these oxabicycles.

In a previous paper[1] we described our initial efforts to prepare aryl-substituted tropones. The rationale for this work was the known anti-tumour activity of the aryl-tropolone (1)[2], which has some structural resemblance to colchicine (2). In continuation of this work we now describe the synthesis of various 2- and 2,7-disubstituted tropones from readily accessible 8-oxabicyclo[3.2.1]oct-6-en-3-ones[3]

Upon reaction of the 2-phenyl-oxabicycle (3)[4] with trimethylsilyl triflate (compare with the methodology introduced by Föhlisch[5]), the 2-phenyltropone (4) was obtained in excellent yield (82%). Similarly the 2-carboethoxymethyl-oxabicycle (5) [prepared from the parent oxabicycle (6) using ethyl bromoethanoate and LDA] yielded the corresponding 2-substituted tropone (7) in 62% yield.



(1)



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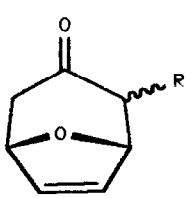
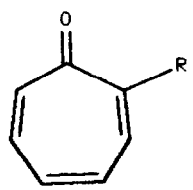


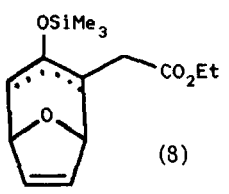
(3) R= Ph
(5) R= CH_2CO_2Et
(6) R=H



(4) R=Ph
(7) R=CH_2CO_2Et

Since these reactions probably proceed via the respective enol silyl ethers, we reasoned that treatment of these with other (cheaper) ether-cleaving reagents might also yield the required tropones. In the event, treatment of enol silyl ether (8) [prepared from (5) in 90% yield] with BF_3.etherate and KI in acetonitrile[6] produced the furans (9) and (10) in yields of 11 and 60% respectively. Reaction of (5) with this same reagent also yielded the furans (17 and 44% respectively).

It was known from the literature[7] that addition of Grignard reagents and alkyl lithiums to tropones led to introduction of the alkyl or aryl group alpha to the carbonyl; but the corresponding reactions with cuprates had not been investigated. We reacted tropone (7) with dimethyl-cuprate and obtained the adduct (11) (R=Et) (as a mixture of stereoisomers) in 68% yield. Treatment of this with pyridinium bromide perbromide followed by DBU yielded the 2,7-disubstituted tropone (12) (R=Et) in a yield (not optimised) of 55%, together with small amounts of the enol lactone (13). The corresponding tert-butyl ester of (7) provided the dienone (11) (R=^{t}Bu) (65%), and thence the tropone acetic acid (12) (R=H) after sequential treatment with trifluoroacetic acid in dichloromethane then iodine (a non-optimised overall yield of 24%).



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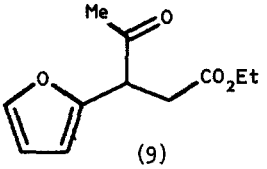

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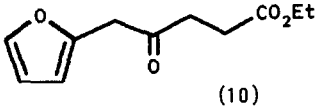

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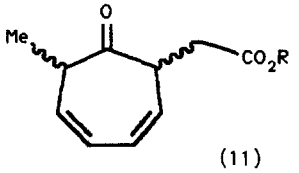

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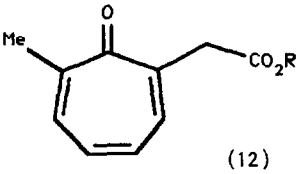

