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Access to 4-substituted 3,4-dihydroquinolin-2(1*H*)-ones by an unusual radical cyclisation of a secondary amide

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Abstract—A novel route to 3,4-dihydroquinolin-2(1*H*)-ones involving two radical addition steps is reported, starting from readily accessible xanthates and *N*-aryl-3-butenamides.

Although quinolin-2(1*H*)-one skeletons are rarely found in naturally occurring substances, these heterocycles possess varied and powerful biological properties.[1] For example, compound **A** is a strong inhibitor of HIV-1 reverse transcriptase, whereas **B** (carteolol) is a β-adrenergic blocking agent (Fig. 1).[2]

Development of new synthetic pathways to these compounds has thus recently attracted some attention from organic chemists, broadening the scope of substrates classically obtained by Friedländer-type methods or Friedel–Crafts cyclisations.[3] These new routes include, for instance, multi-component reactions,[4] palladium chemistry or rhodium catalysis.[5] In contrast, radical chemistry has not been considered in this context.[6] This is, in part, a consequence of the reluctance of the pharmaceutical industry to deal with heavy metal residues especially associated with organotin chemistry, and also because of the relative difficulty of building six-membered rings by radical cyclisation onto an aromatic nucleus. The tin-free xanthate radical chemistry we have developed[7] formally gives a longer lifetime to the intermediate radicals, allowing them to undergo difficult transformations. This technology provides a useful tool for the construction of the desired dihydroquinolinone skeleton under mild conditions.

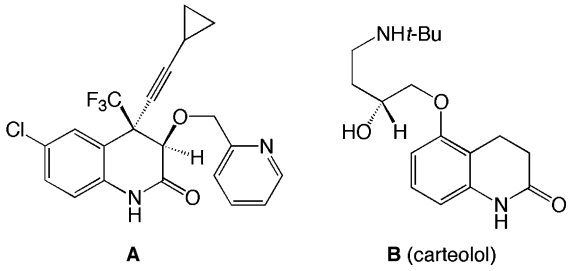

Figure 1.

In the course of our studies centred around the preparation of new xanthates by conjugate addition of xanthic acid to various electrophiles,[8] xanthate **1** was prepared in poor yield (15%) by reaction of the corresponding *N*-crotonanilide with potassium *O*-ethyl xanthate in a mixture of trifluoroacetic acid (TFA) and dichloromethane (DCM). However, to our surprise, refluxing **1** in chlorobenzene or 1,2-dichloroethane (DCE) in the presence of a stoichiometric amount of lauroyl peroxide led to dihydroquinolinone **2** in 57% yield (Scheme 1). This result was particularly unexpected in view of the trans-conformational preference of most secondary amides[9] and because of related studies,[10a] which seemed to indicate that substitution of the free position on the amide nitrogen was required to achieve radical cyclisation in synthetically useful yields. Only in the synthesis of homophthalimides could we perform the ring closure in the absence of a substituent on the nitrogen but this required a reaction temperature of 160 °C.[10b]

To circumvent the lack of reactivity of the parent anilide towards conjugate addition, an electron-withdrawing isobutoxycarbonyl group was placed on the nitrogen

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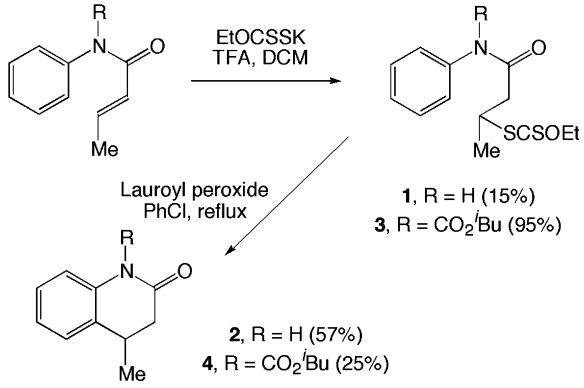
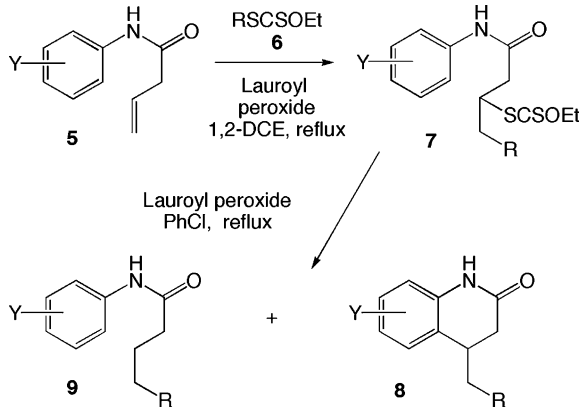


