tainty whether species **8** or **11** are involved in either or both of the Rh(II) and Pd(II) reactions [or whether the metal remains at the 2-position (e.g., **8**)[7] or actually migrates to the distal carbon (e.g., **10**/**11**) of the alkyne], at the very least these reactions do not both proceed via nonmetal-mediated rearrangements (e.g., of the cyclopropene **9**[5,8a,b]). We hypothesize that the strain in **9**[9] is a key factor in the success of these polycyclizations; **9** either is never formed or is readily reconverted[8b–e] into species like **8**, **10**, and **11**. An attractive intermediate by which to rationalize formation of furan **7** is the rhodacycle **12**.[10]

Reactions of the α-diazo ketones **13**[6b] were examined next using a variety of metal catalysts (Table I). Once again the product array was quite dependent upon the specific catalyst, but products **15**–**20** can be simplistically viewed as arising by pathways diverging from the vinylogous α-keto carbene **14**.[11] To rule out the possibility that any of the non-cyclopropanes **16**–**21** arose via secondary, metal-catalyzed,[12a–c] or thermal[12d] isomerizations of the strained vinylcyclopropane, control experiments with pure **15a** and each of the catalysts under conditions listed in the table (both in the absence and presence of added ethyl diazoacetate) gave no indication of consumption of **15a**.

The question of the degree and nature of association of the metal atom with the alkyne carbons in these reactions is a mechanistically significant issue, and additional studies to probe this point are in progress.

Acknowledgment. This investigation was supported by Grant GM-38854 awarded by the DHHS and by an award from the Alfred P. Sloan Foundation.

Supplementary Material Available: Spectral and characterization data for compounds **5**–**7**, **13a**/**b**, **15a**/**b**, *E*- and *Z*-**16a**/**b**, **17a**–**19a**, **20a**/**b**, and **21a**/**b** (5 pages). Ordering information is given on any current masthead page.

---

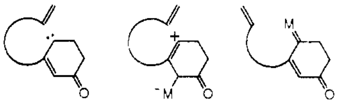
[7] (a) The Doyle mechanism[4e,7b] for Rh(II)-catalyzed diazocarbonyl/olefin cyclopropanation involving an electrophilic attack of the carbene carbon on the alkene with no prior complexation of the olefin and metal has a vinylogue which may be be envisioned to proceed via species 8. (b) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.

[8] (a) Mykytka, J. P.; Jones, W. M. *J. Am. Chem. Soc.* **1975**, *97*, 5933. (b) Binger, P.; Buch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (c) Cho, S. K.; Liebeskind, L. *J. Org. Chem.* **1987**, *52*, 2631. (d) Binger, P.; Müller, P.; Benn, R.; Mynott, R. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 610. (e) Müller, P.; Pautex, N.; Doyle, M. P.; Bagheri, V., manuscript submitted for publication.

[9] Billups, W. E.; Huley, M. M.; Lee, G. A. *Chem. Rev.* **1989**, *89*, 1147.

[10] Cf.: (a) Doyle, M. P.; van Leusen, D. *J. Org. Chem.* **1982**, *47*, 5326. (b) Semmelhack, M. F.; Tamura, R.; Schattner, W.; Springer, J. *J. Am. Chem. Soc.* **1984**, *106*, 5363. (c) McCallum, A. S.; Kunng, F. A.; Gilbertson, S. R.; Wulff, W. D. *Organometallics* **1988**, *7*, 2346.

[11] Likewise, the products **21** (along with several polycyclic cyclohexenones from the $Rh_2(OAc)_4$-catalyzed decomposition of **13**—submitted manuscript) could arise via the free carbene i (an isomer of **14**) or the metal complexes ii and/or iii.



i *ii* *iii*

[12] (a) Gassman, P. G.; Williams, F. *J. Am. Chem. Soc.* **1970**, *92*, 7631. (b) Masamune, S.; Yamaguchi, H.; Westberg, H. H.; Sakai, M. *J. Am. Chem. Soc.* **1971**, *93*, 4610. (c) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020. (d) Piers, E.; Maxwell, A. R. *Can. J. Chem.* **1984**, *62*, 2392.

