Remote functionalization by tandem radical chain reactions

David Wiedenfeld
Beckman Institute, California Institute of Technology, Pasadena, CA 91125, USA

Normal radical relay chlorination of cholestan-3α-ol directed by an attached m-iodobenzoate ester group affords a 9α-chloro steroid, but when the same reaction is conducted in the presence of an excess of CBr₄, the product is a 9α-bromo steroid. Similarly, when the same radical relay reaction is carried out in the presence of an excess of (SCN)₂, rather than CBr₄, the product is a 9α-thiocyanato steroid. Several other examples of these reactions have been developed. These tandem remote functionalization reactions succeed because an intramolecular hydrogen abstraction by a complexed-chlorine atom generates a specific substrate radical in each case.

Some years ago the remote radical chlorination of steroids and of linear alkanols directed by attached templates was described. These template-directed reactions differed from those of the traditional synthetic style as geometric constraints, rather than just intrinsic chemical reactivity, were a dominant factor in product formation. Furthermore, without template control a low yield of a complex product mixture would have resulted in each case. The novel steroid products were also of potential medicinal interest and would be difficult to prepare by the traditional synthetic approach. Therefore, it was of interest to generalize the remote chlorination chemistry to other functional groups. Recently the extension of this chemistry to the formation of carbon-bromine and carbon-sulfur bonds by tandem radical chain reactions on one substrate was communicated. This report describes how general the latter reactions were with more of the previously developed radical relay systems.

Results and discussion

A general strategy for introducing remote functional groups other than chlorine has been developed (Scheme 1). The template-complexed chlorine atom would be produced as in normal remote radical chlorination chemistry. In the first radical chain propagation step, an intramolecular HCl elimination reaction would take place. In the second step, an additive X-Y (X ≠ Cl) would react with the substrate radical to give the functionalized product as well as a free radical that was capable of propagating the chain. Implicit in this strategy was the necessity to identify additives which reacted with the substrate radical at a rate similar to that at which the chlorine sources did. This strategy towards remote functionalization was of the tandem type: one reagent was responsible for substrate radical formation, while a second was responsible for the substrate radical functionalization.

The initial substrate chosen to test the tandem strategy was cholestan-3α-yl m-iodobenzoate 1 (Scheme 2). This ester was reported to afford 9α-chloride 2 upon reaction with phenyliodine dichloride (PID) under radical relay conditions (Scheme 3). Chloride 2 was found to be a robust material at room temperature and treatment with base or Ag⁺ was necessary to effect elimination. The initial additive tried in the tandem scheme was Br₂ since this material has long been known to react with alkyl radicals to produce alkyl bromides (Scheme 1). However, photolysis of 2 equiv. of Br₂ along with 1 equiv. of PID and 1 equiv. of ester 1 in CH₂Cl₂ led only to the 9-chloride 2 (20%) and recovered starting material 1 (80%). Increasing the number of equivalents of Br₂ led to even lower conversions into products.

A possible explanation was that the second radical chain propagation step (X, Y = Br in Scheme 1) was operational to some extent, as envisioned, but that the formed bromine radical then failed to propagate the chain.

Remote bromination CBrCl₃ and CBr₄ have been reported to brominate various hydrocarbons via a free radical mechanism. Elevated temperatures have occasionally been used for these reactions, but the radical chain propagation step that involved bromine abstraction from CBrCl₃ by an alkyl radical appeared to be exothermic.
and facile. This seemed likely to be true for \(\text{CBr}_4\) also. Thus, it seemed possible that the second chain propagation step might be competitive with the normal substrate radical reaction with the chlorine source if either of these reagents were used as \(X\) in Scheme 1. With either of these reagents, the third propagation step three was correct. The apparent usefulness of the chlorine source and \(\text{Br}_3\) under radical relay conditions as above, led to no functionalization of the steroid. These observations supported the tandem sequence outlined in Scheme 1 with \(\text{PID}\) as the chlorine source and \(\text{Br}-\text{CBr}_4\) as \(X\).

In the bromination of ester 1 with \(\text{PID}\) and \(\text{CBr}_4\), a lower conversion into products was observed than in the normal radical relay chlorination reaction. The low conversions noted when \(\text{Br}_2\) was an additive were rationalized as a failure of radical chain propagation step three in Scheme 1. It seemed possible that the lower than expected conversion in the \(\text{CBr}_4\) reaction could also have been due to some sluggishness in this step and so a different chlorine source was used.

It has been previously demonstrated that templates could be competitive with the normal substrate radical reaction with the chlorine source if either of these reagents were used as \(X\) in Scheme 1. It seemed possible that the lower than expected conversion in the \(\text{CBr}_4\) reaction could also have been due to some sluggishness in this step and so a different chlorine source was used.

Photolysis of 2 equiv. of \(\text{CBr}_4\) with 1 equiv. of \(\text{PID}\) and 1 equiv. of ester 1 led to a significant conversion into products. A new product was assigned by \(\text{H}^1\) NMR spectroscopy to be the desired 9-bromide 4 (Scheme 3) and the isolated reaction mixture consisted mainly of the bromide and corresponding olefin formed upon \(\text{HBr}\) elimination. Integration of the 18-methyl and aromatic regions gave estimates of the yield of the new material 4 (20%), the \(\Delta^{(11)}\) olefin 3 (25%), the 9-chloride 2 (25%) and 1 (30%).

