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THE RADICAL RELAY CHLORINATION OF FLEXIBLE NICOTINATE ESTERS

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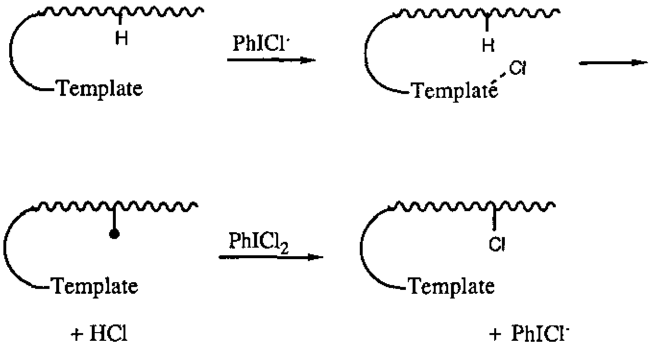
Abstract —— Dodecyl and hexadecyl nicotinates undergo radical relay chlorination with selectivities consistent with molecular models and with results in steroids. Alternating effects are seen, reflecting straight-chain conformations. A novel sequence for product analysis is validated, and used to compare the nicotinate template, and its N-oxide, with previously studied iodoaryl templates.

Derek Barton pioneered in the useful application of intramolecular functionalization reactions of unactivated carbons by neighboring oxygen radicals. Photolysis of a nitrite ester, in the Barton reaction, generates an alkoxy radical that attacks a nearby hydrogen atom over a six-membered ring. The resulting carbon radical is then nitrosated.

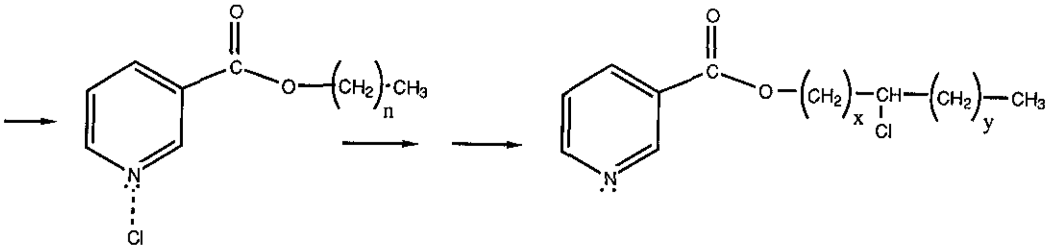
We have developed a process we called Remote Oxidation[1] that literally extends this concept. By the use of rigid structural elements we direct selective intramolecular hydrogen abstraction over as much as a 21-membered ring. In our most useful application of this concept, template directed Radical Relay chlorination[2] can functionalize unactivated C-H bonds in the presence of much more reactive groups, such as double bonds. With inflexible steroid substrates our processes can be quite regioselective, but with



Radical Relay Chlorination

flexible substrates such as n-alkyl chains we see a distribution of products. While such a distribution is less useful synthetically, it contains important conformational information.[3] By the use of <u>two</u> electrostatic bonding interactions we have been able to stretch out a flexible chain so that well defined regioselective functionalization is seen.[4]

In the past we have used templates for radical relay chlorination containing iodoaryl groups[5], diaryl sulfides[6], thiophenes[7], and thioxanthones[8], but we have recently found that pyridine rings[9] can bind chlorine atoms with three-electron bonds[10] and that templates containing pyridine or related heterocyclic rings can be used to direct chlorinations in steroids. Indeed, they seem to be the most practical regioselective catalysts for these processes. Thus we have examined the template directed chlorination in flexible esters of nicotinic acid. The work had three goals: 1) to establish whether the pyridine template could direct chlorination to less reactive methylene groups, not just the tertiary hydrogens of the steroid examples; 2) to see how selective the process is, and compare the geometry observed with that seen in the rigid steroid cases; and 3) to see whether the "penultimate effect" we had observed earlier in benzophenone insertion reactions[3] and in iodoaryl-directed chlorinations of flexible chains[3] was also seen here.



First we did a controlled reaction to test for template directed intramolecular radical relay reaction. Irradiation of a mixture of 15mM n-dodecyl nicotinate and 15mM n-dodecyl acetate in CH_2Cl_2 with 15mM $PhICl_2$ gave a 45-50% yield (nmr) of chlorinated nicotinate ester, and no detectable (nmr) chlorinated acetate ester. Next we examined the product distribution in the chlorinated dodecyl nicotinate.