A Complex Induced Proximity Effect in the Anionic Fries Rearrangement of *o*-Iodophenyl Benzoates: Synthesis of Dihydro-*O*-methylsterigmatocystin and Other Xanthones

Stephen Horne

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

Russell Rodrigo*

Department of Chemistry, Wilfrid Laurier University, Waterloo, Ontario, Canada N2L 3C5

Received May 14, 1990

Summary: The success of an anionic Fries rearrangement, used to synthesise dihydro-*O*-methylsterigmatocystin and other xanthones, is dependent on the presence of a remote methoxyl substituent.

The anionic Fries rearrangement of *o*-bromophenyl esters initiated by lithium–bromine exchange proceeds in moderate yield to the ortho rearranged product only, by an intramolecular pathway.[1] Our current concern with the development of versatile synthetic routes to xanthones in general and the *Aspergillus* mycotoxins in particular[2] led us to reexamine this reaction in spite of the very poor yield of *o*-hydroxybenzophenone (7%) obtained[1] in the rearrangement of *o*-bromophenyl benzoate.

Eighteen benzoates (Table I) prepared from the *o*-iodophenols[2] (or *o*-bromophenols) were rearranged by treatment with *n*-butyllithium or *sec*-butyllithium (entries 11 and 16) at −100 °C followed by warming to −70 °C. After 2 h at that temperature the reaction mixtures were quenched with aqueous ammonium chloride and the products were isolated.

The intramolecular nature[3] of the reaction makes it obligatory that a benzoxetane intermediate is formed by 4-*exo-trig* attack of the lithiated carbon atom at the ester carbonyl group. The experimental results compiled in Table I suggest that a juxtaposition of the reacting centers suitable[4] for such a nucleophilic addition is favored by methoxyl substitution at specific sites, in particular by the presence of a methoxyl group at the R_1 position ortho to the ester carbonyl. The dramatic divergence observed in

---

[1] Miller, J. A. *J. Org. Chem.* **1987**, *52*, 322–3. Hellwinkel, D.; Lämmerzahl, F.; Hofmann, G. *Chem. Ber.* **1983**, *116*, 3375–3405.

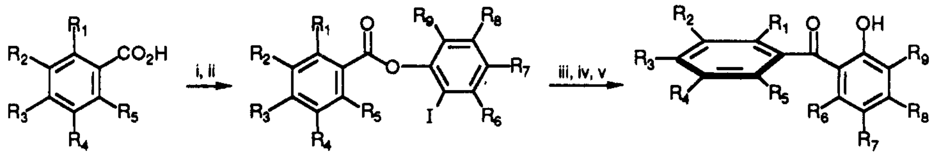
[2] Horne, S.; Weeratunga, G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1990**, 39–41.

[3] We have confirmed this by a "crossover" experiment. An equimolar mixture of benzoates (entries 2 and 7) rearranged under the standard conditions provided only the products of the intramolecular reaction pathway (i.e. the benzophenones in entries 2 and 7). No trace of a crossover product was detected.

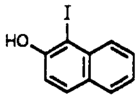
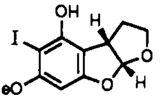
[4] Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153–61.

0022-3263/90/1955-4520$02.50/0 © 1990 American Chemical Society

Table I

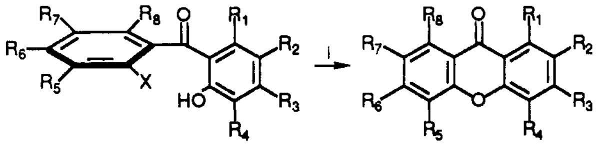


(i) $(COCl)_2$, cat. DMF, THF; (ii) iodophenol, pyridine; (iii) n-BuLi, −100 °C, THF/ether/hexanes; (iv) −70 °C, 2 h; (v) saturated aqueous NH_4Cl

