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FACILE SYNTHESIS OF FUNCTIONALISED SPIROETHERS VIA RADICAL CYCLISATIONS

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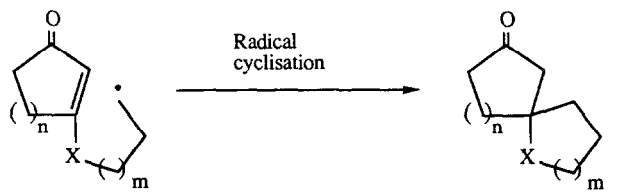
ABSTRACT: Alcohols bearing suitable chains for radical initiation are smoothly condensed with cyclic β-diketones to afford systems which undergo radical cyclisation to give various spiroether products.

During the last few years, there has been an enormous interest in the development of synthetic methods which rely on free radicals to form new carbon-carbon bonds.[1] Intramolecular radical cyclisations, and tandem bis-cyclisations have proven especially useful, and have found elegant applications in natural product synthesis.[2] We were attracted to the possibility of using radical cyclisations for the synthesis of spiro-systems such as (1), Scheme 1.



(1) X = CH_2, O, NR
n,m = 1, 2 . .

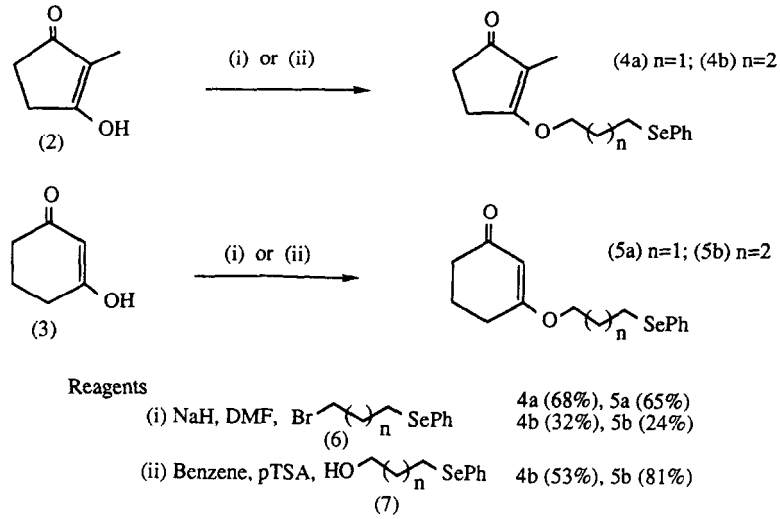
Scheme 1

We anticipated that this approach would avoid potential problems associated with generating sterically hindered spiro-centres, such as β-elimination (for X=O), whilst allowing us to incorporate a variety of useful functionality in the products.

A variety of natural products incorporate subunits related to (1), for example the ginkgolides ($X=CH_2$),[3] the histrionicotoxin and cephalotaxus alkaloids (X=NR),[4] and a variety of oxaspirocyclic terpenes (X=O).[5] Although a number of methods are available for the synthesis of such compounds [6] the preparation of spiro-systems by means of radical reactions has been largely ignored.[7]

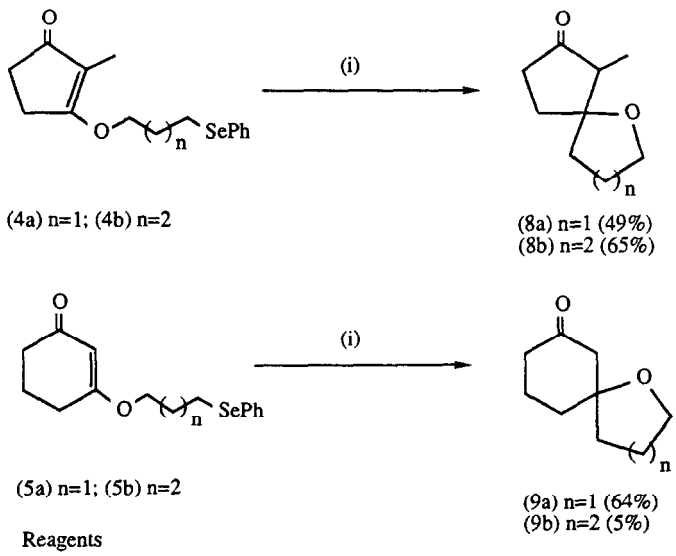
Here we describe direct and versatile radical chemistry which furnishes a variety of functionalised spiroethers, starting from simple β-diketones, and readily available alcohols which are substituted with functional groups suitable for the initiation of the cyclisation process outlined above.

The commercially available β-diketones (2) and (3) were converted straightforwardly to the intermediates (4) and (5) having terminal phenylseleno groups, Scheme 2.