We have described a scheme for such determinations in the past.[3] The essential point is that Ei Ms of thioketals (dithianes) leads to selective fragmentation forming substituted dithiane cations. From the masses of these fragments, the positions of the thioketals can be deduced. Previous control reactions, and new ones as part of this work, establish that the mass spectral distribution reflects the quantitative distribution of a carbonyl group in a straight-chain compound, with one exception. The unsubstituted dithiane cation that would be derived from a terminal aldehyde is also formed to some extent by rearrangement of other dithiane cations. Thus the analytical scheme is reliable for carbonyl groups on most of the carbons, except the terminal one. This is quite unreactive in any case; nmr examination of the products suggests that little of the chlorination occurs on the terminal methyl group of a straight chain.

We have also described a scheme[3] for converting chlorinated carbons to thioketals, so that this mass spectral method can be used to determine chlorination sites. We displaced the chlorine with thiophenoxide ion, and then converted the resulting thioether to a ketone. Pummerer rearrangement of the corresponding sulfoxide was not useful, so we devised a novel route involving t-butyl perbenzoate and copper, then oxidation. However, the overall yield of this route was not high, and selective losses might bias the analysis. Thus we have re-examined the Pummerer rearrangement scheme, and find that the thioether sulfoxides are easily converted to a mixture of ketone and enethioethers with trifluoroacetic anhydride. This mixture is directly converted to the thioketal with ethanedithiol. As a check, a mixture of authentic 5-chlorododecyl acetate and 12-chlorododecyl acetate was converted to the thioketal mixture in 68% overall yield by this new scheme. An original ratio C-12/C-5 of 1.47 analyzed as 1.43, 1.44, 1.47, and 1.54 in different runs. Thus this analytical method seems valid.

The results are plotted in Figure 1. Radical relay chlorination of dodecyl nicotinate produces a significant excess of C-5 chlorination, with almost none closer to the ester link. A similar result is seen in the chlorination of n-hexadecyl nicotinate (Figure 2). For comparison, the pattern in radical relay chlorination of dodecyl m-iodobenzoate was redetermined by this new analytical scheme, and the results are also plotted in Figure 1. It can be seen that the results with the two templates are similar, but that the nicotinate is even more selective for C-5.

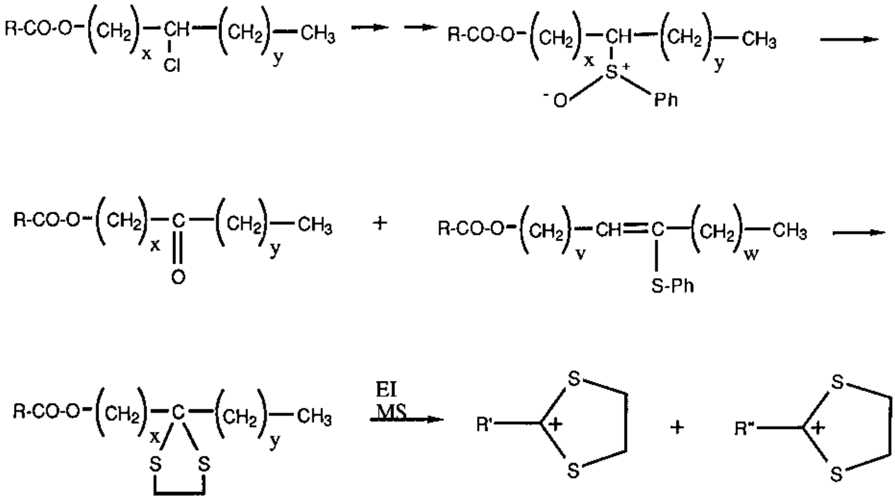
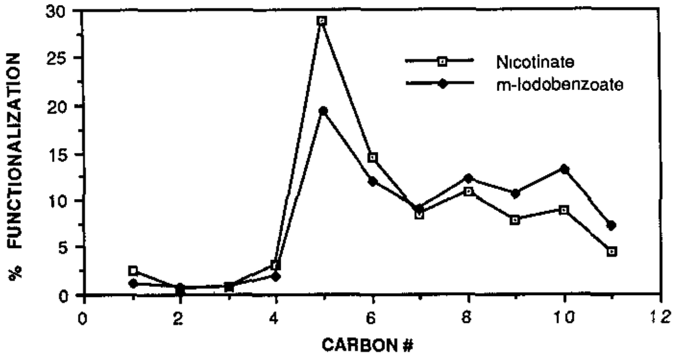
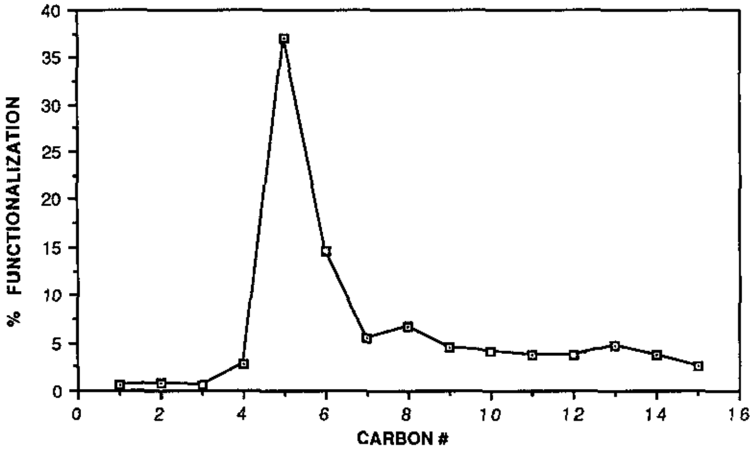