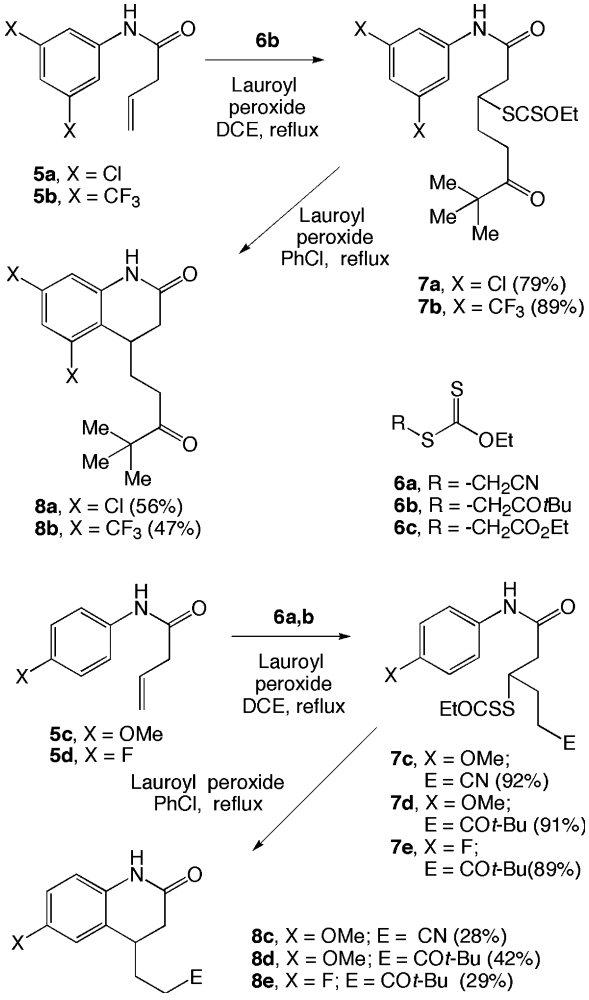
Scheme 1.

of the amide. In this case, the Michael addition proceeded smoothly to give xanthate **3** in excellent yield. Unfortunately, and very surprisingly, the radical cyclisation of the latter was more sluggish, leading to dihydroquinolinone **4** in only 25% isolated yield.

This is the first instance to our knowledge where a secondary amide cyclises more efficiently than a substituted imide. The unexpected lack of reactivity in the present case may arise from the geometry of the system which puts the radical centre too far from the aromatic ring, slowing down the process and thus allowing side reactions to occur. Selective removal of the isobutoxycarbonyl group in the presence of the xanthate proved difficult.[11] Another strategy outlined in Scheme 2 was therefore considered, relying on the xanthate transfer method. An efficient access to cyclisation precursors could indeed be provided by means of the powerful intermolecular radical addition of xanthates to unactivated olefins. Hence readily accessible, unprotected, butenanilides **5a–d**[12] underwent the radical addition of xanthates **6a–c** to give the desired adducts **7a–e** in very good isolated yields (Scheme 3). These adducts were then refluxed in chlorobenzene in the presence of stoichiometric amounts of lauroyl peroxide, added portionwise, to give the desired 4-substituted dihydroquinolinones **8a–e**, which were isolated in moderate yield (28–56%) along with 9–13% of the reduced noncyclised material (corresponding to **9** in Scheme 2).



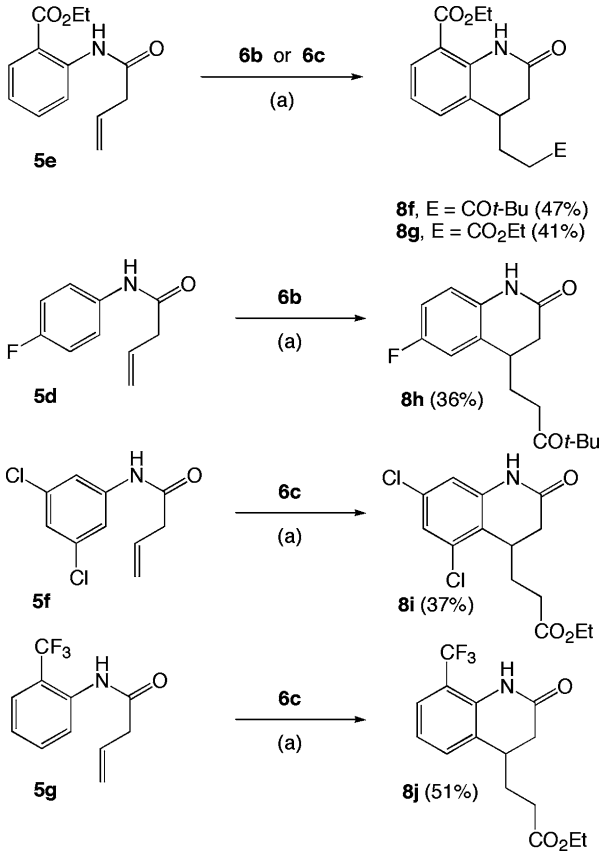
Scheme 2.



