Efficient oxidative radical spirolactamization†

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An efficient xanthate-based method for the preparation of azaspirocyclic cyclohexadienones *via* an *ipso* oxidative radical cyclization of *p*-oxygenated *N*-benzylacetamides and *N*-phenetylacetamide is described.

Azaspirocyclic cyclohexadienones are pivotal synthetic intermediates in the preparation of an extensive range of biologically active molecules.[1] Recently the azaspirocyclic core was shown to be present in annosqualine **1**, a natural product isolated from the stems of *Annona Squamosa* (Fig. 1).[2] Furthermore, the reduced congeners 2-azaspiro[4.5]decane and 2-azaspiro[5.5]undecane have a variety of biological activities.[3] For instance, the azaspirane **2** has inhibitory action in KB cells and cells of human mammary cancer grown in tissue culture.[4] The spiropiperidine BL1743[5] is an antiviral and L687384[6] is a potent and selective σ-receptor ligand (Fig. 1).

Several strategies have been reported for the construction of azaspirocyclic cyclohexadienone systems. The formation of azaspirocycles from *p*-MeO-benzene derivatives was observed in the acid-catalyzed cyclization of aromatic diazoacetamides[7] and also in the intramolecular addition of stabilized enolates to (η^6-arene)ruthenium complexes.[8] Radical spirocyclization onto a *p*-MeO-aryl ring was first observed by Hey and Todd[9] in 1967, but the process was of limited synthetic value. Zard and co-workers have observed the formation of one azaspirocyclic cyclohexadienone in moderate yield, by a nickel/acetic acid induced oxidative *ipso*-type radical cyclization onto *p*-MeO-benzenoid systems.[10] Very recently, Gonzalez-Lopez de Turiso and Curran[11] reported a similar $(TMS)_3SiH$-mediated cyclization, but only low yields of the spirocyclic systems were obtained. Herein, we describe an efficient method for the preparation of highly substituted azaspirocyclic cyclohexadienones *via* an *ipso* oxidative radical cyclization of *p*-oxygenated *N*-benzylacetamides and homologs thereof (*e.g.*, Scheme 1).[12] Our studies commenced with the readily available xanthate **5a**,[13] which upon reaction with a slight excess (1.2 equiv.) of dilauroyl peroxide in 1,2-dichloroethane at reflux temperature, was converted exclusively into the spirocyclic derivative **6**.[14] Under the same conditions, the *p*-hydroxylated compound **5b** also gave **6** in nearly quantitative yield.

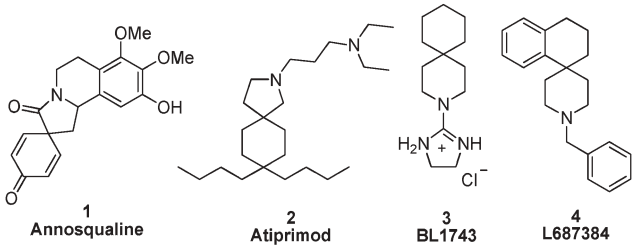
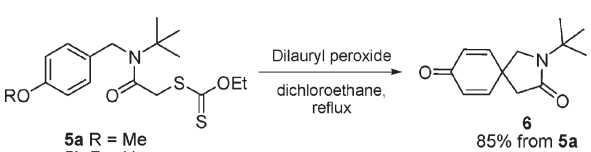


Fig. 1 Azaspirocycles.

To investigate the scope of the spirolactamization process, a series of *p*-alkoxylated *N*-benzyl and *N*-phenethylacetamido derivatives (Table 1) was prepared and subjected to the above reaction conditions. The expected spirolactams were obtained as the exclusive, or major products in all cases. It is noteworthy that the presence of one or more substituents (MeO, Me, Br) *ortho* or *meta* to the *p*-alkoxyl moiety does not derail the spirocyclization process (entries 1–5) and a *p*-isopropoxy group also leads to the expected product (entry 7). Furthermore, 3-azaspiro[5.5]undecane systems (*e.g.*, compounds **20a** and **20b**; entry 7) are readily generated starting from *N*-*p*-alkoxylphenethylacetamides. Secondary xanthates can also be used, in which case azaspirocyclohexadienones containing a methyl substituent α to the lactam carbonyl group are produced (entry 6). The remaining *N*-substituent in the starting materials does not have to be a *tert*-butyl group, since the *N*-isopropyl (entry 7) and the *N*-dimethoxylphenethyl (entry 11) compounds also gave rise to spiro products. The xanthate **21** is a particularly interesting substrate since the formation of both 2-azaspiro[4.5]decane and 3-azaspiro[5.5]undecane systems is possible (entry 8). Nevertheless, the only spiro product isolated (65% yield), containing the [4.5]decane system, was compound **22**. Finally, the formation of the spiro compound **24**, derived from the naphthalene precursor **23** indicates that this process does indeed have considerable scope (entry 9).