FIGURE 1

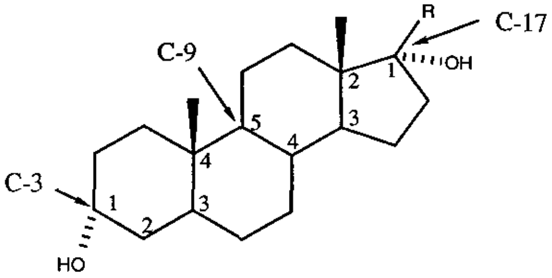


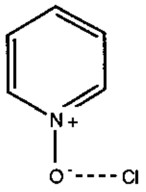
Two other points emerge from Figure 1. We see an alternating effect further out in the chain, with maxima at even carbons and minima at odd carbons. We have seen this type of thing before,[11-13] and it must reflect *the staggered geometry typical of alkyl chains*. Also, we see no maximum at C-11, the penultimate carbon. We had first detected excessive functionalization of penultimate carbons in benzophenone photolysis studies,[3] and had also seen the effect in the attached aryliodine dichloride chlorination of flexible chains.[3] However, that latter study had involved our previous analytical scheme. We now know that there is a systematic problem with that scheme that overindicates the mass spectral fragment corresponding to penultimate functionalization. Our current work makes it clear that there is no such effect (see also Figure 2) in these chlorination reactions. However, the benzophenone work involved a different well-based analytical scheme, and penultimate functionalization made steric sense in that case.

FIGURE 2



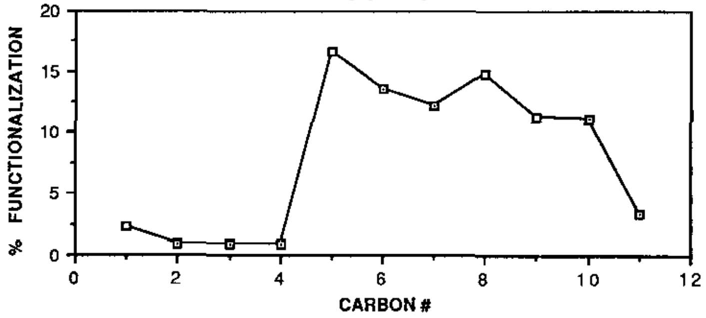
The preferred functionalization at C-5 in these flexible compounds is consistent with the selectivities we have seen in steroids. 3-α-Esters of nicotinic acid or of m-iodobenzoic acid direct chlorination to C-9 of the steroid; furthermore, the same functionalization at C-9 is seen when these templates are esterified at 17-α. As the diagram makes clear, the distance involved corresponds to chlorination of C-5 in flexible esters. Molecular models and molecular mechanics calculations both suggest that these are the positions that should be attacked.





In the steroid series we also found[12] that the N-oxide of the 3-α-nicotinic ester directed chlorination to C-9, a striking coincidence since in this case the chlorine must be bound to oxygen. Thus we examined the chlorination of dodecyl nicotinate N-oxide; the results are plotted in Figure 3. It can be seen that this template is less selective than was the nicotinate itself, but that again the nearest point functionalized is C-5. Chlorine coordinated to the oxygen of an N-oxide apparently has a range of geometries available, but at least some of the time the chlorine is in essentially the same part of space as it would occupy for the pyridine complex.

FIGURE 3



CONCLUSIONS

1. The nicotinate template can direct radical relay chlorination into a flexible alkyl chain, and with a selectivity greater than that of a m-iodobenzoate template.

2. In these flexible systems alternating effects can be seen, reflecting the conformations of flexible chains, but chlorinations do not favor the penultimate carbon.

3. Attack on C-5 in flexible chains directed by nicotinates, m-iodobenzoates, and nicotinate N-oxide templates corresponds well to their template directed functionalizations of C-9 in steroids when they are esterified at either C-3 or C-17 α.

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