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A Convergent Synthesis of 4-Substituted 1,2,3,4-Tetrahydroisoquinolin-1-ones

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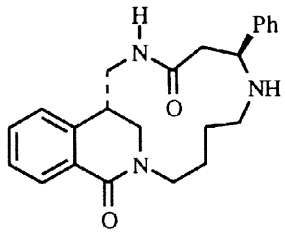
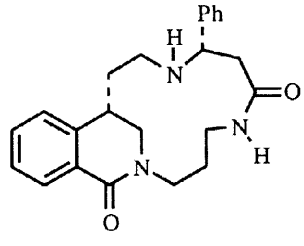
Abstract : A variety of 4-substituted 1,2,3,4-tetrahydroisoquinolin-1-ones **6** can be prepared by a two step radical sequence: intermolecular xanthate transfer addition to an N-allylbenzamide followed by cyclisation onto the aromatic ring.

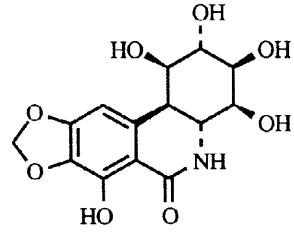
We wish to report a simple, convergent, and versatile route for the construction of 4-substituted 1,2,3,4-tetrahydroisoquinolin-1-ones. The tetrahydroisoquinoline substructure is quite common in natural products (e. g. the large and varied group of isoquinoline alkaloids)[1] and in a number of biologically active synthetic derivatives.[2] The long list of articles and patents dealing with the synthesis of such heterocycles is a testimony to their importance.[3] Thus, in addition to the classical methods, which include the well known Bischler-Napieralski, the Pictet-Spengler, and the Pomeranz-Fritsch reactions, other strategies have emerged in more recent times, and numerous modifications and improvements of the older processes have been devised.[3] 4-Substituted derivatives, exemplified by the two spermidine alkaloids cyclocelabenzine **1a** and isocyclocelabenzine **1b**,[4] are generally less easily accessible than other members of the tetrahydroisoquinoline family. Indeed, in the reported syntheses of **1a** and **1b**, the main difficulty was the synthesis of the tetrahydroisoquinolinone core.[5] Pancratistatine, **2**, is another tetrahydroisoquinolinone natural product (of the *Amaryllidaceae* family) that is attracting much attention because of its remarkable anticancer and antiviral activity.[6]



1a Cyclocelabenzine



1b Isocyclocelabenzine



2 Pancratistatine

Practically all of traditional approaches rely on ionic or, but to a lesser extent, organometallic intermediates.[7] Radical reactions in contrast have hardly been used in this area.[8] Lack of generality and convergence, inaccessibility of appropriate precursors, and the inherent difficulty in building 6-membered

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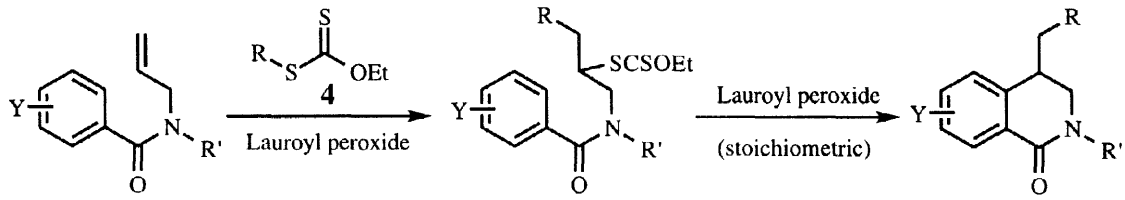
(as compared to 5-membered) rings by a radical cyclisation[9] are some of the main hurdles that must be overcome. The last point is especially important: If the cyclisation is to start from the aromatic site onto a suitably located olefin in the side chain, by the action for example of stannyl radicals on a substituted *o*-bromo- or iodo-benzamide, then allylic hydrogen abstraction by the highly reactive aromatic radicals can compete seriously with the desired cyclisation.[10] If, on the other hand, the radical is first produced on the side-chain, then the cyclisation onto the aromatic nucleus is usually too sluggish to compete with other pathways open to the radical. These alternative pathways depend on the method used; with stannane chemistry, it is the rapid hydrogen atom transfer from the stannane.[9]