The bromide 4 decomposed to olefin 3 with gentle warming and even when kept at room temperature. This elimination product indicated that the initial functionalization was at C-9. The initial amount of olefin 3 detected was the result of \(\text{HBr}\) elimination which resulted from the work-up and delay before analysis. Photolysis of ester 1 with 5 equiv. of \(\text{CBr}_4\) but no chlorine source, under radical relay conditions as above, led to no functionalization of the steroid. These observations supported the tandem sequence outlined in Scheme 1 with \(\text{PID}\) as the chlorine source and \(\text{Br}-\text{CBr}_4\) as \(X\).

### Table 1  Functionalization of cholest-3\(\alpha\)-yl m-iodobenzoate 1 with \(\text{NPID}\) and added \(\text{CBr}_4^+\)

<table>
<thead>
<tr>
<th>(\text{CBr}_4) equiv.</th>
<th>(\text{NPID}) equiv.</th>
<th>Product distribution (%)</th>
<th>(\Delta^{(11)})</th>
<th>(\text{9-Cl})</th>
<th>(\text{SM}^*)</th>
<th>(\text{9-Br}+\Delta^{(11)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>—</td>
<td>—</td>
<td>100</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.00</td>
<td>—</td>
<td>—</td>
<td>88</td>
<td>12</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.50</td>
<td>—</td>
<td>—</td>
<td>90</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.25</td>
<td>31</td>
<td>15</td>
<td>32</td>
<td>22</td>
<td>46</td>
<td>—</td>
</tr>
<tr>
<td>1.25</td>
<td>35</td>
<td>27</td>
<td>17</td>
<td>21</td>
<td>62</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>1.30</td>
<td>20</td>
<td>48</td>
<td>16</td>
<td>68</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>1.30</td>
<td>21</td>
<td>47</td>
<td>11</td>
<td>68</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>1.10</td>
<td>40</td>
<td>19</td>
<td>9</td>
<td>32</td>
<td>59</td>
</tr>
<tr>
<td>20</td>
<td>1.10</td>
<td>51</td>
<td>14</td>
<td>3</td>
<td>32</td>
<td>65</td>
</tr>
<tr>
<td>1.50</td>
<td>26</td>
<td>49</td>
<td>15</td>
<td>10</td>
<td>75</td>
<td>—</td>
</tr>
<tr>
<td>20.50</td>
<td>32</td>
<td>49</td>
<td>7</td>
<td>12</td>
<td>81</td>
<td>—</td>
</tr>
<tr>
<td>20*</td>
<td>1.50</td>
<td>38</td>
<td>19</td>
<td>7</td>
<td>16</td>
<td>77</td>
</tr>
<tr>
<td>10</td>
<td>1.75</td>
<td>17</td>
<td>56</td>
<td>14</td>
<td>13</td>
<td>73</td>
</tr>
<tr>
<td>20</td>
<td>1.75</td>
<td>25</td>
<td>52</td>
<td>9</td>
<td>14</td>
<td>77</td>
</tr>
</tbody>
</table>

* \(\text{SM} = \) Starting material. *

## References

[1] For the synthesis of such a chlorination, a broad resonance at \(\delta 3.80–3.95\) due to...
the methine protons α to the chloride was observed. The yield was estimated by comparison of the integration of this broad resonance with that of the methylene group α to the ester.\textsuperscript{10,11} Long alkyl chain iodobenzoate esters was studied under the conditions used to brominate 1. Photolysis of hexadecyl m-iodobenzoate 5 with 2.5 equiv. of NPID and 10 equiv. of CBr\textsubscript{4} (Scheme 3) produced a new compound as shown by \textsuperscript{1}H NMR spectroscopy; a resonance at δ 3.80–3.95 was barely visible and instead a broad resonance at δ 3.95–4.10 was observed. Integration of this resonance and comparison with that of the methylene group α to the ester indicated a 65% yield of the new product(s). However, the new product(s) could not be separated by silica gel chromatography from residual 1-iodo-4-nitrobenzene which was also produced in the reaction.

Therefore, the reaction was repeated with PID as the chlorine source. The predominant product was again that with a resonance at δ 3.95–4.10. The crude yield was estimated to be 40% and the product(s) were isolated by silica gel chromatography in 23% yield. Mass spectrometry (MS) indicated the product(s) were the monobromides 6.

Formation of the isolable bromide(s) 6 under the identical conditions used for reaction of compound 1 with PID supported the assignment of unstable 4 as a bromide further. Since the same template complexed chlorine atom is responsible for substrate radical formation in both the chlorination and bromination of 5, the latter reaction was template driven by analogy with the former.\textsuperscript{10,11}

**Remote thiocyanation**

Thiocyanogen, (SCN)\textsubscript{2}, has been used to functionalize carbons with activated hydrogens, such as benzyllic carbons, via a free-radical mechanism to give thiocyanates.\textsuperscript{14} Therefore, the reaction of ester 1 (5 mmol) with 1.4 equiv. of PID and 5.7 equiv. of (SCN)\textsubscript{2} in CH\textsubscript{2}Cl\textsubscript{2} conducted under radical relay conditions. The (SCN)\textsubscript{2} was prepared by the oxidation of Pb(SCN)\textsubscript{2} with Br\textsubscript{2}.\textsuperscript{14,15}

Analysis by \textsuperscript{1}H NMR spectroscopy and thin layer chromatography (TLC) revealed a new steroid as the major reaction product. Integration indicated that the reaction mixture contained 68% of the new compound 7 along with 32% of a 2:1 mixture of normal 9-chloride 2 and unfunctionalized material 1. The new compound 7 was isolated in 56% yield by silica gel chromatography. When the same reaction was repeated, except with 11.4 equiv. of (SCN)\textsubscript{2}, the isolated yield of the new material 7 increased to 64%. Mass spectral analysis was consistent with 7 being a thiocyanate or isothiocyanate.

