Tetrahedron Vol. 47, No. 33, pp. 6681-6688, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

A NOVEL EFFICIENT ROUTE TO HEXAHYDRODIBENZOFURAN DERIVATIVES

Christian Berrier, Marie-Paule Jouannetaud, Jean-Claude Jacquesy* and Faustin Kigabo

Laboratoire de Chimie XII - URA CNRS DO 1468
"Chimie des Produits Naturels et de l'Environnement"
Faculté des Sciences, 40, Avenue du Recteur Pineau
86022 POITIERS Cedex (France)

(*Received in Belgium* 30 *April* 1991)

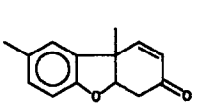
ABSTRACT

Synthesis of 2 and 4-aryl cyclohexenones and of hexahydrodibenzofuran derivatives is described. In anhydrous hydrogen fluoride at 0°C, 4-hydroxy-4 methylcyclohex-2 en-1 one **2** reacted to yield ketone **7** (43%). Reaction of ketone **2** with *para*bromophenol **3b** in HF gave ketone **6** (40%) at - 20°C and ketone **6** (35%) and **7** (13%) at 0°C. Under similar conditions ketone **2** reacted with phenol **3a** to yield 2 and 4 arylated ketones **4a** (4%), **5** (**a+b**) (25%) and **9a** (5%).

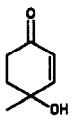
Many efforts have been devoted to the synthesis of molecules such as morphinans, benzomorphans, arylpiperidines..., having simplified morphine structures[1,2].
Few studies have been focused on the synthesis of the tetra (hexa) hydrodibenzofuran ring system which constitutes a part of the morphine skeleton[3]. Pummerer's ketone derivatives have been prepared[4] and analgesic[5] or antitussive[6] activities has been claimed for some of them. Other compounds in this series have been synthesized and exhibit a high affinity on opiate receptors μ and also present activity in the hot plate test[7].
A facile entry into this ring system might have been provided by the oxidative coupling of phenols. Unfortunately, oxidation by one-electron-type chemical oxidants yields complex mixtures[8-11]. For example oxidation of paracresol with ferric chloride gives at least ten compounds, one of which being the known Pummerer's ketone 1[9].
We reported that cyclohexenone **2** reacted in HF with aromatics (benzene, toluene, anisole, *para*bromoanisole) to yield 2-aryl and 4-arylcyclohexenones and 2-aryl-4-fluorocyclohexanones[12]. We would like to describe an efficient route to the hexahydrodibenzofuran ring system using a similar reaction.

RESULTS

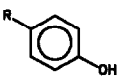
The readily available enone **2**[13] was added, under magnetic stirring, alone or with phenol **3a** or *para*bromophenol **3b** (5 eq.) to HF maintained at -35°, -20° or 0°C. After a given reaction time and usual work up, the crude material was chromatographied on silica gel.
The results are reported in Table.



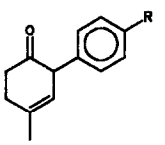
1



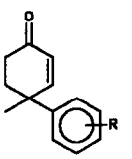
2



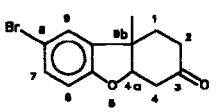
3 a R=H
b R=Br



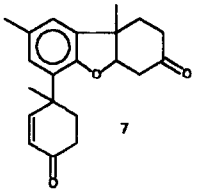
4 a R=OH
b R=OCH_3



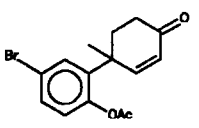
5 a R= 2–OH
b R= 4–OH
c R= 2–OCH_3
d R= 4–OCH_3



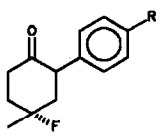
6



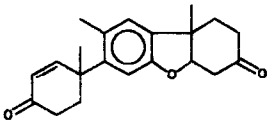
7



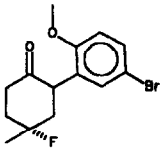
8



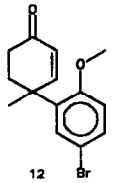
9 a R=OH
b R=OCH_3



10



11



12

FIGURE 1

Starting material	Temperature (°C)	Reaction time (mn)	Product (%)
2 + 3a	-35	1.5	4a(4)+5(a+b)(25)+ 9a(5)
2 + 3b	-20	30	6(40)
2 + 3b	0	10	6(35)+7(13)
2	0	30	7(43)

Ketones **4a** and **5** (**a** or **b**) displayed ^1H NMR spectra very similar to those exhibited by the analogous compounds **4b** and **5** (**c** or **d**) obtained when ketone **2** was reacting with anisole in HF[12].

