Pergamon

Tetrahedron Letters, Vol. 38, No. 26, pp. 4635-4638, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00954-4

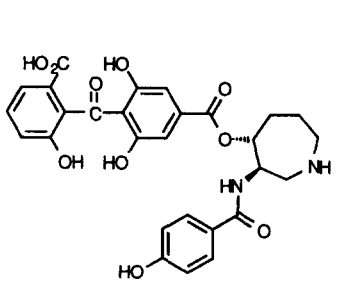
A Divergent Route to Substituted Benzophenones Based on Cationic η^6-(Arene)iron Intermediates.

J. Peter Nilsson and Carl-Magnus Andersson*

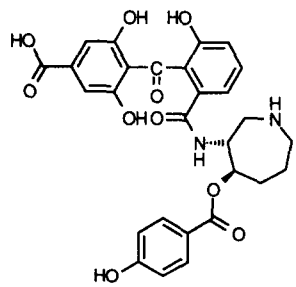
Organic Chemistry 1, Department of Chemistry, Lund University, P. O. Box 124, S-221 00 Lund, SWEDEN

Abstract: A route to *ortho*-substituted benzophenones, based on a novel, multistep construction of a cationic xanthone iron complex followed by nucleophilic ring-opening and a new, one-pot cyanide addition-decomplexation procedure, is described. © 1997 Elsevier Science Ltd.

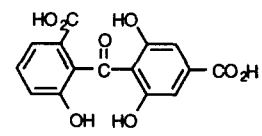
In 1993, Kulanthaivel and co-workers reported[1] the isolation and characterisation of the novel and exceptionally potent protein kinase C inhibitor balanol (**1**), an isomer to the previously known antifungal antibiotic ophiocordin (**2**)[2]. Over the last few years balanol has attracted considerable attention as a new lead for developing clinically useful protein kinase inhibitors.[3] The chemical synthesis of balanol[4,5,6,7] and analogues[8,9] has been achieved by several groups, allowing initial structure-activity studies addressing inhibitory potency as well as kinase selectivity. However, presumably owing to the lack of efficient synthetic methodology, only a few examples of structural variations in the benzophenone moiety (**3**) have appeared.[8,10] Interestingly, such modifications have recently been reported to result in changes in kinase selectivity.[11]



1



2

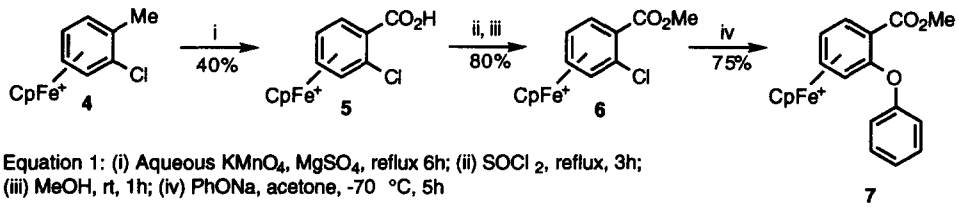


3

We were encouraged to further probe the effects of structural modifications on inhibition selectivity, and required a divergent approach to substituted benzophenones. A strategy involving transition metal arene complexes seemed attractive, based on the anticipation that the well documented nucleophilic substitution and addition reactions facilitated by π-

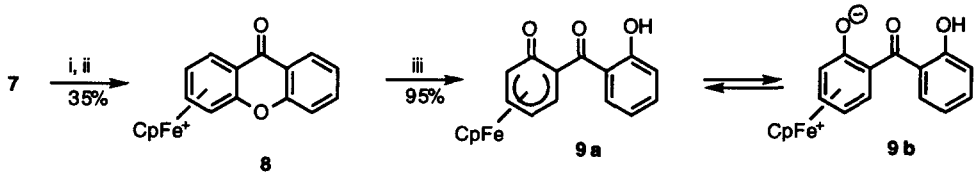
complexation[12] of an arene would allow for structural modifications of advanced intermediates. In particular, the pioneering work of Sutherland *et. al.* on nucleophilic ring-opening reactions of η^6-xanthone-η^5-cyclopentadienyliron hexafluorophosphate[13] and cyanide addition reactions[14,15] implied that organoiron methodology might provide a divergent approach to unsymmetrically *o,o'*-disubstituted benzophenones related to **3**. However, such an approach required development of a new, flexible route to xanthone complexes and successful regiocontrol in nucleophilic substitution and addition reactions for which literature precedence was lacking. Here, we wish to communicate our initial progress towards preparation and ring-opening reactions of the parent system.