The \textsuperscript{13}C NMR spectrum had one more line than that of the starting material 1. Examination in the region where thiocyanates and isothiocyanates resonate showed a line at δ 113.4 which indicated 7 was a thiocyanate.\textsuperscript{16} The IR spectrum also indicated that 7 was a thiocyanate as an absorbance was observed at 2137 cm\textsuperscript{-1}.\textsuperscript{14,16} As reductions of thiocyanates have been reported to yield thiols whereas those of isothiocyanates yield amines,\textsuperscript{14,17} 7 was reduced with lithium aluminium hydride (LAH) in tetrahydrofuran (THF). The major steroid product from the reduction was isolated by silica gel chromatography and MS analysis was consistent with thiol 8 (Scheme 4). The reduction reaction provided further evidence in favour of the assignment of 7 as a thiocyanate.

Thiocyanate 7 was stable at room temperature. However, concentration of solutions of this material had to be carried out without heating or the Δ\textsuperscript{211} olefin 3 was formed. Treatment of the purified thiocyanate 7 with a hot KOH solution led to Δ\textsuperscript{211} olefin 9. These observations were consistent with the known reactivity of thiocyanates.\textsuperscript{18} The formation of this olefin also confirmed that the thiocyanate was located at C-9. Therefore, the major product of the (SCN)\textsubscript{2}/PID reaction was 9α-thiocyanocholestan-3α-yl m-iodobenzoate 7 (Scheme 4).

When ester 1 was photoyslated with (SCN)\textsubscript{2} under radical relay conditions in the absence of a chlorinating reagent, no functionalization of the steroid took place. These observations taken together supported the tandem reaction sequence outlined in Scheme 1 with PID as the chlorine source and (SCN)\textsubscript{2} as X–Y.

Similar results were obtained in the reaction with 1 when PID itself was used to oxidize the Pb(SCN)\textsubscript{2} salt.\textsuperscript{17} However, generation of (SCN)\textsubscript{2} solutions with Br\textsubscript{2} was preferable to the use of PID for these reactions Br\textsubscript{2} acted as a colour indicator for when the (SCN)\textsubscript{2} solution was ready. If the (SCN)\textsubscript{2} solution had not decolourised (i.e. if the colour of Br\textsubscript{2} was still evident), then the thiocyanation led to only low conversions into products. This is consistent with the inhibitory effect that Br\textsubscript{2} has as an additive. On the other hand, some difficulty was experienced when PID was used as the oxidant of the Pb(SCN)\textsubscript{2} since it was not trivial to know when (SCN)\textsubscript{2} generation was complete.

Scheme 4
reacted under the conditions used to functionalize 1. PID (1 equiv., ca. 40 mM) was added to 6 equiv. of (SCN)₂ in CDCl₃. The ¹H NMR spectrum of the resulting solution was monitored for PID disappearance and iodobenzene formation. After 30 min, >95% of the PID (relative to iodobenzene) was still present. A second spectrum was taken 30 min later which indicated >90% of the PID was still present. The amount of PID did not change markedly after an additional 30 min. Similar results were obtained in CDCl₃ solution. These results indicated that a direct reaction between the tandem partners was probably not important under the reaction conditions used in the thioacylation, which is consistent with the proposed mechanism.

Steroids with templates that led to functionalization at positions other than C-9 were also subjected to thioacylation, due to interest in the remote introduction of non-halogen functionality. The template-directed chlorination at C-17 with cholestane-3α-yl 4'-iodobiphenyl-3-carboxylate 10 has been extensively studied (Scheme 5). In the original studies, the solvent of choice for chlorination of ester 10 was CDCl₃ (37% chlorination) rather than CH₂Cl₂ (15% chlorination). Consistent with the literature reports, reaction of 10 with 1.5 equiv. of PID in CDCl₃ led to a 30–40% crude yield of 17-chloride 11 as estimated by ¹H NMR spectroscopy. A repeat of the reaction in the presence of 9 equiv. of (SCN)₂, followed by silica gel chromatography, led to a new product 12 in 41% yield.

The mass, IR and ¹³C NMR spectra of 12 all indicated that it was a monothiocyanate. Reduction of this new compound 12 with LAH in THF afforded a product that gave a MS consistent with thiol 13 (Scheme 5). The reduction product supported the assignment of 12 as a thioacylate.