entry	benzoic acid	o-iodophenol[a]	isolated yield, % benzoate ester	isolated yield, % o-hydroxybenzophenone
1	$R_1 = R_2 = R_3 = R_4 = R_5 = H$	$R_6 = R_7 = R_8 = R_9 = H$	98	<10
2	$R_1 = OMe, R_2 = R_3 = R_4 = R_5 = H$	$R_6 = R_7 = R_8 = R_9 = H$	91	93
3	$R_1 = R_5 = OMe, R_2 = R_3 = R_4 = H$	$R_6 = R_7 = R_8 = R_9 = H$	64	100
4	$R_1 = R_2 = OMe, R_3 = R_4 = R_5 = H$	$R_6 = R_7 = R_8 = R_9 = H$	92	100
5	$R_3 = OMe, R_1 = R_2 = R_4 = R_5 = H$	$R_6 = R_7 = R_8 = R_9 = H$	92	<18
6	$R_1 = OMe, R_2 = R_4 = Cl, R_5 = H$	$R_6 = R_7 = R_8 = R_9 = H$	92	68
7	$R_1 = R_2 = R_3 = OMe, R_4 = R_5 = H$		90	82
8	$R_1 = OMe, R_2 = R_3 = R_4 = R_5 = H$	$R_6 = OMe, R_7 = R_8 = R_9 = H$	83	81
9	$R_1 = R_2 = R_3 = R_4 = R_5 = H$	$R_6 = OMe, R_7 = R_8 = R_9 = H$	95	51
10	$R_1 = R_2 = R_3 = R_4 = R_5 = H$	$R_8 = OMe, R_6 = R_7 = R_9 = H$	91	<16
11	$R_1 = R_2 = R_3 = R_4 = R_5 = H$	$R_6 = R_8 = OMe, R_7 = R_9 = H$	85	47
12	$R_1 = R_2 = R_3 = R_4 = R_5 = H$	$R_6 = CH_3, R_9 = OMe, R_7 = R_8 = H$	75	55
13	$R_1 = R_3 = R_4 = OMe, R_2 = R_5 = H$	$R_6 = CH_3, R_9 = OMe, R_7 = R_8 = H$	70	40
14	$R_1 = R_5 = OMe, R_2 = R_3 = R_4 = H$	$R_6 = OMe, R_7 = R_8 = R_9 = H$	68	9
15	$R_1 = OMe, R_5 = F, R_2 = R_3 = R_4 = H$	$R_6 = OMe, R_7 = R_8 = R_9 = H$	91	88
16	$R_1 = R_3 = OMe, R_5 = F, R_2 = R_4 = H$	$R_7 = R_8 = OMe, R_6 = R_9 = H$	76	89
17	$R_1 = R_5 = OMe, R_2 = R_3 = R_4 = H$		37	0
18	$R_1 = OMe, R_5 = F, R_2 = R_3 = R_4 = H$		95	63

[a] Bromophenol used in entries 11 and 16; sec-BuLi at −100 °C for 1 h, then −70 °C for 2 h.

Table II



(i) KOH, MeOH, Δ

entry	o-hydroxybenzophenone	X	xanthone isolated yield, %
1	$R_5 = OMe, R_1 = R_2 = R_3 = R_4 = R_6 = R_7 = R_8 = H$	OMe	97
2	$R_8 = OMe, R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H$	OMe	83
3	$R_5 = R_6 = OMe, R_1 + R_2 =$ −CH═CH−CH═CH− $R_3 = R_4 = R_7 = R_8 = H$	OMe	94
4	$R_5 = R_7 = Cl, R_1 = R_2 = R_3 = R_4 = R_6 = R_8 = H$	OMe	95
5	$R_1 = CH_3, R_4 = R_6 = R_7 = OMe, R_2 = R_3 = R_5 = R_8 = H$	OMe	100
6	$R_1 = R_8 = OMe, R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H$	F	100
7	$R_2 = R_3 = R_6 = R_8 = OMe, R_1 = R_4 = R_5 = R_7 = H$	F	100