Scheme 3.

The radical cyclisation appears to be rather insensitive to the electronic nature of the aromatic ring. Formation of dihydroquinolones **8b** and **8d** from adducts **7b** and **7d**, containing, respectively, an electron poor and an electron rich aromatic ring, took place in roughly the same yield. This fact is particularly interesting in the case of **8b**. The presence of two strongly electron-withdrawing trifluoromethyl groups essentially eliminates the possibility of relying on the classical Friedel–Crafts-type of reaction to access such a structure. Our method thus allows the easy preparation of fluorinated compounds, which are known to be of some importance in medicinal chemistry as well as in agrochemistry.[13]

In the light of these encouraging preliminary results, the two-step sequence was simplified since the intermediate xanthate adducts could be directly engaged in the cyclisation step without purification. For this purpose, the 1,2-dichloroethane used in the first step was simply replaced by chlorobenzene at the completion of the intermolecular radical addition, as indicated by the disappearance of the starting anilide **5**. The cyclisation was then performed by portionwise addition of a stoichiometric amount of lauroyl peroxide to furnish the desired dihydroquinolones **8f–j** in useful overall yields (36–51%;



Scheme 4. Reagents and conditions: (a) lauroyl peroxide, DCE, reflux, lauroyl peroxide, PhCl, reflux.

this corresponds to an average of 60–70% yield per step) as shown in Scheme 4.[14] Once again the main side product found in the crude mixture (5–16%) is the reduced uncyclised intermediate adduct corresponding to **9** in Scheme 2. The slightly higher yields observed when electron-withdrawing groups are present on the aromatic ring can be ascribed to the moderate nucleophilic character of the cyclising radical.

In conclusion, we have developed a convergent and short access to 4-substituted 3,4-dihydroquinolin-2(1*H*)-ones. These deceptively simple-looking compounds would be quite tedious and difficult to make by classical methods. The starting materials and reagents in the present route are cheap and readily available; the reaction conditions are mild and the process is compatible with a broad spectrum of functional groups, both on the aromatic ring and the xanthate, allowing infinite variations on the structures. But perhaps most importantly, we have documented the first and probably quite rare instance where the radical cyclisation of a secondary amide is more efficient than that of the corresponding fully substituted imide analogue.

Acknowledgements

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11. After some experimentation, the best protecting group for the transformation was found to be a methoxycarbonyl group, giving xanthate **2** in 43% overall yield on the protection/conjugate addition/deprotection/sequence, starting from the crotonanilide.
12. Prepared by reaction of commercial anilines and vinylacetyl chloride in dichloromethane at rt.
13. For a recent review on the use of fluorine in the life science industry, see: Maienfisch, P.; Hall, R. G. *Chimia* **2004**, *58*, 93.
14. The preparation of **8h** is representative: a solution of amide **5d** (370 mg, 2.07 mmol) and xanthate **6b** (300 mg, 1.36 mmol) in 1,2-dichloroethane (3 mL) was refluxed for 15 min under a slow stream of argon before DLP was added (27 mg) from the top of the condenser. Portions of DLP (16 mg) were added every 90 min until complete consumption of the starting xanthate. The solvent was evaporated and replaced by chlorobenzene (15 mL). The mixture was then refluxed for 15 min under argon before adding portions of DLP (110 mg) every 30 min until complete disappearance of the intermediate (TLC monitoring). Concentration under reduced pressure afforded a yellow residue, which was submitted to flash silica gel chromatography eluting with petroleum ether/EtOAc (10–40%) to give **8h** (138 mg, 36%) as a white solid, mp 156–157 °C. IR (CCl_4, cm^{-1}) ν_{max}: 3200, 1706, 1682. ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (9H, s), 1.75–1.91 (2H, m), 2.48–2.54 (3H, m), 2.74 (1H, dd, $^2J = 16.4$ Hz, $^3J = 6.0$ Hz), 2.95–3.00 (1H, m), 6.82–6.90 (3H, m), 9.74

(1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 27.4, 33.0, 35.3, 35.6, 44.1, 114.5 (d, $^2J_{CF} = 23$ Hz), 114.7 (d, $^2J_{CF} = 23$ Hz), 117.1, 128.6 (d, $^3J_{CF} = 7$ Hz), 132.6, 158.6 (d, $^1J_{CF} = 241$ Hz), 171.4, 215.1. MS (CI, *m*/*z*) 295 $[MNH_4]^+$, 278 $[M]^+$. Anal. Calcd for $C_{16}H_{20}FNO_2$: C, 69.29; H, 7.27. Found: C, 69.06; H, 7.24.