Treatment of the 17-thiocyanate 12 with N,N-dimethylaminoethyleamine in refluxing dioxane or heating it in CDCl₃ without base led to the endocyclic Δ⁶ olefin 14. Therefore the location of the thioacylate was at C-17 and 12 was 17-thiocyanocholen-3α-yl 4'-iodobiphenyl-3-carboxylate (Scheme 5). In principle, the side chain could have epimerized during the radical reaction and so the stereochemistry of 12 was not known. From the ¹³C NMR spectrum, it was clear that only one epimer was present. Crystals suitable for an X-ray diffraction study were obtained with the triphenylsilyl ether derivative 15 of thiol 13 (Scheme 5). The crystal structure (Fig. 1) showed that the sulfur was α for ether 15 and, by analogy, the stereochemistry of 12 and 13 was the same. Also by analogy the normal chloride product 11 was α. In principle, knowing the stereochemistry of the chloride should facilitate a molecular modelling study of the elimination which could lead to a better understanding of the partitioning between the endo-cyclic and exocyclic olefins.

Cholestane-3α-yl 5-(4-iodophenyl) nicotinate 16 has been reported to yield the 9,17-dichloro derivative 17 under normal radical relay chlorination conditions (Scheme 6). By analogy to 11, it seemed likely that the chloride at C-17 was α; however, it was shown that the C-9 position was functionalized first in this case and that could have affected the radical that was formed later at C-17.

Consistent with the literature report, treatment of the mixed iodosylation nicotinate with 2.4 equiv. of PID led to a roughly quantitative yield of the dichloride 17. However, when this reaction was repeated in the presence of 23 equiv. of (SCN)₂, a major product was isolated in 73% yield which bore a striking resemblance to the previously prepared 9-thiocyanate 7; the main difference in the ¹H NMR spectrum was in the aromatic (i.e. template) region. The mass, IR, and ¹³C NMR spectra all indicated monothiocyanation. Heating, or treatment with KOH, led to the Δ⁶⁰ olefin. Hence, with the mixed bifunctional steroid ester 16, the major product formed in the thioacylation was 9-thiocyanate 18 (Scheme 6).

One explanation for these results is that the bulky thioacylate group of 18 blocked further template-induced attack at C-17. That initial attack is at C-9 was consistent with the earlier
studies which showed that the ester 16 formed exclusively the 9-thioproduct which resembled (by H NMR) the known 9, 17-di-olefin 18 upon treatment with base. Therefore, the 9-thiocyanate 18 was subjected to reaction with PID alone and also with (SCN)$_2$–PID mixtures.

Photolysis of the 9-thiocyanate 18 with 1.25 equiv. of PID led to a product which resembled (by $^1$H NMR) the known 9,17-dichloride 17 in greater than 70% yield. M S analysis of the new material gave the expected mass for monochlorination of thiocyanate 18. Furthermore, this material yielded the known $\Delta^{14,16}$-di-olefin 19 upon treatment with base. Therefore, the new material produced in the chlorination of the thiocyanate 18 was the 9-thiocyano-17-chlorosteroid 20 (Scheme 7). Howerer, primarily 9-thiocyanate 18 was recovered when subjected to reaction with PID in the presence of (SCN)$_2$.

Previous studies showed that solvent effects on these reactions can be subtle (e.g. compare reactions of 10 in CH$_2$Cl$_2$ versus CHCl$_3$, vide supra).$^{1,10a}$ Perhaps the excess of (SCN)$_2$ changed the effective relative permittivity of the reaction mixture which, in turn, affected the packing of the template underneath the steroid preventing formation of the C-17 steroid radical.

Significantly, the (SCN)$_2$–PID reaction with steroid ester 16 demonstrated that the tandem scheme also worked with pyridine-based templates. Furthermore, the monothiocyanated and monochlorinated derivative 20 was the first case of a steroid derivative formed by sequential and different remote functionalization reactions.

Summary

Through the use of a new tandem scheme, the remote radical chlorination reaction was extended to remote thiocyanoation and remote bromination. In successful cases, comparable yields and the same specificity observed in the original chlorination were obtained. The novel products would be very challenging targets if one used traditional organic synthetic methods. These results further demonstrated the utility of template-directed reactions for selective synthetic transformations. Without template control, a low yield of a mixture of products would instead have been obtained in each case.

E xperimental

G eneral

(A) Chemicals and procedures. Most starting reagents were obtained from Aldrich. THF was dried by distillation under Ar from K-benzophenone or Na-benzophenone and CH$_2$Cl$_2$ was dried by distillation under Ar from CaH$_2$. Anhydrous CCl$_4$ and pyridine were obtained in SureSeal$^\text{TM}$ bottles from Aldrich. KI-starch test paper was obtained from Beckman Instruments. Ar was obtained from Matheson. Steroid esters and compound 5 were either already present in house or were prepared as described previously.$^{1,10,13}$ Unless specified otherwise, reactions were carried out under Ar in flame-dried round-bottom flasks which were equipped with magnetic stirrer bars. PID was recrystallized from CCl$_4$ before use. NPID was recrystallized from either CCl$_4$ or CCI$_4$-light petroleum before use. In all photoinitiated reactions, a General Electric RSM-6 sunlamp (275 W) placed ca. 15 cm from the reaction vessel was used.

(B) Physical measurements. Except as noted, $^1$H, $^13$C NMR spectra were recorded on Varian VXR 200, 300 or 400 MHz instruments and $^13$C NMR spectra were recorded on a Varian VXR 75 MHz instrument. Residual solvent peaks were used for reference signals and $J$ values are reported in Hz. IR Spectra were recorded with either a Perkin-Elmer 100 or a Perkin-Elmer 1600 Fourier transform spectrometer as KBr pellets. Mass spectra were recorded with a Nermag R-10-10 instrument [for chemical ionization (CI) with NH$_3$ or CH$_4$ ionization gas] or a JEOL JMS-DX-303 HF instrument [for FAB spectra with 3-nitrobenzyl alcohol matrix and Xe ionization gas]. Reversible melting points were not observed in those cases examined; presumably this was due to the known decomposition pathways.