the fate of the lithiated species when entries 1 and 2 are compared seems to point to the operation of a complex induced proximity effect[5] (CIPE) involving the R_1 methoxyl substituent. All highly successful examples (entries 2, 3, 4, 7, 8, 15, and 16) possess this feature, and the success of the rearrangement cannot be attributed to mesomeric effects of the substituents because a methoxyl group para to the ester carbonyl (entry 5, R_3 = OMe) proves to be of little value. An attempt is made in Scheme I to give form to such a complex and to follow its transformation to the benzoxetane and subsequent collapse to the isolated product. The dimeric structure suggested is inspired by those recently elucidated for (2-methoxyphenyl)[6] and (2,6-dimethoxyphenyl)lithium.[7] This postulate[8] accounts for the failure of the rearrangement in the absence of a methoxyl group at R_1. In such instances (entries 1, 5, and 10) the formation of deiodinated materials mixed with products incorporating a butyl group and some polymer, the latter presumably resulting from benzyne formation, betray the occurrence of lithium–iodine exchange and the intervention of competing intermolecular pathways. When three methoxy substituents are present at R_1, R_5, and R_6 (entries 14 and 17), steric interaction of the R_5 and R_6 substituents retards the formation of the complex and severely diminishes the yield. The recovery of deiodinated starting materials in both cases again attests to the success of lithium–iodine exchange. When the offending methoxy substituent (at R_5) is replaced by fluorine (compare entry 14 with 15; 17 with 18) the rearrangement proceeds satisfactorily under the identical conditions. The modest success achieved in entries 9 and 11 is attributed to the

---

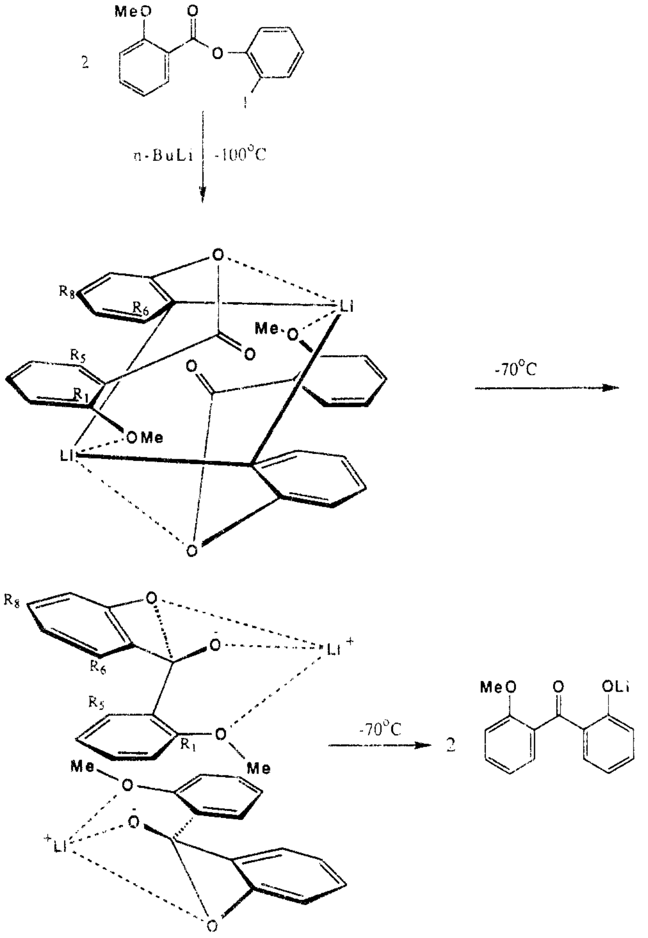
[5] Beak, P.; Meyers, A. I. Acc. Chem. Res. **1986**, 19, 356–363.

[6] Harder, S.; Boersma, J.; Brandsma, L.; van Mier, G. P. M.; Kanters, J. A. J. Organomet. Chem. **1989**, 364, 1–15.

[7] Harder, S.; Boersma, J.; Brandsma, L.; van Heteren, A.; Kanters, J. A.; Bauer, W.; Schleyer, P. v. R. J. Am. Chem. Soc. **1988**, 110, 7802–6.

[8] One referee has suggested that each lithium atom may be coordinated to the carbonyl oxygen instead of the ester oxygen as shown in Scheme I. This will better assist the intramolecular nucleophilic addition that leads to the benzoxetane.

