Unusual Oxidation in Thionyl Chloride: Novel Synthesis of Methyl 3-alkoxy-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylates

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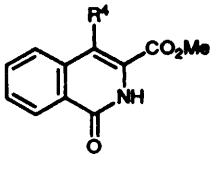
Oxidation of methyl 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **1** with thionyl chloride gives an unstable intermediate that reacts with alcohols to give 3-alkoxy-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylates (*e.g.* **6**) and that is reduced with *N*-acetylcysteine to regenerate **1**. In this system thionyl chloride is a convenient alternative oxidant to lead tetraacetate for the preparation of these masked equivalents of the unusual and reactive dienophile methyl 1,4-dioxo-1,4-dihydroisoquinoline-3-carboxylate **7**.

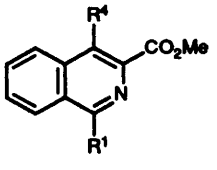
In an attempt to refunctionalise methyl 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **1**[1] at the amidic carbonyl C-1 we attempted a selective chlorination using thionyl chloride. However, the reaction took an entirely different course and gave an unidentified intermediate that was converted in good yield by treatment with dry methanol into an homogenous crystalline product. Since thionyl chloride is known[2] to induce a variety of unexpectedly interesting reactions with enols and active methylene compounds, we investigated this very facile reaction and we now describe the characterisation of its products.

Results and Discussion

Reaction of **1** with thionyl chloride gave none of the expected chlorination products **2**–**4**; instead a single labile procuct **5** was obtained that could not be purified but that underwent characteristic reactions.

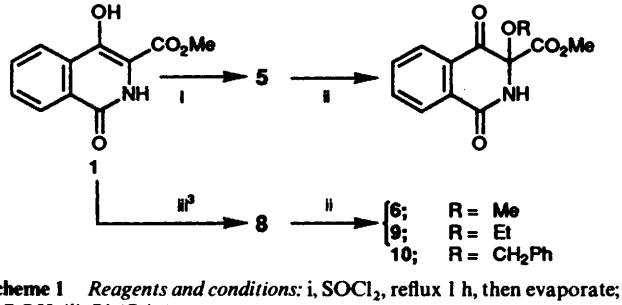


1; R^4 = OH
2; R^4 = Cl



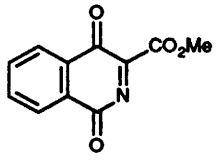
3; R^1 = Cl, R^4 = OH
4; R^1 = R^4 = Cl

Evaporation of the excess of thionyl chloride and then methanolysis of the labile residue of **5** gave a methyl ether that crystallised after chromatographic purification. Spectroscopic and analytical data established the structure of the product as methyl 3-methoxy-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**6**) (Scheme 1); the tetrahydroisoquinolinedione had undergone an unexpected oxidation to a masked azaquinone.



Scheme 1 *Reagents and conditions:* i, $SOCl_2$, reflux 1 h, then evaporate; ii, ROH; iii, $Pb(OAc)_4$

The compound **6** has been described previously as a convenient precursor to the unusual and reactive azanaphthoquinone dienophile **7** by Soto and coworkers,[3] who prepared it



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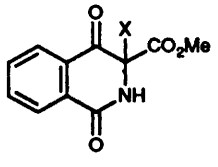


8; X = OAc
11; X = S(O)Cl
12; X = Cl

in two stages from the same methyl 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **1** by oxidation with lead tetraacetate followed by methanolysis of the intermediate acetate **8** (61% overall). Our assignment was confirmed by comparison of our data with those previously published.[3]