(C) Chromatography, EM. Science pre-coated 0.25 mm thickness silica gel (60 F 254) plates, which contained a fluorescent indicator, were used for analytical TLC. Compounds were visualized under shortwave UV light and/or by use of a phosphomolybdic acid stain. Flash silica gel chromatography$^{24}$ was normally carried out with 32–60 μm Universal Scientific silica gel. Except where noted, preparatory plate chromatography utilized EM Science plates (0.25, 0.50 or 1.00 mm).

the solution after which it was irradiated at room temperature (water bath) for 30 min. At this time, the solution gave a negative KI-starch test. The solution was then transferred to a separatory funnel and washed with 5%aq Na₂SO₄ (1x) and sat. aq NaHCO₃ (1x). The layers were separated and the aqueous layer was extracted with CHCl₃ (2x). The combined organic extracts were dried (Na₂SO₄) and concentrated. The H NMR of the crude material showed 58% 9-bromide 4, 20% 9-keto olefin 3, 7% 9-chloride 2, 13% starting material 1, and an unknown impurity (ca. 2%, 18-methyl at δ 0.75).

The 18-methyl region was assigned as follows: 9α(11) olefin 3, δ 0.59 (s), ester 1: δ 0.65 (s), 9-chloride 2 and 9-bromide 4: δ 0.67 (s) (the last two singlets are only partially resolved at 200 MHz resolution). The aromatic proton ortho to the iodide and ester group (H 1 in Scheme 2) region was assigned as follows: starting material 1 and olefin 3: δ 8.34 (s), 9-chloride 2: δ 8.44 (s), 9-bromide 4: δ 8.54 (s).²⁸ This solution was heated in the H NMR tube at 45°C for 20 min after which the spectrum was re-recorded. The spectrum showed 51% 9-bromide 4, 32% 9-keto olefin 3, 4% 9-chloride 2, 11% starting material 1 and 2% of the unknown impurity. The solution was kept at room temperature overnight and the spectrum was recorded once more. Analysis as before showed 29% 9-bromide 4, 55% 9-keto olefin 3, 6% 9-chloride 2, 4% of the starting material 1 and 3% of an unknown impurity.

Large-scale reaction. Ester 1 (102 mg, 0.165 mmol), CBr₄ (1.094 g, 2.298 mmol) and N Pd(D (79 mg, 0.25 mmol) were dissolved in dry CH₂Cl₂ (13 cm³), [steroid] = 13 mm]. The colourless solution was degassed by bubbling purified N₂ (99.98%, M atheon) through it for 30 min. After 75 min irradiation, the solution was green and gave a negative KI-starch paper test. The solvent was then removed in vacuo and the crude reaction mixture was analysed by H NMR spectroscopy. Integration indicated that the mixture contained 39% 9-bromide 4, 37% of the δ 3.84 olefin 3, 5% of the 9-chloride 2, 16% starting material 1 and 9% of an unknown impurity.

The reaction mixture was then impregnated on silica gel with CH₂Cl₂ and chromatographed with 5% diethyl ether-hexanes. The CBr₄ was separated from the steroidal material and two fractions of steroidal material were recovered. The first was a mixture of the starting material 1, the 9α(11) olefin 3 and 1-iodo-4-nitrobenzene. The second contained more polar steroidal material which, in the original H NMR assay, would have been assigned to be ca 1:1 9-chloride 2: starting material 1.

The fraction containing the starting material 1 and 9α(11) olefin 3 was further purified in 1:1 1-dioxane–methanol solution (15 cm³) and stirred overnight. The solvents were removed in vacuo and the resulting residue was partitioned between CH₂Cl₂ and water. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2x). The combined organic layers were dried (MgSO₄) and concentrated. This material was filtered through silica gel (5% diethyl ether-hexanes-diethyl ether) and the steroidal alcohols were easily separated from residual 1-iodo-4-nitrobenzene. Since a H NMR spectrum of the collected material showed that some of the crude benzoates had not been hydrolysed, the hydrolysis procedure was repeated with refluxing in 10%H₂O solution (15 cm³) for 2 h. This reaction was worked up in the same manner (but, without filtration through silica) and 64 mg of a steroidal alcohol mixture was recovered.

This material was refluxed overnight with dry benzene (20 cm³), pyridine (2 cm³) and acetic anhydride (2 cm³). The solvents were then removed and the crude material was taken up in diethyl ether and washed with 10%aq HCl (4x), 10%aq NaHCO₃ (2x) and brine (1x). The organic layer was then dried (Na₂SO₄) and concentrated.

The resulting yellow oil was chromatographed with 2.5% diethyl ether-hexanes as eluent on AgNO₃-imregnated silica gel.¹³⁻¹⁶⁸ Five fractions were collected and analysed by H NMR and TLC (30%aq H₂SO₄ stain). The first (4mg) was cholestan-3α-yl acetate (e.g. unfunctionalized steroid) contaminated by an unknown impurity. The second (26mg) contained a ca. 9:1 mixture of cholest-9(11)-3-en-3α-yl acetate and cholestan-3α-yl acetate. The third fraction (25mg) was pure 9α(11) acetate. The fourth fraction (5mg) contained unknown, polar steroidal material. The final fraction (8mg) was collected with diethyl ether as eluent and was also unknown, polar steroidal material.