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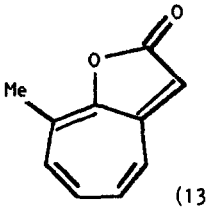
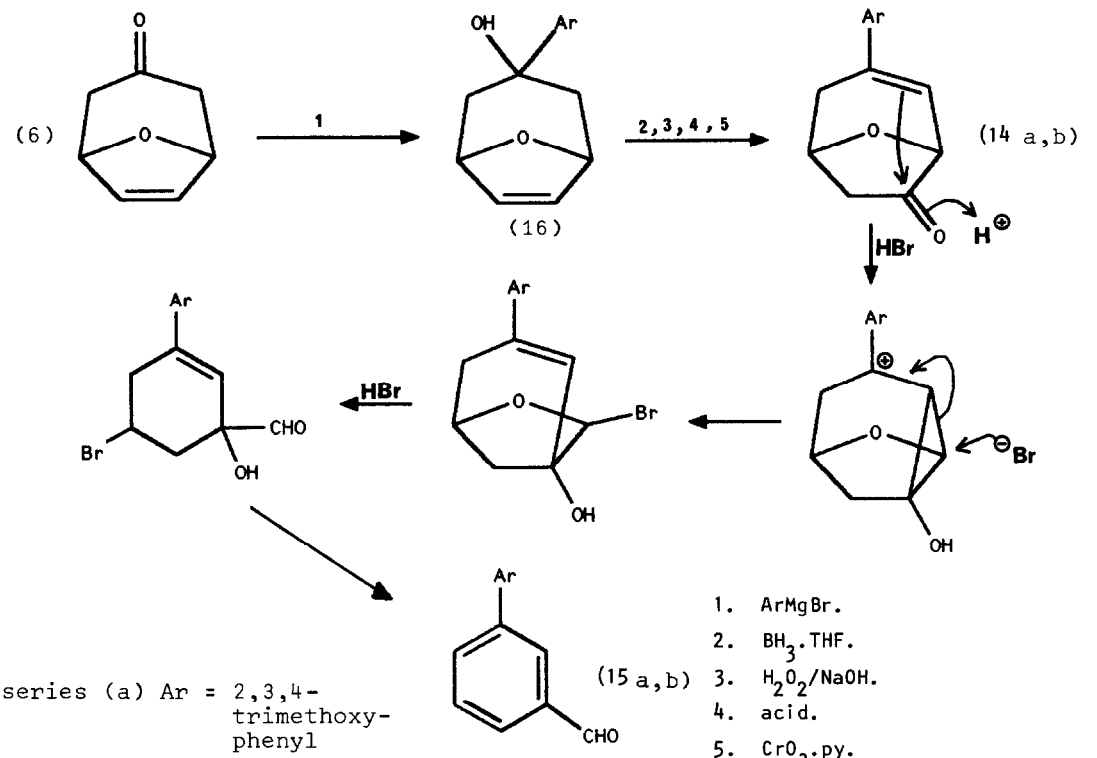


(13)

Finally, attempts to prepare 4-aryltropones were thwarted because the 3-aryl-8-oxabicyclo[3.2.1]oct-2-en-7-ones (14) (Ar=2,3,4-trimethoxyphenyl and 3-trifluoromethylphenyl) underwent rearrangement to yield 3-arylbenzaldehydes (15) when treated with ether-cleaving reagents (HBr or Me_2BBr). The synthesis of the oxabicycles (14) and a proposed mechanism for these interesting rearrangements is shown in the Scheme[8]. Other complex rearrangements of oxabicyclo[3.2.1]-species have been reported[9], but the present methodology allows a particularly easy access to 3-substituted unsymmetrical biaryls.



SCHEME

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 881 double beam grating spectrophotometer; n.m.r. spectra were recorded with a Perkin-Elmer R34 (220MHz) instrument or with a Varian T-60 (60MHz) instrument, using tetramethylsilane as internal standard; flash chromatography was performed using Crosfield Sorbsil C60 (40-60 μm); solvents were purified according to Perrin[10], and petrol refers to petroleum ether b.pt. range 40-60°.

2-Phenylcyclohepta-2,4,6-trien-1-one (4)

To a stirred solution of 2-phenyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (3) (0.3g, 1.5mmole) and triethylamine (0.45ml, 3.1mmole) in CCl_4 (1.5ml) held at 0°C under an atmosphere of nitrogen, trimethylsilyl triflate (0.6ml, 3.1mmole) was added dropwise. After 30 minutes, satd. aqueous $NaHCO_3$ (20ml) was added, and the product was extracted into ethyl acetate. Purification by flash chromatography (petrol:diethyl ether 1:3) provided 0.225g (83%) of (4). M.pt. 80-82° C. (lit. value[11] 84.5-85.5°); i.r. ($CHCl_3$) ν_{max} 1625 cm^{-1}; n.m.r. ($CDCl_3$, 60MHz) 6.80-7.70 (mult., aryl H); m/z (%) 182 (M^+, 100), 154 (M^+ -CO, 80), 77 (40).