Ketone **6** showed an ion peak at m/e 280-282 ($M^{+\cdot}$) in its mass spectrum corresponding, an account of its analysis, to the molecular formula $C_{13}H_{13}O_2Br$. The ^1H NMR spectrum showed signals consistent with the assigned structure and similar to those displayed by analogous compounds[4,7b,11] possessing a cis ring junction. Reaction of ketone **6** with BF_3-Et_2O in benzene and acetic anhydride yielded ketone **8**. In the ^1H NMR spectrum the olefinic protons appeared as doublets (J = 10 Hz) at 6.02 and 6.93 ppm. Ketone **6** is recovered after treatment of ketone **8** with KOH-MeOH.

Ketone **7** showed an ion peak at m/e 324 ($M^{+\cdot}$) in its mass spectrum and in ^1H NMR displayed signals very similar to those observed for ketone **6**. Furthermore only two aromatic protons appeared as singlets at 6.80 and 6.85 ppm, with a singlet at 2.28 ppm for the protons of the methyl group on the aromatic ring which is tetrasubstituted. Two olefinic protons at 6.02 and 7.06 ppm coupled together (J = 10 Hz) imply the presence of a 4.4-disubstituted cyclohexenone[12,14]. Two structures **7** and **10** are consistent with these features. Attempts to open the dihydrofuran ring in **7** (or **10**) with BF_3-Et_2O-Ac_2O, were made unsuccessfully. However, taking into account the directing effect of the oxygen group in the aromatic ring in similar acidic conditions[12] (*vide infra*) the more likely structure is **7**.

Ketone **9a** exhibited in its ^1H NMR spectrum signals very similar to those reported for ketones **9b** and **11**[12], and by analogy, we can assume that the fluorine atom and the aryl group are trans in the cyclohexane ring.

REACTION MECHANISMS

We have shown that reaction in HF of cyclohexenone **2** with aromatics (benzene, toluene, anisole, *para*bromoanisole) afforded 2-aryl and 4-arylcyclohexenones and 2-aryl-4-fluorocyclohexanones. For example, anisole yielded ketones **4b**, **5** (**c** or **d**) and **9b**, whereas *para*bromoanisole gave only ketones **11** and **12**, the presence of the bromine atom making the