A possible mechanistic rationalization for the formation of the spiro compounds is depicted in Scheme 2. The cyclohexadienyl radical **26** produced from the *ipso*-cyclization, is then oxidized to the oxonium ion **27**, or the corresponding protonated species, by lauroyl peroxide. The oxonium ion would then be transformed into the observed product in the reaction medium or upon workup of the reaction mixture. The success of the reaction is dependent on



Scheme 1

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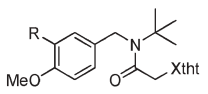
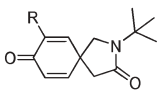
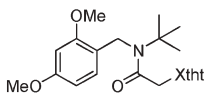
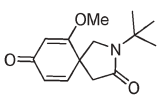
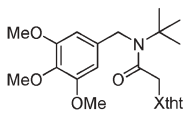
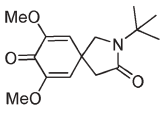
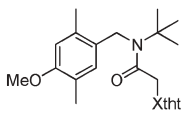
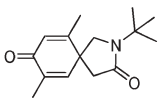
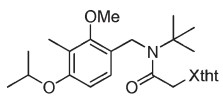
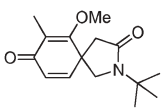
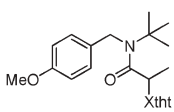
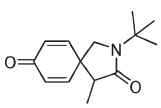
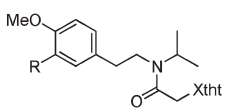
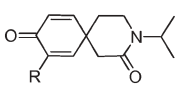
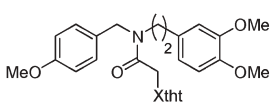
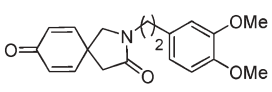
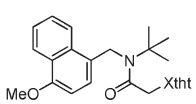
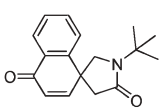
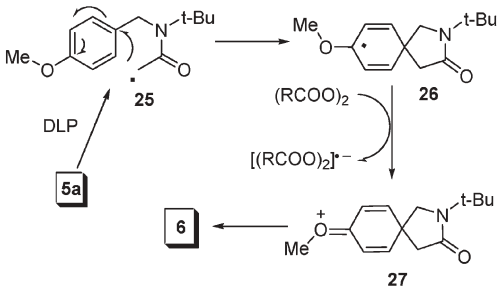
[b]*Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior S. N., Ciudad Universitaria, Coyoacán, México D. F. 04510, México. E-mail: lmiranda@sevidor.unam.mx; Fax: (+52) 55 56 16 22 17; Tel: (+52) 55 56 22 44 40*
† Electronic supplementary information (ESI) available: Experimental details and spectroscopic data for all new compounds. See DOI: 10.1039/b705397e

Table 1

Entry	Xanthate	Azaspirocycle
1	 **7a** R = OMe **7b**, R = Me **7c** R = Br	 **8a** R = OMe 75% **8b**, R = Me 83% **8c** R = Br 75%
2	 **9**	 **10**, 85%
3	 **11**	 **12**, 70%
4	 **13**	 **14**, 65%
5	 **15**	 **16**, 74%
6	 **17**	 **18**, 68%
7	 **19a** R = H **19b**, R = OMe,	 **20a** R = H 65% **20b**, R = OMe 57%
8	 **21**	 **22**, 65%
9	 **23**	 **24**, 65%

[a] Xtht = SC(S)OEt.



Scheme 2

the use of slightly more than one equivalent of the peroxide, and this stoichiometry is consistent with the proposed oxidation mechanism.

The efficacy of the *ipso* cyclization may be a consequence of both a polarity match between the attacking electrophilic radical and the nucleophilic *ipso* benzenoid carbon (*para* to the methoxyl group) as well as to the formation of the highly resonance stabilized radical **26**.

In short, we have developed a novel, simple, and efficient procedure for the synthesis of highly functionalized 2-azaspiro-[4.5]decan-3-ones and 3-azaspiro[5.5]undecan-4-ones. We are currently studying the synthetic consequences of, and the mechanistic questions which, have been raised by the results described herein.

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Notes and references

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14 *Typical procedure for radical spirocyclization*. A deaerated solution of the corresponding xanthate (1.0 mmol) in 1,2-dichloroethane (5 mL) was heated at reflux and 10% mol lauryl peroxide (1.2–1.5 mmol) was then added every 1 h until complete consumption of the xanthate was observed by TLC. The solvent was removed under reduced pressure and the residue purified by chromatography on a silica gel column (hexane–EtOAc) to furnish the desired product. *Selected spectral data for* **6**. IR (neat, cm^{-1}): 1676, 1628; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, 2H, J = 10.2 Hz), 6.34 (d, 2H, J = 10.2 Hz), 4.49 (s, 2H), 2.54 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 185.0, 171.6, 150.1, 129.3, 54.6, 53.0, 42.6, 40.8, 27.6; EI-MS *m/z* (%) 219 (M^+, 65); HRMS (FAB+) *m/z* calc. for $C_{13}H_{18}NO_2$ ($M + H^+$) 220.1338, found 220.1337.