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RADICAL RELAY CHLORINATION OF CHOLESTANOL DIRECTED BY AN ATTACHED DIPHENYLSULFIDE TEMPLATE

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In his classic work on chlorinations modified by aromatic solvents, Russell[1] showed that the complexing of Cl˙ to iodobenzene and to diphenylsulfide was unusually strong and apparently involved direct bonding to the heteroatom rather than to the aromatic ring. We have utilized this concept, attaching an iodophenyl group as a template onto a steroid[2,3] or non-steroid[4] substrate. Free radical chlorination then occurs by a radical relay mechanism: the chlorinating species transfers Cl˙ to the iodine, and it is thus directed to abstract the accessible hydrogen substrate in accord with the geometry of the template. We now wish to report that a diphenylsulfide group can also be used as a template. Again the heteroatom geometry directs the reaction, so the Cl˙ is apparently relayed by temporary attachment to sulfur. Furthermore, in the case we have explored in detail the process is much cleaner than with an analogous iodophenyl template.

p-Thiophenoxyphenylacetic acid was prepared by Friedel Crafts acetylation of diphenyl sulfide, followed by a Willgerodt reaction.[5] Reaction of the acid chloride with 3α-cholestanol afforded the ester 1, m.p. 55-58° (m/e 614) after careful purification by short column chromatography.

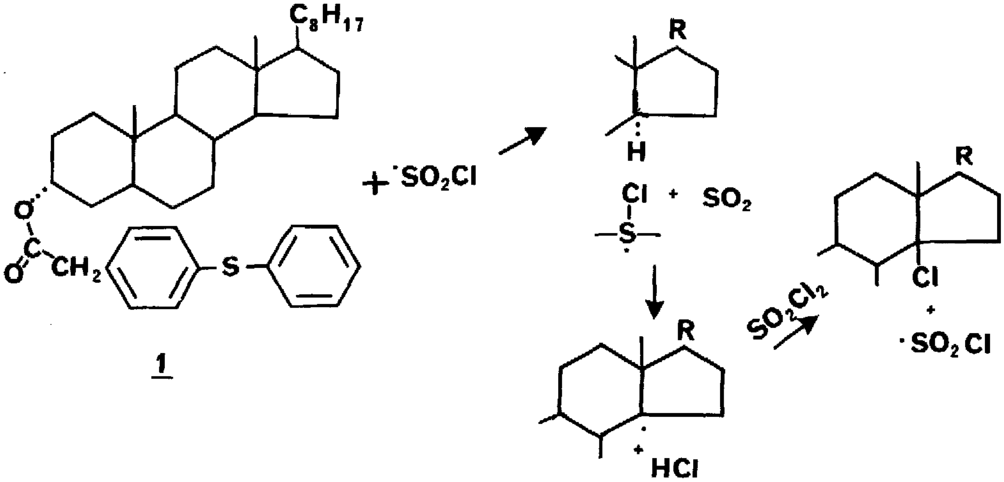
In a typical experiment, a solution of purified ester 1 (460 mg, 0.73 mmol), sulfuryl chloride (120 μl, 1.48 mmol), and azo-bis-isobutyronitrile (AIBN, 5 mg) in dry CCl_4 (40 ml) under strictly anhydrous conditions in an argon atmosphere (most conveniently in a sealed vessel) was irradiated with a 275 W sunlamp over 4 hr with cooling by an ice-water bath. Solvent was evaporated and the product saponified and dehydrochlorinated by heating it at reflux for 2 hr with 6.0 g KOH in methanol (27 ml), dioxane (8 ml) and water (2 ml). The sterol product was conveniently separated by acetylation and chromatography on 10% Ag_2O-impregnated silica gel, affording pure Δ14-cholestenyl-3α-acetate identical with authentic material. The isolated yield was 64% uncorrected for recovered unfunctionalized cholestanol, 89% after such correction. No other steroid olefin was detected, and the remainder must be mechanical losses and possibly a small amount of polar side products.

In a control experiment, there was *no* functionalization of 3α-cholestanyl acetate using *unattached* diphenylsulfide under otherwise identical conditions. Thus the radical relay mechanism both directs and *catalyzes* substrate chlorination, as we had concluded previously[2] with the iodine template.

Comparing the sulfur with the iodine template, the sulfur system gives much cleaner functionalization (the iodophenylacetate analogous to 1 produced the 14-chloro product in 18% yield with 27% of polar impurities[2]). On the other hand, traces of moisture with the sulfur template lead to oxidation of the sulfur instead of substrate functionalization, and the iodine template is not so sensitive.

A further contrast is that $PhICl_2$ could be used as the halogenating agent along with an attached iodophenyl template but not with the sulfur case. Chlorine transfer to the iodine template is isothermal, but $PhICl^{\cdot}$ will not transfer chlorine to the sulfur template in 1, which would apparently be an endothermic step.

This work demonstrates that specific functionalization by template-directed radical relay processes can be generalized. Furthermore, the sulfur-containing templates have some advantages over our original aryl iodide templates.[6]



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