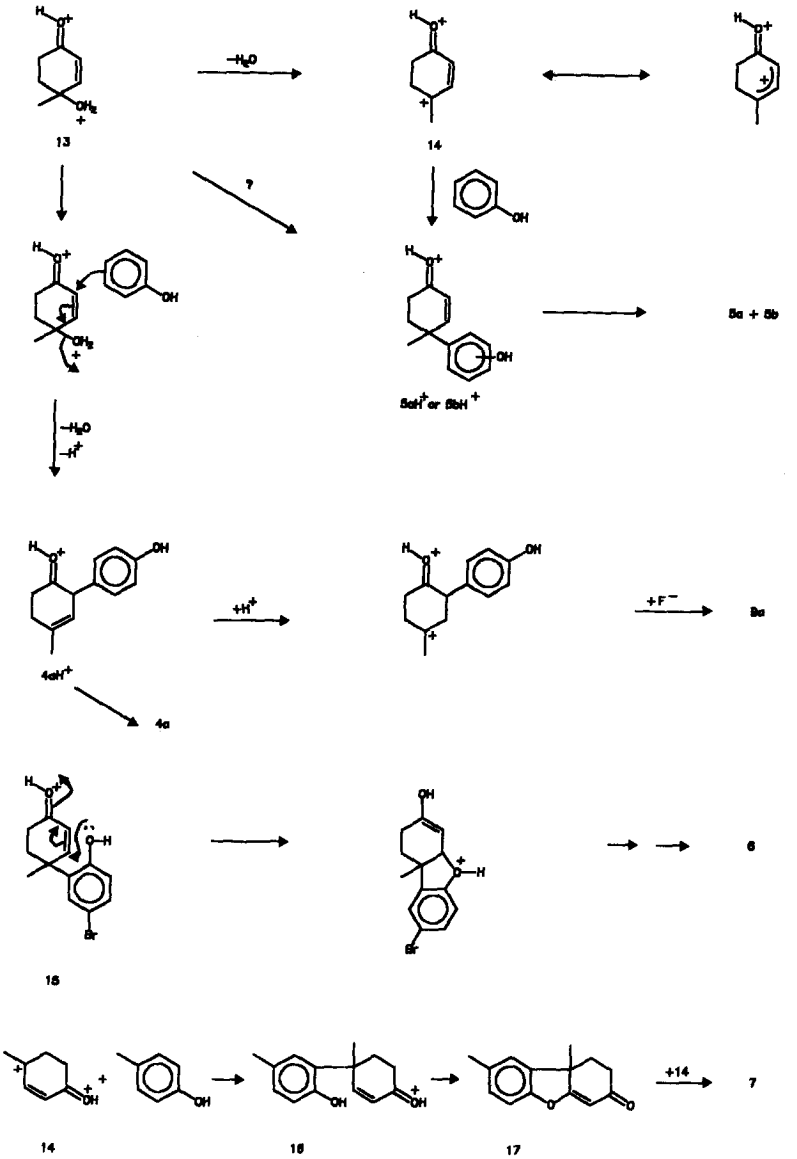


FIGURE 2

aromatic substitution more regioselective.

Formation of the products proceeds by electrophilic substitution on the aromatics with ions **13** and **14**, resulting from protonation of ketone **2** and subsequent dehydration, respectively (Figure 2) :

With phenol **3a** formation of ketones **4a** and **9a** from ion **13** and of ketones **5** (**a** or **b**) from ion **14** seems reasonable, the reverse processes (**5** from **13** and **4a** and **9a** from **14**) are less favorable.

With the less reactive phenol **3b** the products were ketone **6** at -20°C and ketones **6** and **7** at 0°C. At 0°C, assuming the intermediate formation of paracresol from ketone **2** (dehydration and deprotonation of ion **14** being favored by higher temperature) reaction with ion **14** would give initially protonated phenol **16** and finally ketone **17**. This product could further react with ion **14** to yield ketone **7**, the aromatic ring being more activated than in ketone **6**.

One thing is noteworthy. Compound **5a** obtained from phenol **3a** did not cyclize to the furan ring system whereas the *para*bromoderivative did yield ketone **6**. This apparent discrepancy should be due ether to the higher basicity of the aromatic ring in ion $\mathbf{5aH}^+$ whose protonation disfavors the formation of the furan ring or to a reversible cyclization.

The reported one-step synthesis of hexahydrodibenzofuran derivatives constitutes a novel efficient route for building such products. We are now exploring the potentialities offered in organic synthesis by this new reaction to prepare analogues of natural products.

EXPERIMENTAL

Melting points were determined on a Tottoli Büchi 510 melting point apparatus and uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker WP 200 SY. Chemical shifts were reported in ppm downfield relative to tetramethylsilane (Me_4Si) as standard. Low resolution mass spectra were obtained on a Kratos MS 25 spectrometer.

High resolution mass spectra were performed by the "Service Central d'Analyse du CNRS de Lyon" (France). Microanalyses were carried out by the CNRS Central facilities in Lyon, the purity of the compounds was estimated to be ± 0.3 %. Monitoring of reactions and control of purity were performed on silica gel plates (Kieselgel 60 F_{254}, 0.2 mm) or with a Waters HPLC (column Lichrosorb Si 60-5 m, 250 x 4.6 mm). Separations and purifications were carried out by column chromatography on SiO_2 (Merck Kieselgel 60 (0.063-0.2 mm)), by medium pressure chromatography on SiO_2 (Merck Kieselgel 60 Type H) with a Jobin Yvon Chromatospac Prep 10 apparatus or by preparative TLC using plates coated with silica gel (Merck 60 F_{254}, 1 mm).

Reaction of cyclohexenone 2 with phenol 3a

To HF (15 ml) at -35°C, were added successively phenol **3a** (1.13g-12 mmols) then

cyclohexenone **2** (500mg-4 mmols). After a reaction time of 1.5 mn and usual work-up, the products were isolated by column chromatography over SiO_2 (100g)(eluent : hexane/ethylacetate, 75/25; v/v).

