An unusual approach to spirolactones and related structures

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Spirocyclic structures can be obtained by an *ipso*-type radical cyclisation onto a furan or a suitably substituted pyrrole followed by oxidation of the stabilised radical adduct.

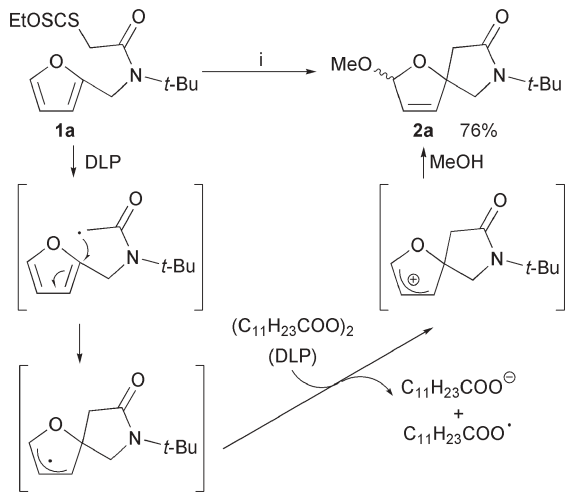
The intramolecular radical cyclisation to aryl rings followed by re-aromatisation is well known for the synthesis of polycyclic derivatives. In contrast, the *ipso*-type radical cyclisation, which proceeds with overall de-aromatisation, is less well documented, although spirocyclisation examples exist of various aromatic rings such as benzenes,[1] pyrroles,[2] indoles[3,4] or benzofurans.[4] This reaction has also been studied with furans, but only in the particular case of vinyl radicals, resulting in a mixture of the spirocyclic compound and the product of fragmentation.[5]

We have previously noted, in one particular case, that a furan could lead to a product of spirocyclisation upon radical addition. This may be due to the poorer aromatic character of a furan in comparison with a benzene ring, which furnishes the product of normal cyclisation and re-aromatisation under the same conditions.[6] We have now found that this process is in fact quite general with furans and opens the way to complex spirocyclic structures. In the past, such structures have been constructed by electrosynthesis[7] or through a vinylogous Mannich reaction of 5-alkoxyfurans.[8]

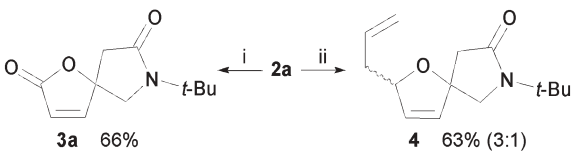
We first prepared xanthate **1a** and found that it was converted into spirocyclic derivative **2a** in good yield upon exposure to stoichiometric quantities of lauroyl peroxide in a refluxing 3 : 1 mixture of 1,2-dichloroethane (DCE) and methanol (Scheme 1). In a first step, the radical generated from the xanthate cyclises onto the C-2 position of the furan and not the C-3. The allylic radical thus produced is then oxidised to the allylic cation by electron transfer to lauroyl peroxide. The cation is then quenched with a nucleophile present in the medium, methanol in this case.

Spirolactam **2a** was obtained in good yield and the acetal function could be oxidised to lactone **3a** by *m*CPBA.[9] This eliminated one asymmetric center and facilitated the interpretation of the NMR spectra. However the acetal could also be used to introduce other functionalities such as an allyl group by a Sakurai reaction with allyltrimethylsilane (Scheme 2).

In the first instance, we briefly studied the influence of substituent R^1 on the nitrogen (entries 1 and 2, Table 1). The best result was obtained with the bulkier group (*t*-Bu). We next introduced substituents on the α position to the carbonyl (R^3) or α to the nitrogen (R^2) of the amide function (entries 3 to 5, Table 1). In all cases, good yields were obtained with the formation of two major diastereoisomers. In the case of the R^2 substituent, α to the nitrogen, the selectivity was much better and the diastereoisomers were separable. Curiously, the substrate with the smaller methyl group exhibited a better selectivity during the spirocyclisation than the analogous ethyl substituted derivative (entries 4 and 5, Table 1).