2-(Ethoxycarbonylmethyl)-2,4,6-cyclohepta-2,4,6-trien-1-one (7)

Trimethylsilyl triflate (3.74ml, 23.24mmole) was added dropwise to an ice-cooled solution of (5) (2.44g, 11.6mmole) and triethylamine (3.36ml, 23.4mmole) in CCl_4 (8ml) under an atmosphere of nitrogen. After two hours, the reaction was worked up as before, and the product purified by flash chromatography (petrol:EtOAc 1:1) to yield the tropone (7) (1.38g, 62%) as a white crystalline solid. M.pt. 66-67° (from ether); i.r. ($CHCl_3$) ν_{max} 1728, 1632 and 1580 cm^{-1}; n.m.r. ($CDCl_3$, 220MHz) 1.25 (t, J 7.5Hz, Me), 3.48 (s, CH_2), 4.18 (q, J 7.5Hz, OCH_2), 6.70-7.00 (m, 4-H and 5-H), 7.08-7.15 (m, 6-H and 7-H), 7.25-7.35 (m, 3-H) ppm; calculated for $C_{11}H_{12}O_3$ C 68.73%, H 6.29%, found C 68.64%, H 6.35%.

Ethyl-3-(2'-furyl)-4-ketopentanoate (9) and Ethyl-5-(2'-furyl)-4-ketopentanoate (10)

Trimethylsilyl chloride (0.45ml, 3.57mmole) was added to a stirred solution of (5) (0.5g, 2.38mmole) and DBU (0.53g, 3.7mmole) in dry dichloromethane (5ml) under an atmosphere of nitrogen. After reaction at 60-65° for one hour, the mixture was cooled to RT, and the silyl ether (8) extracted into petrol. This extract was washed with aq. $NaHCO_3$ then water, dried and concentrated to yield an orange oil (0.62g, 92%).

BF_3.etherate (0.25ml, 2.0mmole) was added to an ice-cooled solution of (8) (0.3g, 1.06mmole) and KI(0.67g, 3mmole) in acetronitrile (4ml), and the resultant mixture stirred for 20 minutes at RT. Subsequent treatment with satd. aq. $NaHCO_3$ and extraction into ether, was followed by washing of the combined organic extracts with $Na_2S_2O_3$ and water. After drying and concentration, the resultant red oil was purified by flash chromatography (petrol:ether 3:1) to yield the furans (9) (25mg, 11%) and (10) (135mg, 60%), as pale yellow oils.

Data for (9): i.r.(neat) 1725, 1589 and 1503 cm^{-1}; n.m.r. ($CDCl_3$, 220MHz) 1.30 (t, J 7.5Hz, Me), 2.25 (s, MeCO), 2.60 (dd, J 6 and 17Hz, 2-H), 3.20 (dd, J 8.5 and 17Hz, 2-H), 4.10 (q, J 7.5Hz, OCH_2), 4.30 (dd, J 6 and 8.5Hz, 3-H), 6.15 (d, J 3Hz, 3'-H), 6.30 (dd, J 3 and 1.5Hz, 4'-H), and 7.35 (d, J 1.5Hz, 5'-H)ppm; high resolution mass spec. 210.0872, $C_{11}H_{14}O_4$ requires 210.0888.

Data for (10): i.r.(neat) 1726, 1596, and 1504 cm^{-1}; n.m.r. ($CDCl_3$, 200MHz) 1.25 (t, J 7.5Hz, Me), 2.40-2.90 (m, 2-H and 3-H), 3.75 (s, 5-H), 4.05 (q, J 7.5Hz, OCH_2), 6.15 (d, J 3.5Hz, 3'-H), 6.25 (dd, J 3.5 and 1.5Hz, 4'-H), and 7.25 (d, J 1.5Hz, 5'-H)ppm; high resolution mass spec. 210.0877, $C_{11}H_{14}O_4$ requires 210.0888.

2-(Ethoxycarbonylmethyl)-7-methyl-cyclohepta-3,5-dien-1-one (11)

Methyl lithium (3.78ml of a 1.6M. solution in ether, 6.06mmole) was added to an ice-cooled solution of cuprous iodide (0.557g, 2.92mmole) in anhydrous ether (15ml). The resultant mixture was stirred at 0^o for 15 minutes prior to the addition of tropone (7) (0.487g, 2.54mmole) in ether 10ml). After an additional hour at 0^o, the reaction was quenched by the addition of aq. HCl (30 ml of 2M), and the product extracted into ether (4x30ml). The combined organic extract was dried and concentrated to yield a brown oil, which was purified by flash chromatography (petrol: ether 1:1). The diene (11) was obtained as a yellow oil (0.373g, 71%). I.r. (neat) 1734, 1715, 1632, and 1589 cm^{-1}; n.m.r. ($CDCl_3$, 60MHz) 1.20 (t, J 7Hz, ester Me), 1.28 and 1.38 (2xd, J 6.5Hz, Me of two isomers), 2.40-3.30 (m, CH_2, 2-H and 7-H), 4.00 (q, J 7Hz, ester CH_2), 5.45 (br.dd, J 10 and 3.5Hz, 3-H and 6-H), 6.00 (br.t, J 10Hz, 4-H and 5-H)ppm; high resolution mass spec. 208.1099, $C_{12}H_{16}O$ requires 208.1099.