The most flexible preparative route should accomodate substituents in the uncoordinated aromatic ring of the xanthone π-complex. We chose to attempt construction of such a complex starting from the known η^6-*o*-chlorotoluene-η^5-cyclopentadienyliron hexafluorophosphate (**4**).[16] This material was oxidised, using aqueous potassium permanganate,[17] to the benzoic acid complex (**5**)[18] which could be converted into the methyl ester (**6**) via reflux in thionyl chloride followed by reaction with excess methanol.



Equation 1: (i) Aqueous $KMnO_4$, $MgSO_4$, reflux 6h; (ii) $SOCl_2$, reflux, 3h; (iii) MeOH, rt, 1h; (iv) PhONa, acetone, -70 °C, 5h

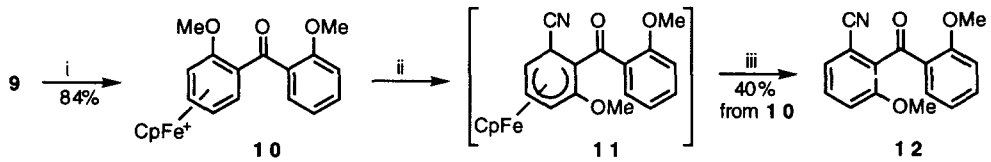
The methyl *o*-chlorobenzoate complex **6** reacted smoothly and regioselectively with sodium phenoxide in acetone to provide the diaryl ether **7**. This critical regioselectivity highlights the powerful activation for nucleophilic aromatic substitution induced by the cyclopentadienyl iron moiety. Hydrolysis of the methyl ester with lithium hydroxide in methanol, followed by ring closure in warm polyphosphoric acid secured the xanthone complex **8**. To our knowledge, this is the first example of a Friedel-Crafts reaction involving an arene iron complex.



Equation 2: (i) LiOH, MeOH/H_2O, rt, 16h; (ii) PPA, 100 °C, 3h; (iii) NaOH (10 eq), MeOH/H_2O, rt, 3h

Complex **8** has previously been reported to undergo regioselective nucleophilic ring-opening upon reaction with amines under mild conditions.[13] With harder nucleophiles, alternative reaction pathways such as attack at the carbonyl group or addition to the 2- or 4-positions of the complexed ring might be apprehended. Our initial efforts employing sodium methoxide

in methanol did not lead to the desired *o*-methoxy-*o'*-hydroxy benzophenone complex. However, treatment of **8** with an excess of sodium hydroxide in methanol, followed by careful acidification, cleanly delivered the zwitterionic complex **9** as a red solid, which could be purified by silica gel chromatography. Upon NMR analysis, the material gave spectral characteristics consistent[19] with the pentahapto oxocyclohexadienyl structure (**9a**) rather than the corresponding phenoxide (**9b**). Further spectral characterisation using solvent mixtures corroborated the assignment of this tautomer.[20] Compound **9** and substituted analogues could prove useful for the preparation of unsymmetrically *o,o'*-disubstituted benzophenones, if the metal conveys sufficiently different properties to the two phenolic groups. Preliminary experiments have indicated that protonation of **9a** provides the corresponding acid as a yellow solid, and that the hydroxy group of the uncoordinated arene moiety appears more reactive towards alkylating agents under basic conditions.



Equation 3: (i) MeI (30 eq), KO^{t}Bu (5 eq), acetone/CH_2Cl_2, rt, 48h; (ii) Bu_4NCN, DMF, 48h; (iii) DDQ, DMF, 1h

Compound **9** reacted only sluggishly with an excess of iodomethane in the presence of potassium *tert*-butoxide. Complete conversion into the dimethoxy derivative **10** required two days at room temperature. Work-up using aqueous ammonium hexafluorophosphate returned a yellow solid which was purified by recrystallisation. Whereas the literature procedure[14] for cyanide addition to xanthone complex **8** could be readily reproduced, the hexafluorophosphate of **10** failed to provide any isolable cyanide addition product when treated with excess sodium cyanide in wet dimethyl formamide. However, NMR spectra obtained for a reaction mixture containing **10** and, the more soluble, tetrabutylammonium cyanide in dimethyl formamide indicated that **11** was indeed formed in what appeared to be a readily reversible equilibrium. Encouragingly, oxidative decomplexation in situ, effected with 2,3-dichloro-5,6-dicyanoquinone,[21] gave the appropriately functionalised benzophenone **12** in modest isolated yield.[22]

We conclude that organoiron methodology shows promising features with respect to divergent preparation of substituted benzophenones relevant as building blocks for balanol and ophiocordin analogue synthesis.