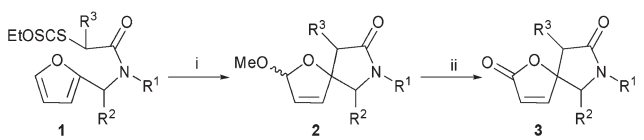


Scheme 1 *Reagents and conditions:* (i) Lauroyl peroxide (DLP), 1,2-DCE–MeOH, reflux, 76%.



Scheme 2 *Reagents and conditions:* (i) *m*CPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20/−15 °C, 66% (ii) allylTMS, TMSOTf, CH_2Cl_2, −78 °C, 63% (3 : 1).

Table 1



(i) 180–210% DLP, 1,2-DCE–MeOH, reflux (ii) *m*CPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2

Entry	R^1	R^2	R^3	Yield (**2**) (ratio)	Yield (**3**) (ratio)
1	*t*-Bu	H	H	**2a** 76% (1 : 1)	**3a** 66%
2	Boc	H	H	**2b** 59% (1 : 1)	**3b** 23%
3	*t*-Bu	H	Me	**2c** 73% (3 : 3 : 1 : 1)	**3c** 84% (3 : 1)
4	*t*-Bu	Me	H	**2d** 68% (10 : 10 : 1 : 1)[a]	**3d** 67%[b]
5	*t*-Bu	Et	H	**2e** 52% (6 : 6 : 1 : 1)[a]	**3e** 76%[b]

[a] Separable diastereoisomers. [b] Obtained from the two major diastereoisomers.

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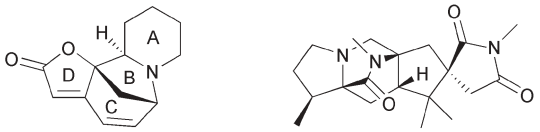
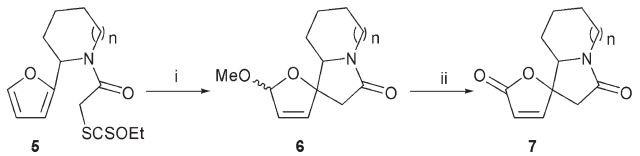


Fig. 1 (-)-Securinine and asperparaline A (1).

Table 2



(i) 180–210% DLP, 1,2-DCE–MeOH, reflux (ii) *m*CPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2

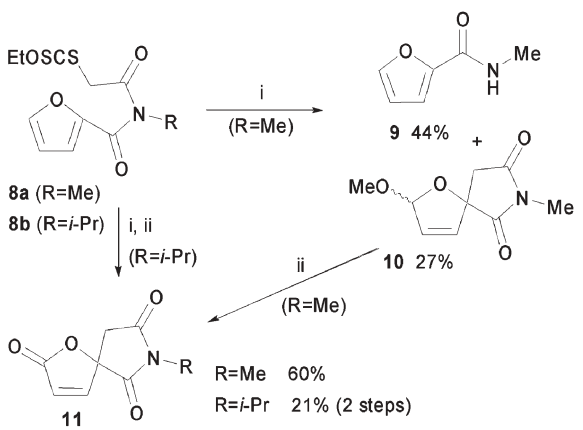
Entry	*n*	Yield (**6**) (ratio)	Yield (**7**) (ratio)
1	0	**6a** 65% (3 : 3 : 1 : 1)	**7a** 68% (3 : 1)
2	1	**6b** 48% (1 : 1 : 1 : 1)	**7b** 65% (1 : 1)[a]
3	2	**6c** 50% (1 : 1 : 1 : 1)[a]	**7c** 74% or 46%[b]

[a] Separable diastereoisomers. [b] These yields correspond to the oxidation of the separated pairs of diastereoisomers **6c**.

The two major diastereoisomers gave only one isomer after oxidation. 2D NOESY experiments indicated a relative configuration where the R^2 group is anti to the furan oxygen.

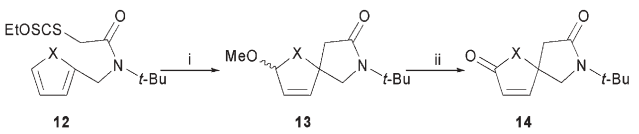
We applied this approach to the expedient synthesis of the tricyclic A,B,D system of securinine (Fig. 1) and analogues.[10,11] This system was obtained in good yield in the case of a 5, 6 and 7-membered ring A but unfortunately with little or no selectivity (Table 2).