Scheme 2

Thus, alkylation of the sodium anion of (2) or (3) with the selenobromides (6, n=1,2) gave the desired products (4a) and (5a) in good yield. However, direct condensation of selenoalcohol (7, n=2) with diketones (2) or (3) under Dean-Stark conditions was found more convenient and higher yielding for the preparation of (4b) and (5b).[8] Slow addition of a mixture of Bu_3SnH and AIBN in benzene to a solution of (4) or (5) in refluxing benzene (0.02M) over 6h resulted in cyclisation to give the anticipated products as shown in Scheme 3.[9]



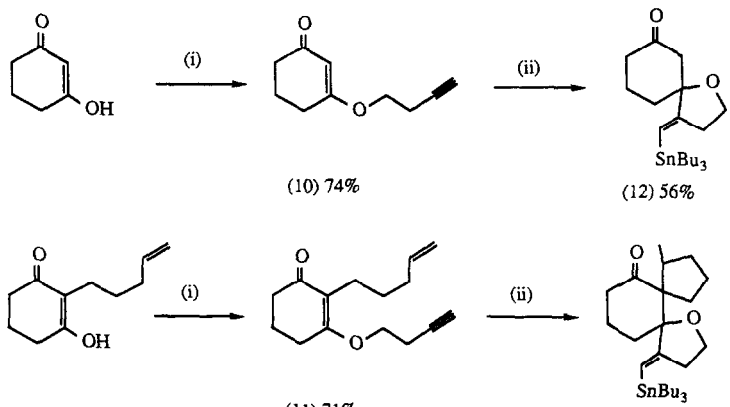
Scheme 3

The five-membered ring products (8a) and (8b) were both formed as mixtures of diastereoisomers (*ca* 1:1) in contrast to the formation of (13) as a single diastereoisomer, *vide infra*..

Under these reaction conditions simple reduction of the starting material was minimised, although this still proved the major reaction pathway in the case of (9b).[10]

In our hands the use of selenides (as opposed to the corresponding bromides) was preferred, since this avoided the need for a work-up procedure; reaction mixtures were simply evaporated and the residue directly chromatographed.[11]

In order to further examine the scope of this chemistry, and to provide more complex functionalised spiroether products, we next prepared the acetylenic compounds (10) and (11) by condensation of the appropriate diketone with 3-butyn-1-ol. These compounds appeared ideally suited to the recently reported hydrostannylation-cyclisation procedure, and we were pleased to find that reaction with Bu_3SnH under our standard conditions provided products (12) and (13) both as single geometric isomers about the vinyl stannane double bond.[12]



Reagents

(i) Benzene, pTSA, 80°C, HO

(ii) Bu_3SnH, Benzene, AIBN, 80°C

Scheme 4

Remarkably the tricyclic product (13) was also isolated as a single diastereomer, thus a new olefin and three new chiral centres had been formed in one step with a high level of stereocontrol.[13] Presumably this result reflects the more efficient stereoelectronic control operating in cyclisation onto the six-membered ring leading to (13), compared with the five membered ring (to give 8a or 8b), as well as the greater steric demand for bis-cyclisation as opposed to simple H· abstraction. Further investigation of the stereochemical aspects of these reactions as well as extension to spiroamine systems is underway.

The simple and direct synthesis of the polyfunctionalised spiroethers (12) and (13) indicates the potential of this method as a synthetic avenue to a variety of hetero-spirocyclic natural products.

Acknowledgements

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7. The synthesis of spiroalkanes ($X=CH_2$) by this method has received some attention, see; O. Moriya, Y. Urata, Y. Ikeda, Y. Ueno, and T. Endo, J. Org. Chem., 1986, 51, 4708; R. Scheffold, G. Rytz, L. Walder, R. Orlinski, and, Z. Chilmonczyk, Pure and Appl. Chem., 1983, 55, 1791; S.Danishefsky, S. Chackalamannil, and B - J. Uang, J. Org. Chem., 1982, 47, 2231.
8. As can be seen from the yields, whilst the alkylation of (2) or (3) with (6, n=1) was quite satisfactory, the use of (6, n=2) gave poor results. We attribute this to difficulties in the preparation and purification of (6, n=2) from the corresponding alcohol (using NBS/PPh_3 in CH_3CN). The direct condensation of alcohols with the diketones gives better results and avoids the need to prepare the bromides (6).
9. In the preparation of (9a) we conducted the radical cyclisation reaction at a number of concentrations. The percentage of cyclised and reduced product in each case was; 0.25M (30%, 54%); 0.08M (42%, 48%);0.02M (64%, 27%). Further dilution did not significantly increase the yield of cyclised material.
10. Danishefsky reports similarly low yields (10%) in the radical cyclisation leading to the analogous spiro carbocyclic product, see reference 7.
11. The preparation of (9a) is representative of our standard procedure: To a refluxing solution of enone (5a) (0.912 g, 2.94 mmol) in benzene (100 ml) was added a mixture of Bu_3SnH (0.941 g, 1.1 eq.) and AIBN (96 mg, 0.2eq.) in benzene (50 ml), dropwise over 6h. After refluxing for an additional hour the solution was cooled, concentrated *in vacuo* , and chromatographed (10-40% ether in petroleum ether) to yield the spiroether (9a) (0.291 g, 64%).
12. In the cases of (12) and (13) the olefin geometry shown has not been proven, and is based on previous literature results; see; K. Nozaki, K. Oshima, and K. Utimoto, J. Am. Chem. Soc., 1987, 109, 2547; G. Stork and R. Mook Jr., J. Am. Chem. Soc., 1987, 109, 2829.
13. We have been unable to detect the presence of stereoisomers of (13), and are currently attempting to assign the relative stereochemistry of this compound.

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