The yields of the collected products were calculated to be 69% of cholest-9(11)-3-en-3α-yl acetate and 9% of cholestan-3α-ol acetate (i.e. unfunctionalized material). Additionally, ca. 6% of polar materials were collected after the photoreaction and an additional ca. 18% polar materials were collected after the processing steps. The yields of these latter materials were estimated with the assumptions that the weights of the initially collected polar materials were similar to that of the starting material 1, while those of the second batch of polar materials were similar to that of cholestan-3α-ol acetate. H NMR spectral data for 9α-bromocholestan-3α-yl m-iodobenzoate 4 (CDCl₃), δ 0.67 (3 H, s, 18-Me), 1.14s (19-Me), 0.80–2.10 (steroid envelope), 2.3–2.5 (1 H, br, m), 2.6–2.8 (1 H, br, m), 5.2–5.3 (1 H, br, s, 3β-H), 7.18 (1 H, t, 7.6), 7.86 (1 H, d, J 7.6), 8.06 (1 H, d, J 7.6) and 8.55 (1 H, s).

CB₄₂A. Arylidiyne dichloride functionalization of hexadecyl m-iodobenzoate 5

Hexadecyl m-iodobenzoate 5 (40 mg, 0.085 mmol) and CBr₄ (281 mg, 0.847 mmol) were dissolved in dry CH₂Cl₂ (14 cm³). [J] = 6.1 μm]. Pd (0.070 g, 0.25 mmol) was then added to the solution after which it was irradiated at ca. room temperature (controlled with a water bath) for 1 h. The solution was then transferred to a separatory funnel and washed with 5%aq Na₂SO₄ (1x). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2x). The organic layers were combined, dried (MgSO₄) and concentrated. The H NMR spectrum of the crude material showed a new peak centred at δ 3.95–4.10 which had the same line shape as the methine peak associated with the chloro compound(s) which appeared at δ 3.80–3.95.¹⁰⁻¹¹ A assuming that the new peak represented the desired bromide(s) 6 integration versus the protons α to the ester linkage at δ 4.2–4.4 indicated ca. 40% of the new material had been formed in the reaction.

The crude mixture was subjected to preparatory plate chromatography (0.50 mm plate, 5% EtOAc-c-hexanes, 2 elutions) and three fractions were recovered. The first contained residual CBr₄ and starting material 5 (unweighed). The second contained ca. 80% of the starting material 5 and ca. 20% of the new compound (H NMR analysis, 17 mg). The remainder of the spectrum was quite similar to that of the starting material except that four of the methylene groups had been shifted from δ 1.2–1.4 to δ 1.6–1.9. M UV absorption (Cl, NH₂) of this material showed peaks at 551 and 553 which corresponded to those expected for 6 (i.e. M + 1 with the bromine isotopic distribution). In addition, the corresponding M + Na₄⁺ peaks were observed at m/z 568 and 570.

9α-1 Thiocyanatocholestan-3α-yl m-iodobenzoate 7

To prepare the necessary (SCH)₃ solution, a reaction flask was charged with Pb(SCN)₃ (500 mg, 1.55 mmol) and then CH₂Cl₂ (15 cm³). The A ring was replaced with a ground glass joint bearing a stopper which had a Teflon sleeve and Br₂ (0.028 cm³, 0.028 cm³ and finally 0.014 cm³, 1.4 mmol total) was added at 1 h intervals using a Drummond autopipette. Throughout this period the reaction suspension was stirred vigorously. After the last Br₂ addition, a second portion of Pb(SCN)₃ (250 mg, 0.78 mmol) was added and stirring was continued until a virtually colourless suspension was obtained after several hours. More CH₂Cl₂ (10 cm³) was added and the suspension was filtered...
through a Pasteur pipette which contained a small cotton plug into a round-bottom flask. The flask was then equipped with an Ar balloon and a magnetic stirrer bar. The resulting nearly colourless solution of (SCN)_2 was then concentrated at room temperature. Silica gel chromatography (5% EtOAc–hexanes) and concentration of the desired fractions at room temperature gave the 9-thiocyanate as a colourless foam (53 mg, 64%). Concentration of the early fractions (only higher Rf material was visible in the TLC of the crude reaction mixture) gave 18 (0.50 g, 1.5 mmol), the yield of recovered thiocyanate was lower (ca. 25%) presumably due to some exposure to air during filtration of the (SCN)_2 solution; (SCN)_2 0.84, 0.88 and 0.91 (methyl region not well resolved, 18-Me, 19-Me, 26-Me and 27-Me) and 1.02 (d, J = 6.4, 21-Me) 1.1–2.1 (steroid envelope), 2.4–2.6 (1 H, m), 5.25–5.35 (1 H, br s, H-3); (CI-MS; NH_4^+) 127.98, 128.63, 128.87, 128.98, 130.57, 131.09, 131.76, 138.01, 139.74, 140.30 and 165.76 (C=O); (UV, PMA) 0.37 (UV+, PMA+).