Acknowledgments.
We thank the Swedish Natural Science Research Council and Crafoordska Stiftelsen for financial support.

References and Notes.

(1) Kulanthaivel, P.; Hallock, Y. F.; Boros, C; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 6452.
(2) König, W. A.; Sinnwell, V.; Witt S.; Kneifel, H.*Chem. Ber.* **1980**, *113*, 2221.
(3) For a recent review on protein kinase C inhibitors, see: Hu, H. *Drug Discovery Today*, **1996**, *1*, 438.
(4) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith S. H.; Hu, H. *J. Org. Chem.* **1994**, *59*, 5147.
(5) Nicolaou, K. C.; Bunnage M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402.
(6) Adams, C. P. ; Fairway, S. M.; Hardy, C. J.; Hibbs, D. E.; Hursthouse, M. B.; Morley, A. D.; Sharp, B. W.; Vicker, N.; Warner, I. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2355.
(7) Tanner, D.; Almario, A.; Högberg, T. *Tetrahedron* **1995**, *51*, 6061.
(8) Nicolaou, K. C.; Koide, K.; Bunnage, M. E. *Chem. Eur. J.* **1995**, *1*, 454.
(9) Jagdmann Jr., G. E.; Defauw, J. M.; Lampe, J. W.; Darges, J. W.; Kalter, K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1759, and references cited therein.
(10) Heerding, J. M., Lampe, J. W.; Darges, J. W.; Stamper, M. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1839.
(11) Koide, K.; Bunnage, M. E.; Paloma, L. G.; Kanter, J. R.; Taylor, S. S.; Brunton, L. L.; Nicolaou, K. C. *Chem. Biol.* **1995**, *2*, 601.
(12) Semmelhack, M. F. in: *Comprehensive Organic Synthesis* (Trost, B. M. Ed.) Pergamon, vol 4, chapter 2.4.
(13) Lee, C. C.; Gill, U. S.; Sutherland, R. G. *J. Organomet. Chem.* **1984**, *267*, 157.
(14) Sutherland, R. G.; Chowdhury, R. L.; Piorko, A.; Lee, C. C. *J. Organomet. Chem.* **1987**, *319*, 379.
(15) Zhang, C. H.; Chowdhury, R. L.; Piorko, A.; Lee, C. C.; Sutherland, R. G. *J. Organomet. Chem.* **1988**, *346*, 67.
(16) Khand, I. U.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc C.* **1968**, 2261.
(17) Oleinik, I. I.; Litvak,V. V.; Shteingarts, V. D. *Metalloorg. Khim.* **1991**, *4*, 626 (*Organomet. Chem. USSR.* **1991**, *4*, 307).
(18) All new compounds were characterised by NMR, IR and HRMS spectroscopy.
(19) Piórko, A.; Zhang, C. H.; Reid, R. S.; Lee, C. C.; Sutherland, R. G. *J. Organomet. Chem.* **1990**, *395*, 293.
(20) A paper discussing the structure of oxocyclohexadienyl iron complexes appeared during the preparation of this manuscript; Djakovitch, L.; Moulines, F.; Astruc, D. *New J. Chem.* **1996**, *20*, 1071.
(21) Sutherland, R. G.; Chowdhury, R. L.; Piorko, A.; Lee, C. C. *J. Org. Chem.* **1987**, *52*, 4618.
(22) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.83 (1H, dd), 7.53 (1H, m), 7.45 (1H, t), 7.30 (1H, dd), 7.15 (1H, dd), 7.06 (1H, dt), 6.92 (1H, dd), 3.72 (3H, s), 3.61 (3H, s). Mp: 105-6 °C. HRMS (EI, 70 eV): m/z 267 (M^+, 40%), calcd for $C_{16}H_{13}NO_3$: 267.0895, found: 267.0898.

(*Received in UK* 13 *February* 1997; *accepted* 15 *May* 1997)