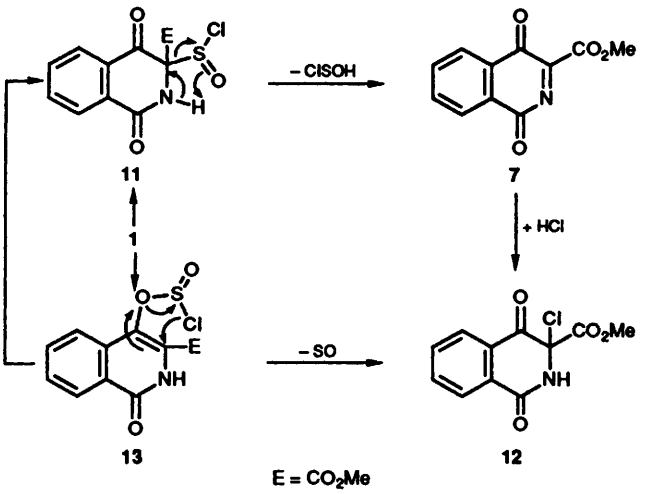
Commercial thionyl chloride can contain a plethora of impurities that are more obvious oxidants[4] than thionyl chloride. However, the oxidation also proceeded smoothly with purified[5] thionyl chloride. Alcoholysis of the labile intermediate **5** gave the methoxy,[3] ethoxy,[3] and benzyloxy derivatives **6** (72%), **9** (46%), and **10** (47%) respectively (Scheme 1). These compounds are labile as oils and the lower yields of the ethoxy and benzyloxy derivatives **9** and **10** are attributed to the extra difficulty experienced in crystallising them.

Interestingly, although the asymmetry at C-3 is apparent in the ABX_3 coupling pattern of the ethoxy-group of **9**, the two benzylic protons of the benzyloxy derivative **10** are almost isochronous and appear as a broadened singlet.

In contrast to the formation of ethers from the intermediate **5** and alcohols, treatment of the intermediate **5** with *N*-acetylcysteine gave no trace of a sulfide: instead the starting material was regenerated by reduction.

Oxidative functionalisation at C-3 has good precedents: thionyl chloride has often been reported[2] to react with enols and active methylene compounds at C-α. Enol ethers also react, by addition of thionyl chloride to the double bond.[6]

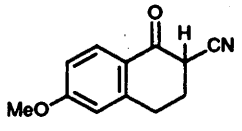
The 3-chlorosulfinyl and 3-chloro derivatives **11** and **12** are the strongest monomeric candidates for the unstable intermediate **5**. The high enol content of the substrate dione **1** suggests that it should react with thionyl chloride to produce the 3-chlorosulfinyl derivative **11** either directly or *via* isomerisation of the enol chlorosulfinate **13**. In the presence of an excess of thionyl chloride such α-chlorosulfinyl derivatives can rearrange by a Pummerer rearrangement[2] to give α-chloro-α-chlorosulfenyl derivatives, which is blocked in this case by substitution. However, elimination–addition would lead to the



11 7 13 12

Scheme 2

3-chloro analogue **12** even in this case. Alternatively, the enol chlorosulfinate **13** could form the 3-chloro derivative **12** directly by electrocyclic fragmentation* (Scheme 2). Similar overall



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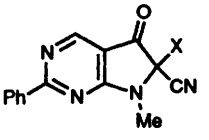

15; X = H
16; X = Cl

transformations have been observed for the carbocyclic analogue **14**[7] and for the 5-membered heterocyclic analogue **15**.[8]

In the latter closely related system Kim and Santilli[8] were able to isolate and characterise the chloro derivative **16**, so establishing the nature of their reaction. For these reasons we also favour the 3-chloro derivative **12** as the probable structure of the unstable intermediate **5**.

Whatever the nature of the intermediate(s) **5**, its formation clearly re-emphasises that the apparently straightforward conversion of a hydroxy into a chloro heterocycle using thionyl chloride may take a quite different course.[2] In consequence, we found that methyl 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**1**) may be quickly and conveniently oxidised in commercial thionyl chloride to a masked form of the reactive quinonoid dienophile methyl 1,4-dioxo-1,4-dihydroisoquinoline-3-carboxylate (**7**). We believe that this finding represents a significant simplification of the existing method.

Experimental

General Procedures.—Thionyl chloride (97%, Aldrich) was purified[5] by distillation from triphenyl phosphite (97%, Aldrich) to give a constant boiling middle fraction (b.p. 74 °C, uncorrected; lit.,[5] b.p. 76 °C). NMR spectra were obtained using a Bruker AM200 at 200 MHz. Coupling constants are in Hz.