A solution of thiocyanate (18 mg, 0.024 mmol) in dioxane (5 cm^3) was treated with N,N-diisopropylethylamine (0.5 cm^3) and the resulting mixture was first heated to reflux for 5 h and then stirred at room temperature overnight. After the mixture had been evaporated in vacuo, the resulting material was partitioned between EtOAc and 1% aqueous HCl. The layers were separated and the organic layer was extracted with 5% aq. Na_2SO_4 and silica gel chromatography (5% EtOAc–hexanes) gave the 17-thiocyanate as a colourless foam (64 mg, 41%). Concentration of the earlier fractions gave 82 mg of a ca. 4:1 mixture of starting material: 17-chloride 11 (H NMR analysis). When this reaction was conducted with the same procedure on a larger scale (500–700 mg of steroid 10), the yield of recovered thiocyanate was lower (ca. 25%) presumably due to some exposure to air during filtration of the (SCN)_2 solution; (SCN)_2 0.84, 0.88 and 0.91 (methyl region not well resolved, 18-Me, 19-Me, 26-Me and 27-Me) and 1.02 (d, J = 6.4, 21-Me) 1.1–2.1 (steroid envelope), 2.4–2.6 (1 H, m), 5.25–5.35 (1 H, br s, H-3); (CI-MS; NH_4^+) 127.98, 128.63, 128.87, 128.98, 130.57, 131.09, 131.76, 138.01, 139.74, 140.30 and 165.76 (C=O); (UV, PMA) 0.37 (UV+, PMA+).

A solution of the 17-thiocyanate (18 mg, 0.024 mmol) in dioxane (5 cm^3) was treated with triphenylsilane (0.53 g, 2.0 mmol, 1.1 equiv.) in anhydrous Et_2O to be 15% 9-thiocyanate and 11% 11-thiocyanate, 25%) presumably due to some exposure to air during filtration of the (SCN)_2 solution; (SCN)_2 0.84, 0.88 and 0.91 (methyl region not well resolved, 18-Me, 19-Me, 26-Me and 27-Me) and 1.02 (d, J = 6.4, 21-Me) 1.1–2.1 (steroid envelope), 2.4–2.6 (1 H, m), 5.25–5.35 (1 H, br s, H-3); (CI-MS; NH_4^+) 127.98, 128.63, 128.87, 128.98, 130.57, 131.09, 131.76, 138.01, 139.74, 140.30 and 165.76 (C=O); (UV, PMA) 0.37 (UV+, PMA+).

A solution of the 17-thiocyanate (18 mg, 0.024 mmol) in dioxane (5 cm^3) was treated with N,N-diisopropylethylamine (0.5 cm^3) and the resulting mixture was first heated to reflux for 5 h and then stirred at room temperature overnight. After the mixture had been evaporated in vacuo, the resulting material was partitioned between EtOAc and 1% aqueous HCl. The layers were separated and the organic layer was extracted with 5% aq. HCl (2×) and water (1×), dried (MgSO_4) and concentrated at room temperature (controlled by a water bath) for 1 h. Work-up as previously (except using 5% aq. Na_2SO_4 and silica gel chromatography (5% EtOAc–hexanes) gave the 17-thiocyanate as a colourless foam (64 mg, 41%). Concentration of the earlier fractions gave 82 mg of a ca. 4:1 mixture of starting material: 17-chloride 11 (H NMR analysis). When this reaction was conducted with the same procedure on a larger scale (500–700 mg of steroid 10), the yield of recovered thiocyanate was lower (ca. 25%) presumably due to some exposure to air during filtration of the (SCN)_2 solution; (SCN)_2 0.84, 0.88 and 0.91 (methyl region not well resolved, 18-Me, 19-Me, 26-Me and 27-Me) and 1.02 (d, J = 6.4, 21-Me) 1.1–2.1 (steroid envelope), 2.4–2.6 (1 H, m), 5.25–5.35 (1 H, br s, H-3); (CI-MS; NH_4^+) 127.98, 128.63, 128.87, 128.98, 130.57, 131.09, 131.76, 138.01, 139.74, 140.30 and 165.76 (C=O); (UV, PMA) 0.37 (UV+, PMA+).

A solution of the 17-thiocyanate (18 mg, 0.024 mmol) in dioxane (5 cm^3) was treated with triphenylsilane (0.53 g, 2.0 mmol, 1.1 equiv.) in anhydrous Et_2O to be 15% 9-thiocyanate and 11% 11-thiocyanate, 25%) presumably due to some exposure to air during filtration of the (SCN)_2 solution; (SCN)_2 0.84, 0.88 and 0.91 (methyl region not well resolved, 18-Me, 19-Me, 26-Me and 27-Me) and 1.02 (d, J = 6.4, 21-Me) 1.1–2.1 (steroid envelope), 2.4–2.6 (1 H, m), 5.25–5.35 (1 H, br s, H-3); (CI-MS; NH_4^+) 127.98, 128.63, 128.87, 128.98, 130.57, 131.09, 131.76, 138.01, 139.74, 140.30 and 165.76 (C=O); (UV, PMA) 0.37 (UV+, PMA+).