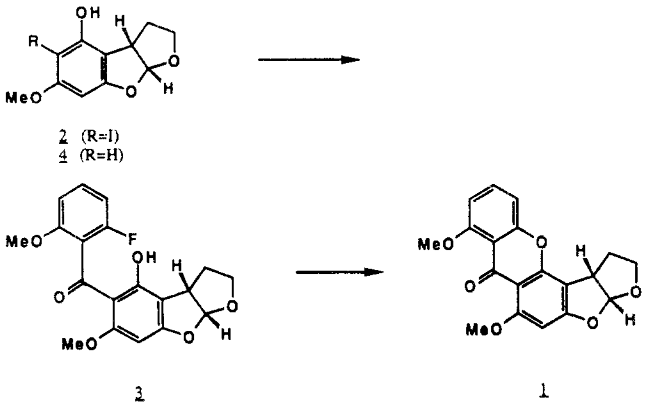
Scheme I



formation of a slightly different complex. This time, complexation with the R_6 methoxy and ester oxygen atoms of the "anionic" benzene ring, like that found[7] in (2,6-dimethoxyphenyl)lithium, might anchor this ring firmly enough to permit capture of the carbonyl group by the anionic center in suitable conformations of the freely rotating benzoyl moiety. Again, byproducts of these reactions are deiodinated and show butyl incorporation. Even this moderate success is lost when the methoxyl group is moved to the para position (R_8 = OMe, entry 10). The results in entries 3, 4, 10, and 11 taken together imply that the degree of electron excess in the migrating phenyl ring does not influence the outcome of the rearrangement. Aromatic chloro and methyl substituents are also found to be reasonably compatible with the conditions of the reaction (entries 6, 12, and 13), but the methylated examples were the only instances when byproducts still containing aromatic iodide were observed. This might be due to the acidity of the aromatic methyl group; further investigations are in progress.

The versatility of the rearrangement and the ready availability of the starting materials makes it a useful conduit to xanthones. Seven examples of such usage of

Scheme II



the *o*-hydroxybenzophenones are shown in Table II, and the last two[9] are particularly noteworthy for their use of fluoride as the nucleofugal entity. The substitution reaction in these cases is completely regiospecific, cleaner, and faster. The xanthone synthesized in entry 7 has been previously isolated[10] from *Guttiferae* species.

An especially satisfying application, illustrating the tolerance of this three-step sequence to sensitive structural units in the substrate, is provided by the synthesis of dihydro-*O*-methylsterigmatocystin, **1** (Scheme II). The highly sensitive tricyclic iodophenol **2**[2] is converted to its 2-fluoro-6-methoxybenzoate (entry 18, Table I) and rearranged to the benzophenone **3** (60% for the two steps), which is quantitatively converted to the natural mycotoxin[11] with methanolic potassium hydroxide. The only existing synthesis[12] of this compound employs successive Ullman and Friedel–Crafts reactions to prepare it from the furobenzofuran **4** in 16% yield.

Further applications of the rearrangement to synthesize acridones from *N*-phenylbenzamides and isobenzofurans from esters of *o*-iodobenzyl alcohols are under current investigation.[13]

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for support of this work.

Supplementary Material Available: Experimental procedures and data and NMR spectra for compounds in Tables I and II (44 pages). Ordering information is given on any current masthead page.

---

[9] 2-Fluoro-6-methoxybenzoic acid was prepared from the corresponding nitrile (Lancaster Synthesis) in 98% yield (30% aqueous KOH, reflux, 3 h). 2-Fluoro-4,6-dimethoxybenzoic acid was prepared from 3,5-dimethoxyfluorobenzene (Sigma) by successive treatment with *sec*-butyllithium, TMEDA (−78 °C, THF) and $ClCO_2Et$ followed by hydrolysis of the ester with methanolic KOH (62% overall).

[10] Jefferson, A.; Scheinmann, F. *J. Chem. Soc. C* **1966**, 175–178.

[11] Cole, R. J.; Kirksey, J. W.; Schroeder, H. W. *Tetrahedron Lett.* **1970**, 3109–3112.

[12] Rance, M. J.; Roberts, J. C. *Tetrahedron Lett.* **1969**, 277–8.

[13] All compounds prepared in this study had analytical and spectral properties consistent with their structures. Full details will be published elsewhere.