- *Ketone **4a** (32mg-4%)*

^1H NMR ($CDCl_3$) : 1.87 (3H, s, $-CH_3$), 3.95 (1H, sl, H-2), 5.50 (1H, sl, H-3), 6.17 (1H, sl, -OH), 6.76 (2H, d, J = 8 Hz, H aromatics *ortho*), 7.14 (2H, d, J = 8 Hz, H aromatics *meta*).

HRMS :($C_{13}H_{14}O_2$) : Calculated : 202.09938; Found : 202.09880

MS : m.z = 202(23), 200(100), 199(22), 171(11), 160(39), 159(47), 145(45).

- *A mixture of ketones **5a** and **5b** (203mg-25%)*

^1H NMR (CD_3COCD_3) : 1.50 (3H, s, $-CH_3$), 6.00 (1H, d, J = 10 Hz, H-2), 6.83 and 7.23 (2H each, d, J = 8 Hz, H aromatics in **5b**), 6.99 (1H, d, J = 10 Hz, H-3), 6.75- 7.25 (4H, complex massif, H aromatics in **5a**), 8.45 and 8.55 (1H, 2 sl , -OH).

HRMS : ($C_{13}H_{14}O_2$) : Calculated : 202.09938; Found :202.09840

MS : m/z = 202(90), 187(100), 174(51), 160(40), 159(69), 145(80), 131(54).

- *Ketone **9a** (44mg-5%)*

^1H NMR ($CDCl_3$) : 1.49 (3H, d, J = 20 Hz, $-CH_3$), 2.89 (td, $J_1 = J_2 = 14$ Hz, $J_3 = 6$Hz, H-6 axial), 3.99 (1H, dd, $J_1 = 13.5$ Hz, $J_2 = 5.5$ Hz, H-2 axial), 6.20 (1H, sl, -OH), 6.74 (2H, d, J = 8 Hz, H aromatics *ortho*), 6.94 (2H, d, J = 8 Hz, H aromatics *meta*).

HRMS : ($C_{13}H_{15}O_2F$) : Calculated : 222.1; Found :222.10610

MS : m/z = 222(74), 194(7), 165(59), 159(34), 147(100), 133(54), 120(27), 107(39).

*Reaction of cyclohexenone **2** with phenol **3b***

To HF (40 ml) at -20°C, were added phenol **3b** (6.9g-40mmoles) then cyclohexenone **2** (1g-8 mmols). After a reaction time of 30 mn and usual work up, the products were isolated by column chromatography over SiO_2 (200g) (eluant : hexane/ethylacetate, 60/40; v/v).

- *Ketone **6** (889mg-40%)*

IR (CH_2Cl_2) : 1720 cm^{-1}; ^1H NMR ($CDCl_3$) : 1.49 (3H, s, $-CH_3$), 2.69 (1H, dd, $J_1 = 17$ Hz, $J_2 = 3$ Hz, H-4), 2.87 (1H, dd, $J_1 = 17$ Hz, $J_2 = 3$ Hz, H-4), 4.77 (1H, t, J = 3 Hz, H-4a), 6.68 (1H, d, J = 8 Hz, H-6), 7.28 (1H, dd, $J_1 = 8$ Hz, $J_2 = 2$ Hz, H-7), 7.40 (1H, d, J = 2 Hz, H-9); MS : m/z = 282(98), 280(100), 225(60), 223(59), 146(98), 115(61).

Anal. calcd. for $C_{13}H_{13}O_2Br$: C, 55.53; H, 4.66; Found : C, 55.40; H, 4.68.

*Reaction of cyclohexenone **2** in HF*

To HF (20 ml) at 0°C, was added cyclohexenone **2** (500mg-4mmols). After a reaction time of 30 mn and usual work up, the product was isolated by column chromatography over SiO_2 (150g) (eluent : hexane/ethylacetate 60/40; v/v).

- *Ketone **7** (183mg-43%)*

IR (CH_2Cl_2) : 1710, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) : 1.49 (3H, s, $-CH_3$), 2.28 (3H, s, $-CH_3$), 2.75 (1H, dd, $J_1 = 20$ Hz, $J_2 = 3$ Hz, H-4), 2.94 (1H, dd, $J_1 = 20$ Hz, $J_2 = 3$ Hz), 4.76 (1H, t, J = 3 Hz, H-4a), 6.02 and 7.06 (1H each, 2d, J = 10 Hz, olefinic protons), 6.80 and 6.85 (1H each, s, aromatic protons); MS : m/z = 324(100), 309(15), 281(17), 267(31),

251(34). Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.54; H, 7.45; Found : C, 77.6; H, 7.50.