A solution of the 17-thiocyanate (18 mg, 0.024 mmol) in dioxane (5 cm^3) was treated with N,N-diisopropylethylamine (0.5 cm^3) and the resulting mixture was first heated to reflux for 5 h and then stirred at room temperature overnight. After the mixture had been evaporated in vacuo, the resulting material was partitioned between EtOAc and 1% aqueous HCl. The layers were separated and the organic layer was extracted with 5% aq. HCl (2×) and water (1×), dried (MgSO_4) and concentrated. H NMR analysis of the crude reaction showed that 14 had the same Rf value as the authentic 14 olefin 14. A similar result was observed when the 17-thiocyanate was heated in CDCl_3 overnight at 50 °C.
CCl₄ (40 cm³) for 1 h. Since residual Br₂ in the mixture was evident as judged by the reaction mixture colour, a second portion of triphenylsilane (0.08 g) was added to it and stirring continued for another 1 h. At this point, a final portion of triphenylsilane was added (0.03 g, 1.25 total equiv.) to the mixture and stirring was continued for 1.5 h. The solvents were removed on a vacuum line and the resulting colourless solid dried in vacuo for several hours and then used.

Triphenylsilyl bromide (65 mg, 0.19 mmol, 4.0 equiv., uncorrected for excess of triphenylsilane) was added to a pre-weighed round-bottom flask under argon. The resulting mixture was heated at 50°C over a period of 30 min. The reaction mixture was then transferred to a round-bottom flask and the solvent was removed. The residue was then treated with 1:1 dioxane-10% KOH in methanol for 2 h. The reaction mixture was worked up as described for the corresponding reaction for the thiocyanate. A second H NMR spectrum was recorded and it showed that the mixture now contained ca. 30% of the Δ[20] olefin (with the template intact) and ca. 70% of the thiocyanate 18. The mixture was then transferred to a round-bottom flask and the solvent was removed. The residue was then treated with 1:1 dioxane-10% KOH in methanol for 2 h. The reaction mixture was worked up as described for the corresponding reaction for the thiocyanate. A second H NMR analysis showed the known Δ[20] olefin 9 to be the only steroidal product (4.1 mg).

9α-Thiocyanato-17-chlorocholestan-3α-yl-5-(4-iodophenyl)-nicotinate 20

A solution of thiocyanate 18 (11 mg, 0.015 mmol) and PID (5 mg, 0.018 mmol) in CH₂Cl₂ (5 cm³, [solv] = 3 m) was irradiated at ca. room temp. overnight (rotovap, 0.5–1 m) for 45 min. The solution was transferred to a separatory funnel and extracted with 5% aq. Na₂SO₄ (1×). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (1×). The organic layers were combined, dried (MgSO₄) and concentrated without heating. A second H NMR analysis of the crude material showed that one major product was formed in the reaction. It was characterized by a 21-M e shift at 1.02 (d, J 6) and 2.02 (m) and most of the 21-M e group was shifted downfield with respect to that of the starting material 18. An estimate of the yield of 20 was >70%. Steroid 20 can be isolated by preparatory plate chromatography (2.5% tert-butyli methyl ether–CHCl₃, [solv] = 20 cm, 0.5 mm) using a 1:1 dioxane–10% KOH in methanol mixture. The reaction mixture was worked up in the same fashion as for the similar elimination reaction of 9-thio-cholestan-3α-yl-5-(4-iodophenyl)-nicotinate 20 which took place with the template intact. A second H NMR spectrum of the crude recovered material showed that the known cholestan-9(11),16-dien-3α-ol 19 was the major steroidal product as indicated by the shifts of the 18-methyl, 21-methyl and vinyl protons.

AAcknowledgements

Most of the described experiments were completed in the laboratories of Professor Ronald Breslow at Columbia University. Professor Breslow is gratefully acknowledged for helpful suggestions and encouraging submission of this manuscript. The National Institutes of Health supported this work. Dr Sonny Lee is gratefully acknowledged for growing crystals of 15 suitable for X-ray analysis and for his expertise in solving the X-ray data. Dr Joe Ziller collected the X-ray data at the UC Irvine facility. Dr Lars Skov made helpful suggestions during the revision and proofreading of this manuscript.

Supplementary material available

The X-ray structural data for compound 15 have been deposited with the Cambridge Crystallographic Data Centre. Any request for this material should be accompanied by a full bibliographic citation together with the reference number Ccdc 20763.

References


11 Thanks to Dr Branco Jursic for a sample of NPID.

12 D. A. Bekoe and R. Hulme, Nature, 1956, 177, 1230.


17 Reaction of PID with Pb(SCN)$_2$ has been reported to give (SCN)$_2$ as well as phenyliodine dithiocyanate. However, no evidence to support the latter structure was given. Furthermore, it has been reported that reaction of 2 equiv. of PID with 1 equiv. of Pb(SCN)$_2$ gave CI$\text{SCN}$, PbCl$_4$ and iodobenzene. This report seemed to preclude the postulated formation of phenyliodine dithiocyanate.


19 (a) R. Neu, Chem. Ber., 1939, 72, 1505; (b) A. Varvoglis, Synthesis, 1984, 709.


25 In the $^1$H NMR spectrum of the 9-chloride, two methine proton peaks are shifted downfield of the steroidal envelope to $\delta$ 2.2–2.4 and 2.5–2.7. In the spectrum of the steroid 9-bromide, two new peaks shifted downfield of the steroidal envelope, each of which had the same general line shape as those of the two methine proton peaks observed in the spectrum of the 9-chloride, were observed at $\delta$ 2.3–2.5 and 2.6–2.8.


© Copyright 1997 by the Royal Society Chemistry


Paper 6/00172F

Received 8th January 1996
Accepted 2nd September 1996