CARBONYL RADICAL CYCLIZATIONS: PREPARATION OF SOME HETEROCYCLIC KETONES

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This communication is dedicated to Professor Sir Derek H.R. Barton F.R.S. on the occasion of his 70th birthday.

Abstract - It has been possible to synthesize 3-methylchromanone, 3-methylthiochromanone and 2,3-dihydro-3-methylquinolin-4-one from salicylic acid, thiosalicylic acid and anthranilic acid respectively by carbonyl radical cyclizations.

The application of free radical cyclization reactions in organic synthesis is an area of much current interest and a number of review articles have been published[1] recently. By far the most common approach adopted is that involving the rearrangement of substituted 5-hexenyl radicals to substituted cyclopentylmethyl radicals; radical generation is most commonly achieved by reaction of a stannyl radical with an alkyl halide or pseudo-halide and chain transfer by hydrogen abstraction from a stannane. This approach, albeit an excellent method for the formation of five membered rings, suffers from one major disadvantage in so far as it converts a bifunctional substrate into a product devoid of functionality useful for further synthetic operations. Various approaches have been devised or discovered, which overcome this limitation. Thus Clive and others have focused[2] on cyclization onto alkynes and nitriles and Stork has introduced[3] vinyl radical cyclizations. Curran has demonstrated[4] the applicability of iodine atom transfer reactions to organic synthesis, Pattenden has adopted[5] an approach based on organocobaloximes and Fraser-Reid has shown[6] how aldehydes function as efficient intramolecular radical traps. Cyclizations with chain transfer by attack at sulphur and selenium have been achieved by Barton[7] and Ueno[8] respectively whilst a totally different approach, illustrated[9] by Danishefsky, involves a tandem cyclization/elimination sequence.

We have concentrated[10] on the use of carbonyl radical cyclizations with a view to the direct generation of cycloalkanones. Furthermore we have deliberately

directed our work towards the preparation of six-, rather than the more usual five-membered, rings in an attempt to expand the domain of radical cyclization reactions. A similar approach has been taken up[11] by Bachi following his successful synthesis[12] of α-methylene-γ-lactones by alkoxycarbonyl radical cyclizations. We wish to report here the extension of our carbonyl radical cyclization reactions to the preparation of some simple six-membered heterocyclic ketones as well as on some apparent limitations of the method.

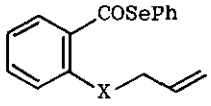
Thus selenol esters (1) and (2)[13] were prepared from O-allylsalicylic acid and S-allylthiosalicylic acid, in 69 and 48% yields, respectively by treatment of the derived acyl chlorides with sodium phenylseleno(triethoxy)borate[14] in ethanol. In our opinion, when the acyl chlorides are accessible, this procedure is much more convenient than that used[15] by Graf involving their treatment with selenophenol in benzene. Treatment of (1) and (2) in benzene at reflux with tri-n-butyltin hydride and a catalytic quantity of azobis(isobutyronitrile) (AIBN) gave, after column chromatography on silica gel, the chromanone (5) and the thiocromanone (6) in moderate to good yields (Table, entries 1 and 2).

Attempts at the formation of a selenol ester (4) from acid (3), itself obtained in 44% isolated yield by treatment of N-acetylanthranilic acid with excess sodium hydride and then allyl bromide in dimethyl sulphoxide (DMSO), by a procedure analogous to that for (1) and (2) were unsuccessful. However an excellent yield, 85%, of crystalline (4) was achieved by treatment of (3), in tetrahydrofuran at -15°C, with N-methylmorpholine and isobutyl chloroformate according to a procedure[16] widely applied in peptide synthesis, followed by ethanolic sodium phenylseleno(triethoxy)borate. Reaction of (4) with tri-n-butyltin hydride and AIBN at 80°C afforded the dihydroquinolinone (7) in moderate yield (Table, entry 3).

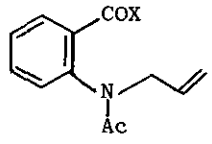
In an attempt to extend the method to the formation of homochiral pyrrolizidine derivatives L-pyroglutamic acid (8) was treated with excess sodium hydride and allyl bromide in DMSO to give 71% of the N-allyl allyl ester (9) which was saponified to (10) in 72% yield. Application of the mixed anhydride/sodium phenylseleno(triethoxy)borate methodology gave the selenol ester (11) in 69% yield. Unfortunately reaction of (11) with tri-n-butyltin hydride under the standard conditions gave only the product (12) of reductive decarbonylation (Table entry 4). In a similar vein S-allyl-L-cysteine, protected as its N-benzyl

oxycarbonyl derivative (13), was transformed, in 73% yield by the mixed anhydride/ sodium phenylseleno(triethoxy)borate method, to the selenol ester (14), but here too attempts at radical cyclization were unsuccessful with decarbonylation followed by β-elimination apparently being the major pathway. Evidently the use of α-aminocarbonyl radicals is precluded by their rapid decarbonylation to stabilized aminoalkyl radicals.

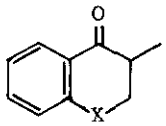
Finally by replacing tri-n-butyltin hydride with the activated allylstannane (15), prepared [17] according to Baldwin, we were able to synthesize chromanone (16) from selenol ester (1) in a one pot tandem radical cyclization/addition/β-elimination sequence (Table, entry 5).



(1) X = O
(2) X = S



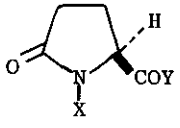
(3) X = OH
(4) X = SePh



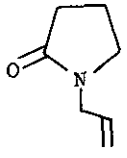
(5) X = O
(6) X = S
(7) X = NAc

Table

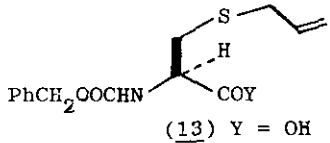
Entry	Substrate	Product (% Yield)
1	(1)	(5) (52)
2	(2)	(6) (66)
3	(4)	(7) (44)
4	(11)	(12) (73)
5	(1)	(16) (23)



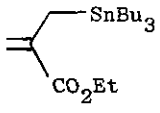
(8) X = H, Y = OH
(9) X = $CH_2CH{=}CH_2$, Y = $OCH_2CH{=}CH_2$
(10) X = $CH_2CH{=}CH_2$, Y = OH
(11) X = $CH_2CH{=}CH_2$, Y = SePh



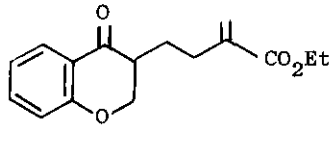
(12)



(13) Y = OH
(14) Y = SePh



(15)



(16)

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