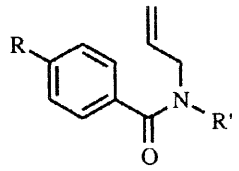
Many of these shortcomings disappear if the radical in the side chain is created starting from a xanthate, according to an original process we have developed over the past few years.[11] Because of the redundancy of the main side reaction, the intermediate radicals acquire a long effective lifetime enabling them to undergo some quite difficult cyclisations, including 5- or 6-membered ring closures onto aromatic rings.[12] Moreover, it is possible to perform *intermolecular* additions on unactivated olefins. The desired precursors for the synthesis of the tetrahydroisoquinolones can therefore be readily assembled, in a highly convergent and versatile manner, as outlined in Scheme 1.



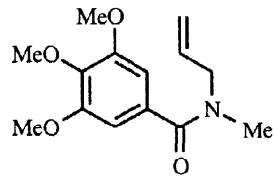
3 **5** **6**

Scheme 1

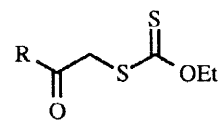
The synthesis of the starting N-allyl benzamides is accomplished very simply, either by reacting the aroyl chloride with the appropriate substituted allylamine or by alkylating an unsubstituted N-allyl aroylamide in the presence of base. We used the latter route in most cases. As for the xanthate partner **4**, it is made by treating the corresponding halide with commercially available and cheap potassium *O*-ethyl xanthate. The first radical addition was performed by heating xanthates **4a-e** (2 eq.) with variously substituted benzamides **3a-f** in refluxing 1,2-dichloroethane under an inert atmosphere, using dilauroyl peroxide as initiator. This first step is a chain reaction and only a small amount of peroxide (0.25 eq., added portionwise over several hours) is required.



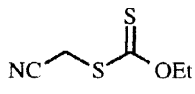
3a, R = H; R'= Et
3b, R = OMe; R'= Me
3c, R = Br; R'= Me
3d, R = F; R'= Me
3e, R = F; R'= CO_2Me



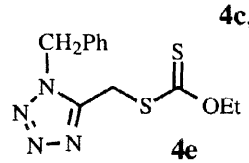
3f



4a, R = Me
4b, R = ^tBuO-
4c, R = Me_3C-

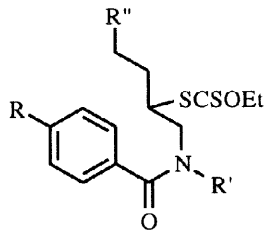


4d

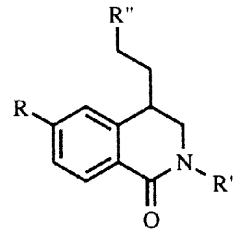


4e

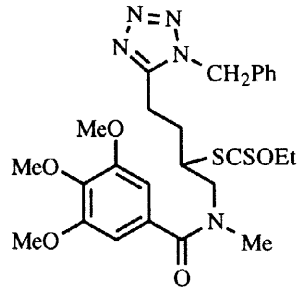
In this manner, the desired precursors **5a-k** were obtained in 41%-65% yield. The cyclisation step, in contrast, is not a chain; and stoichiometric amounts of the peroxide are needed, both to generate the radical from the xanthate and to oxidise (and thus aromatise) the intermediate cyclohexadienyl radical adduct.[12a,13] The reaction is performed by adding dropwise a solution of lauroyl peroxide (1.2 eq.) in chlorobenzene over about one hour to a refluxing solution of the xanthate in chlorobenzene under an inert atmosphere. Evaporation of the solvent and chromatographic purification over silica gel furnishes the corresponding tetrahydroisoquinolinones **6a-k** in 46-63% yield.



