Tetrahedron Letters,Vol.28,No.28,pp 3187-3188,1987
Printed in Great Britain

0040-4039/87 $3.00 + .(
Pergamon Journals Ltd.

THE THIOXANTHONE SYSTEM AS A TEMPLATE IN FREE RADICAL RELAY CHLORINATION OF A STEROID

Ronald Breslow* and Tao Guo
Department of Chemistry
Columbia University
New York, NY 10027

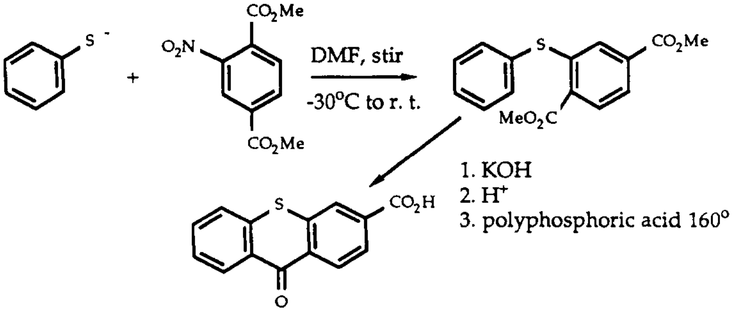
The 3-α-cholestanyl ester of thioxanthone-3-carboxylic acid undergoes selective chlorination of the steroid C-9 carbon by a radical relay mechanism directed by the thioxanthone template.

We have described a process called free radical relay chlorination.[1] A chlorine carrying species such as PhICl• transfers the chlorine to a template that is covalently linked to a substrate. Next the resulting chlorine-template complex delivers the chlorine to a geometrically accessible hydrogen of the substrate. The resulting substrate carbon radical then reacts with $PhICl_2$ to form a C-Cl bond and regenerate PhICl•. Related reactions occur with other chlorinating species, such as SO_2Cl_2.[2]

As templates we originally used iodoaryl derivatives,[1,2] and the PhICl• transferred its chlorine to the template iodine. Subsequently we were able to relay chlorine using the sulfur atom in diaryl sulfide templates[3] or in thiophene templates.[4] Most recently we have found that the nitrogen atom of pyridine derivatives (e.g. in steroid nicotinate esters) can capture a transferred chlorine atom and deliver it to the attached substrate with geometric control.[5]

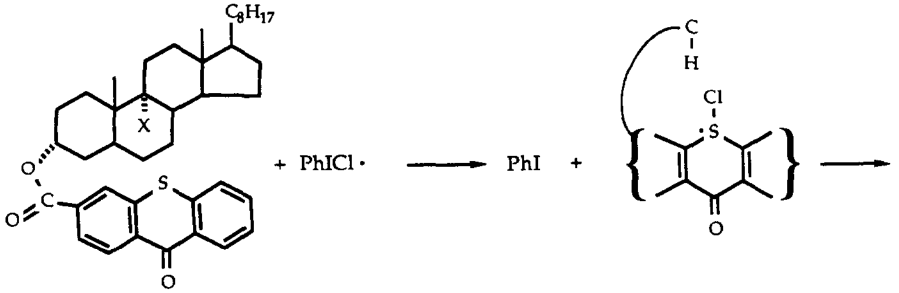
Many of these template systems have disadvantages. For instance, the iodine of iodoaryl templates can be lost,[2] and diaryl sulfides easily oxidize.[3] We now wish to describe an authentic example[6] of the use of a thioxanthone template in such a process. The very stable thioxanthone ring is quantitatively recovered after directing a geometrically controlled steroid chlorination.

Thioxanthone-3-carboxylic acid[7] (I) was prepared by reaction[8] of sodium thiophenoxide with nitroterephthalic acid dimethyl ester, then hydrolysis and cyclization. The yellow crystals had m.p. 302-304° (rept'd.[7] 314-315°) and correct mass and NMR spectra. Mitsunobu reaction with 3β-cholestanol afforded the ester II, m.p 164-166°.

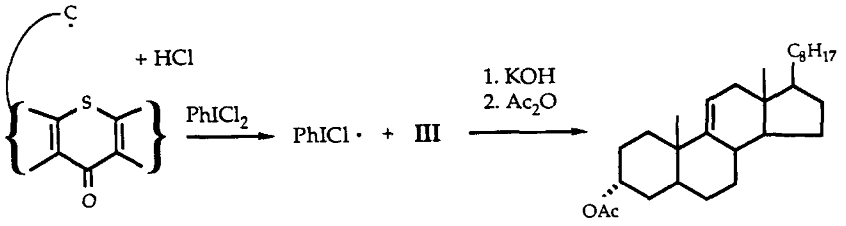


I

Ester II (314mg) was irradiated (Sunlamp) in 33 mL CH_2Cl_2 with 165 mg (1.2 equiv) of freshly recrystallized $PhICl_2$ for 60 min. Hydrolysis of the product esters with KOH/MeOH and acetylation of the neutral fraction afforded recovered I (97% recovery), 20% unreacted steroid, and 80% conversion of the steroid to a product consisting of the 9(11) olefin IV (77%) identical with authentic material[2] and 23% polar impurities. With 3 equiv. of $PhICl_2$ no unreacted steroid was found, and IV was formed in 71% yield. We have found in the past[2] that 9-chlorosteroids form the 9(11) olefin with base; molecular models suggest that a chlorine atom on the sulfur of II should indeed attack the C-9 hydrogen.



II X = H
III X = Cl



IV

Thus as reported[6] thioxanthones can indeed serve as stable templates in free radical relay reactions. It remains to be seen whether they prove superior to pyridine derivatives[5] or iodoaryl templates[1,2], and whether they can be utilized in catalytic reactions with significant turnover.

References

1. R. Breslow, R.J. Corcoran, and B.B. Snider, *J.Am. Chem. Soc.*, **96**, 6791 (1974).
2. R. Breslow, R.J. Corcoran, B.B. Snider, R.J. Doll, P.L. Khanna and R. Kaleya, *J. Am. Chem. Soc.*, **99**, 905 (1977).
3. R. Breslow, R.L. Wife, and D. Prezant, *Tet. Letters*, 1925 (1976).
4. R. Breslow, D. Heyer, *J. Am. Chem. Soc.*, **104**, 2045 (1982).
5. R. Breslow, M. Brandl, J. Hunger, and A. Adams, *J. Am. Chem. Soc.*, in press.
6. R. Breslow and M.P. Mehta, *J. Am. Chem. Soc.*, **108**, 6417 (1986); this paper has been retracted.
7. H.F. Hodson and J.F. Batchelor, U.S. Patent 4,103,015 (1978).
8. J. Ackrell, Y. Antonio, F. Franco, R. Landeros, A. Leon, J. Muchowski, M. Maddox, P. Nelson, W. Rooks, A. Roszkowski, and M. Wallach, *J. Med. Chem..*, **21**, 1035 (1978).

(Received in USA 24 April 1987)