2-(Ethoxycarbonylmethyl)-7-methyl-cyclohepta-2,4,6-trien-1-one (12)

A mixture of diene (11) (0.104g, 0.5mmole) and pyridine hydrobromide perbromide (0.166g, 0.52mmole) in glacial acetic acid (4ml) was stirred

at RT for 6 hours. After addition of water, the products were extracted into ether. The combined ethereal extract was washed with satd. $NaHCO_3$ then water, dried and concentrated to a brown solid. This was dissolved in THF (4ml) and reacted with DBU (0.152g, 1mmole). After 5 hours at RT, purification by flash chromatography (petrol:ether 1:2) yielded tropone (12) (57mg,55%) as an orange oil, and lactone (13) (12mg,12%) as an orange solid. Data for (12): i.r.(neat) 1730, 1622, and 1566 cm^{-1}; n.m.r. (60MHz,$CDCl_3$) 1.30 (t, J 7.5Hz, ester Me), 2.35 (s, Me), 3.62 (s, CH_2), 4.20 (q, J 7.5Hz, ester CH_2), 6.80-7.50 (m, olefinic H)ppm; high resolution mass spec. 206.0939, $C_{12}H_{14}O_3$ requires 206.0939. Data for (13): i.r. ($CHCl_3$) 1740, 1602, 1568 and 1540cm^{-1}; mass spec. 160.0524, $C_{10}H_8O_2$ requires 160.0522.

3-(exo-2,3,4-Trimethoxyphenyl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol (16)

Oxabicycle (6) (7.67g,62mmole) in THF (100 ml) was added dropwise over 15 minutes to 2,3,4-trimethoxyphenyl magnesium bromide [from Mg (3.03g, 125mmole) and 2,3,4-trimethoxybromobenzene (30.4g,123mmole) in THF (100ml)] held at 0° C. After stirring at RT for 6 hours, the brown solution was poured into saturated aqueous NH_4Cl solution (300ml) and the product extracted with EtOAc. Flash chromatography (ether:EtOAc, 7:1) followed by crystallisation from ether provided white crystals (8.27g, 46%). M.pt. 118-119°C; i.r. ($CDCl_3$ solution) 3590 (OH), 2945, 1600, 1490, 1460, 1410, 1095, 845 and 795 cm^{-1}; n.m.r. ($CDCl_3$, 220MHz) 1.80 (d, J 14.5Hz, 2-H_{endo} and 4-H_{endo}), 2.70 (dd, J 14.5 and 4.5Hz, 2-H_{exo} and 4-H_{exo}), 3.53 (s, OH), 3.87 (s, 2xOMe), 4.04 (s, OMe), 4.93 (d, J 4.5Hz, 1-H and 5-H), 6.56 (s, 6-H and 7-H), 6.67 and 7.24 (2xd, J 9Hz, aryl H)ppm; calculated for $C_{16}H_{20}O_5$: C 65.72%, H 6.90%; found C 66.2%, H 6.76%.

3-(2,3,4-Trimethoxyphenyl)-8-oxabicyclo[3.2.1]oct-2,6-diene (17)

The above alcohol (8.23g, 28mmole) in acetone (150ml) was treated with aq. HCl (2M, 37.5ml). After two hours, elimination was complete, and the product was extracted into dichloromethane after neutralisation. Purification by flash chromatography (ether:petrol:EtOAc 5:4:1) provided a yellow solid (6.72g, 87%). M.pt. 63-4°C (from hexane-ether); i.r. ($CDCl_3$) 2970, 2940, 1600, 1495, 1465, 1415, 1295, 1100 and 795 cm^{-1}; n.m.r. ($CDCl_3$,100MHz) 2.10 (dd, J 18 and 1.5Hz, 4-H_{endo}), 2.95 (m, J 18,

6.5, 2 and 1Hz, 4-H_{exo}), 3.72 (s, OMe), 3.83 (s, 2xOMe), 4.82 (m, J 4.5, 2,1 and 0.5Hz, 1-H), 5.00 (dd, J 6.5 and 2Hz, 5-H), 6.04 (ddd, J 6,2 and 0.5Hz, 6-H), 6.20 (ddd, J 4.5, 2 and 1.5Hz, 2-H), 6.60 (dd, J 6 and 2Hz, 7-H), 6.60 and 6.81 (2xd, J 9Hz, aryl H)ppm; high resolution mass spec. 274.1211, $C_{16}H_{18}O_4$ requires 274.1206.