5

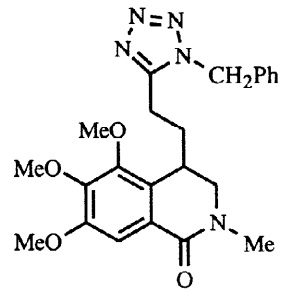


6

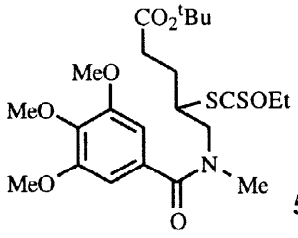


5k (64%)

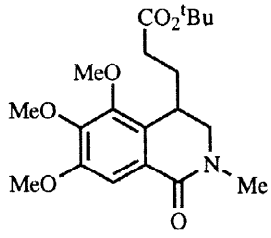
a, R = H; R'= Et; R"= COMe (**5a**, 57%; **6a**, 61%)
b, R = H; R'= Et; R"= CN (**5b**, 60%; **6b**, 49%)
c, R = OMe; R'= Me; R"= COMe (**5c**, 44%; **6c**, 63%)
d, R = OMe; R'= Me; R"= CN (**5d**, 43%; **6d**, 63%)
e, R = OMe; R'= Me; R"= $CO_2{}^tBu$ (**5e**, 47%; **6e**, 60%)
f, R = Br; R'= Me; R"= $CO_2{}^tBu$ (**5f**, 57%; **6f**, 62%)
g, R = F; R'= Me; R"= COMe (**5g**, 58%; **6g**, 57%)
h, R = F; R'= Me; R"= CN (**5g**, 65%; **6g**, 46%)
i, R = F; R'= CO_2Me; R"= COMe (**5g**, 61%; **6g**, 53%)



6k (48%)



5j (43%)

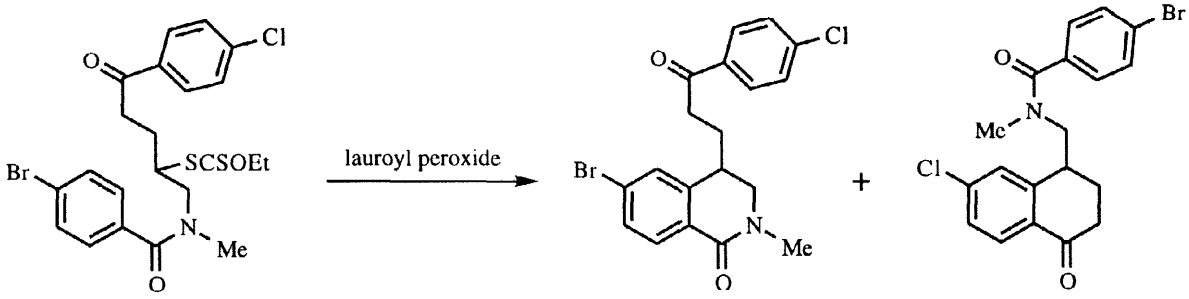


6j (51%)

No attempt has yet been made to optimise the yields, and room for improvement certainly exists. Nevertheless, the advantages of this fairly general approach to 4-substituted tetrahydroisoquinolinones are worth underlining: cheap and almost trivially available starting materials and reagents; mild experimental conditions and tolerance for a variety of functional groups, both on the aromatic ring and on the portion derived from the xanthate; and, finally, a high degree of convergence. The last point is of some importance since quite complex structures (e. g. **6k**) can be assembled using two consecutive radical steps that are normally quite difficult to achieve by more traditional methods. This is especially true for the first intermolecular addition step. It is, incidentally, also possible to have a protecting group on the nitrogen atom (e. g. carbomethoxy group as in compound **6i**), which can be removed and replaced by another substituent, thus further widening the scope.

One final observation is worth mentioning. We found that the presence of the nitrogen atom (with a

non-bulky methyl group) does not apparently affect the rate of cyclisation in comparison with the all carbon analogue. This was revealed by the transformation of xanthate **5l** as pictured in Scheme 2: Both tetrahydroisoquinolinone **5l** and tetralone **7** were obtained in nearly equal amounts.



5l **6l** (33%) **7** (36%)

Scheme 2

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