Methyl 3-*Methoxy*-1,4-*dioxo*-1,2,3,4-*tetrahydroisoquinoline*-3-*carboxylate* (**6**).—A solution of methyl 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **1**[1] (1.00 g) in purified[5] thionyl chloride (*ca.* 10 cm^3) was heated under reflux for 1 h. The mixture was evaporated to dryness and then mixed with anhydrous toluene under reduced pressure. The residual gum **5** was dissolved in anhydrous methanol. The solution was evaporated to give a residue containing some starting material and the product, which was purified chromatographically (MPLC, Merck '10402 Lobar' column). Elution with light petroleum (b.p. 40–60 °C)–ethyl acetate (3:1) gave analytically pure methyl carboxylate **6**, (0.82 g, 72%), m.p. 117–118 °C (lit.,[3] m.p. 115–116 °C) (Found: C, 57.6; H, 4.4; N, 5.4. Calc. for $C_{12}H_{11}NO_5$: C, 57.8; H, 4.4; N, 5.6%); $\delta_H(CDCl_3)$ 3.42 (3 H, s), 3.82 (3 H, s), 6.93 (1 H, br s), 7.77 (1 H, ddd, *J* 1.5, *J* = *J* 7.5), 7.87 (1 H, ddd, *J* 1.5, *J* = *J* 7.5), 8.10 (1 H, dd, *J* 7.5, 1.5) and 8.29 (1 H, dd, *J* 7.5, 1.5); *m/z* 267 (M + NH_4, 33%), 250 (M + H, 77%) and 220 (250 − CH_2O, 100%).

Methyl 3-*Ethoxy*-1,4-*dioxo*-1,2,3,4-*tetrahydroisoquinoline*-3-*carboxylate* (**9**).—The title compound **9** (46%) was prepared by treatment of the intermediate **5** with dry ethanol and purified as described above, m.p. 113–114 °C (lit.,[3] m.p. 112–113 °C) (Found: C, 59.2; H, 4.8; N, 5.2. Calc. for $C_{13}H_{13}NO_5$: C, 59.3; H, 4.9; N, 5.3%); $\delta_H(CDCl_3)$ 1.28 (3 H, t of ABX_3, *J* 7), 3.5–3.8 (2 H, m of *AB*X_3), 3.83 (3 H, s), 6.90 (1 H, br s), 7.76 (1 H, ddd, *J* 1.5, *J* = *J* 7.5), 7.85 (1 H, ddd, *J* 1.5, *J* = *J* 7.5), 8.09 (1 H, dd, *J* 7.5, 1.5) and 8.28 (1 H, dd, *J* 7.5, 1.5); *m/z* = 281 (M + NH_4, 33%), 264 (M + H, 23%) and 220 (264 − MeCHO, 100%).

Methyl 3-*Benzyloxy*-1,4-*dioxo*-1,2,3,4-*tetrahydroisoquinoline*-3-*carboxylate* (**10**).—The title compound **10** (47%) was prepared by treatment of the intermediate **5** with dry benzyl alcohol and purified as described above, m.p. 75–78 °C [twice from pentane–cyclohexane (1:1), initially at −20 °C] (Found: C, 66.2; H, 4.7; N, 4.3. $C_{18}H_{15}NO_5$ requires C, 66.5; H, 4.6; N, 4.3%); $\delta_H(CDCl_3)$ 3.82 (3 H, s), 4.65 (2 H, 's'), 6.98 (1 H, br s), 7.20–7.35 (5 H, m), 7.75 (1 H, ddd, *J* 1.5, *J* = *J* 7.5), 7.85 (1 H, ddd, *J* 1.5, *J* = *J* 7.5), 8.06 (1 H, dd, *J* 7.5, 1.5), 8.27 (1 H, dd, *J* 7.5, 1.5); *m/z* = 343 (M + NH_4, 89%), 326 (M + H, 51%) and 220 (326 − PhCHO, 100%).

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