3-(2,3,4-trimethoxyphenyl)-8-oxabicyclo[3.2.1]oct-2-en-7-one (14a) and regioisomer

To a stirred solution of the above diene (2.00g, 7.3mmole) in THF (50ml) was added 9-BBN (14.6ml of a 0.5M. solution in THF), and the reaction mixture was then stirred at RT for 6 hours, prior to work-up with water (10ml), followed by aq. NaOH (4ml. of 2M) and H_2O_2 (12.5ml of 30%). Extraction into ethyl acetate, followed by chromatography (ether:EtOAc 2:1) provided a white solid (2.00g, 94%) which comprised a 55:45 mixture of the regioisomeric alcohols. This mixture (0.91g, 3.1mmole) was added to the complex formed from CrO_3 (1.81g,18.1mmole) and pyridine (3ml, 37mmole) in dichloromethane (100ml). After one hour, the solvent was removed, and the residual black tar was extracted with several aliquots of ether. The combined extract was washed with 2M. HCl, then purified by flash chromatography (ether:petrol 3:1) to yield crystals (0.64g, 71%) of a mixture of regioisomeric 6- and 7-ones (ca. 1:1). Only the 6-one could be isolated in a completely pure state. M.pt. 96-99° C.; i.r. (KBr disc) 2920, 1735, 1635, 1600, 1405, 1295, 1095, 1070, 815 and 705 cm^{-1}; n.m.r. ($CDCl_3$,500MHz) 2.51 (d, J 17Hz, 7-H), 2.57 (ddd, J 17, 1.5 and 1Hz, 4-H), 2.80 (ddd, J 17, 5.5 and 1Hz, 7-H), 2.92 (ddd, J 17, 6.2 and 1.5Hz, 4-H), 3.73 (s, OMe), 3.83 (s, 2xOMe), 4.40 (dt, J 6.2, 1 and 1Hz, 5-H), 4.98 (dd, J 5.5 and 4.5Hz, 1-H), 6.16 (dt, J 4.5, 1.5 and 1.5Hz, 2-H), 6.62 and 6.82 (2xd, J 8.5Hz, aryl H)ppm; high resolution mass spec. $C_{16}H_{18}O_5$ requires 290.1155, found 290.1157.

3-(2',3',4'-trimethoxyphenyl)benzaldehyde (15a)

A solution of HBr (0.14ml of 48%) in glacial acetic acid (5 ml) was added to the isomeric ketone mixture (0.17g, 0.59mmole), and the solution stirred at RT for 55 hours. After neutralisation, the product was extracted into ether and purified by flash chromatography (ether:petrol 2:1) to yield an oil (0.13g,82%). I.r.(film) 2940, 1700, 1600, 1465, 1090, 830, 795, 730 and 700 cm^{-1}; n.m.r. ($CDCl_3$, 60MHz) 3.70, 3.85 and 3.90 (3xs, 3xOMe), 6.65 (d, J 9Hz, 5'-H), 7.00 (d, J 9Hz, 6'-H),

7.20-7.95 (m, other aryl-H), 10.00 (s, CHO)ppm; high resolution mass spec. $C_{16}H_{16}O_4$ requires 272.1048, found 272.1047 (100%); requires C 70.58%; H 5.92%, found C 70.79%, H 5.97%.

3-[3'-(trifluoromethyl)phenyl]benzaldehyde (15b)

This compound was prepared in the same way from the requisite ketone (14b) and isomer (0.087g,0.32mmole). Yield 0.052g (64%). M.pt. 143-4° C (from ether); i.r.(film) 2930, 2850, 2730, 1700, 1600, 1580, 1335, 1270, 1165, 1125, 1100, 1075, 1050, 790 and 700 cm^{-1}; n.m.r. ($CDCl_3$, 60MHz) 7.30-8.30 (m, all aryl-H), 10.00 (s, CHO)ppm; high resolution mass spec. $C_{14}H_9F_3O$ requires 250.0605, found 250.0599; requires C 67.20%, H 3.65%, found C 67.35%, H 3.57%.

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Acknowledgements

We thank Lilly Research Ltd. and the S.E.R.C. for a C.A.S.E. award to P.D.Wilde, and C.N.P.q. Brazil for a Postgraduate Scholarship awarded to L-C. Almeida Barbosa.