Treatment of ketone 6 with BF_3-etherate

To a solution of ketone **6** (71mg-0.25 mmol) in anhydrous benzene (10ml), was added acetic anhydride (42mg-1.5 eq.) and BF_3-Et_2O (0.4 ml). After two weeks, the reaction mixture was hydrolyzed and worked up by the usual manner. The crude material chromatographied on preparative plates with mixture Hexane/ AcOEt (90/10, v/v) gave the compound **8** (26mg-32%). IR (CH_2Cl_2) : 1660, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) : 1.61 (3H, s, $-CH_3$), 2.22 (3H, s, $-OCOCH_3$), 6.02 and 6.93 (1H each, 2d, J = 10 Hz, olefinic protons), 6.85 (1H, d, J = 8 Hz, aromatic proton *ortho*), 7.42 (1H, dd, J_1 = 8 Hz, J_2 = 2 Hz, aromatic proton *meta*, 7.50 (1H, d, J = 2 Hz, aromatic proton *meta*); MS : m/z = 324(14), 322(14), 282(61), 280(61), 225(46), 187(55), 146(71), 115(100). Anal. Calcd. for $C_{15}H_{10}O_3Br$: C, 55.74, H, 4.67; Found : C, 55.54, H, 4.56.

Action of KOH-MeOH on the compound 8

To a solution of compound **8** (25mg-0.08 mmol) in MeOH (4 ml), was added a 10% solution of KOH (2ml). The reaction mixture was stirred for 15 hours. After evaporation of MeOH, the crude material was worked up by the usual manner and gave the compound **6** (19mg-85%).

ACKNOWLEDGMENTS

The authors thank the CNRS for financial support.

REFERENCES

1. a) Casy, A.F., *Prog. Med. Chem.*, 1970, **7**, Part 2, 229-284.
   b) Casy, A.F., *Prog. Drug. Res.*, 1978, **22**, 149-227.
2. Casy, A.F., Parfitt, R.T., *"Opioid analgesics, Chemistry and Receptors"*, Plenum Press,1986.
3. Levy, J., Sigaut, F., *Tetrahedron Lett.*, 1983, **24**, 4987-4988.
4. Bird, C.W., Chauhan, Y.P.S., Turton, D.R., *Tetrahedron*, 1981, **37**, 1277 -1280.
5. Morlock, E.B., Albright, J.D., Goldman, L., (American Cyanamid Co.), U.S. Pat., 3646060 (1972).
6. Matharu, S.S., Rowlands, D.A., Taylor, J.B., Westwood, R., *J. Med. Chem.*, 1977, **20**, 197.
7. a) Labidalle, S., Zhang, Y.M., Reynet, A., Moskowitz, H., Vierfond, J.M., Miocque, M., *Tetrahedron*, 1988, **44**, 1171-1186;
   b) Labidalle, S., Zhang, Y.M., Thal, C., Miocque, M., Degryse, M., Fortin, M., Delevallée, F., *Eur. J. Med. Chem.*, 1989, **24**, 385-390.

8. Scott, A.I., *Quart. Rev.* (London), 1965, **XIX**, 1.
9. Chen, C.L., Connors, W.J., Shinker, W.M., *J. Org. Chem.*, 1969, **34**, 2966-2971.
10. Anderson, R.A., Dalgleish, D.T., Nonhebel, D.C., Pauson, P.L., *J. Chem. Research* (M), 1977, 265-285.
11. Ajao, J.F., Bird, C.W., Chauhan, Y.P., *Tetrahedron*, 1985, **41**, 1367-1372.
12. Berrier, C., Gaillard, E., Jacquesy, J.C., Jouannetaud, M.P., Kigabo, F. *Bull. Soc. Chim. Fr.*,(1991) in press.
13. Corey, E.J. and Boaz, N.W, *Tetrahedron Lett.*, 1985, **26**, 49, 6015-6018.
14. Jacquesy, J.C., Jouannetaud, M.P., *Bull. Soc. Chim. Fr.*, 1980, II, 265-274, 295-303, 304-308.