As some natural compounds, such as the potent insecticidal asperparalines[12] (Fig. 1), possess a spirocyclic imide function, we replaced the amide with an imide group. Unfortunately, the results were not very satisfactory (Scheme 3). In the case of a methyl group on the nitrogen (**8a**), a competing hydrolysis of the imide by methanol occurred to give amide **9**. The use of a less nucleophilic solvent such as *t*-BuOH, CF_3CH_2OH or AcOH did not improve the result. With a bulkier *iso*-propyl group (**8b**) on the nitrogen, the product of hydrolysis was not observed but the improvement in the overall yield of the reaction remained modest.



Scheme 3 *Reagents and conditions:* (i) Lauroyl peroxide (DLP), 1,2-DCE–MeOH, reflux (ii) *m*CPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20/−15 °C.

Table 3



(i) 300% DLP, 1,2-DCE/–MeOH, reflux (ii) *m*CPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2

Entry	X	Yield (**13**) (ratio)	Yield (**14**) (ratio)
1	S	no reaction	—
2	N–Me	degradation	—
3	N–Ts	34% (1 : 1)	79%

In this preliminary study, we have further briefly examined replacing the furan moiety by other aromatic systems such as a thiophene or a pyrrole (Table 3). No identifiable reaction took place with the thiophene but the radical spirocyclisation was observed with the pyrrole, as long as an electron withdrawing group was placed on the nitrogen. A simple methyl group only led to degradation, presumably because of the instability of the primary spiro adduct. In summary, we have developed a new radical spirocyclisation onto furans which uses tin-free radical chemistry and exploits the possibility of a cross-over from a radical to a polar manifold. This reaction gives access to new spirocyclic and heterocyclic structures, some of which could be used in the synthesis of a number of alkaloids containing such subunits.†

Notes and references

† *Typical experimental procedures.*

Radical spirocyclisation. A solution of the xanthate (1 mmol) in 1,2-dichloroethane and methanol (3 : 1, 5 mL) was heated to reflux for 15 min under a nitrogen atmosphere. Lauroyl peroxide (10 mol%) was then added every 1 h until complete consumption of the xanthate was observed. The solvent was removed under reduced pressure and the residue purified by chromatography on a silica gel column (ethyl acetate–petroleum ether) to furnish the desired product.

Oxidation of the cyclic acetal lactone. A solution of *m*CPBA (1.1 mmol) in dichloromethane (2 mL) was added to a solution of the acetal (1 mmol) in dichloromethane (4 mL) at −20/−15 °C followed by $BF_3{\cdot}OEt_2$ (1.1 mmol). When TLC indicated complete transformation, the reaction was quenched with saturated $NaHCO_3$ solution and extracted twice with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on a silica gel column (ethyl acetate–petroleum ether) to furnish the desired product.

1 J. Boivin, M. Yousfi and S. Z. Zard, *Tetrahedron Lett.*, 1997, **38**, 5985; H. Ohno, S.-I. Maeda, M. Okumura, R. Wakayama and T. Tanaka, *Chem. Commun.*, 2002, 316; F. Gonzalez-Lopez de Turiso and D. P. Curran, *Org. Lett.*, 2005, **7**, 151.

2 K. Jones, T. C. T. Ho and J. Wilkinson, *Tetrahedron Lett.*, 1995, **36**, 6743; C. Escolano and K. Jones, *Tetrahedron Lett.*, 2000, **41**, 8951; C. Escolano and K. Jones, *Tetrahedron*, 2002, **58**, 1453.

3 S. T. Hilton, T. C. T. Ho, G. Pljevaljcic and K. Jones, *Org. Lett.*, 2000, **2**, 2639.

4 A. S. Kyei, K. Tchabanenko, J. E. Baldwin and R. M. Adlington, *Tetrahedron Lett.*, 2004, **45**, 8931.

5 P. J. Parsons, M. Penverne and I. L. Pinto, *Synlett*, 1994, 721; A. Demircan and P. J. Parsons, *Synlett*, 1998, 1215; A. Demircan and P. J. Parsons, *Eur. J. Org. Chem.*, 2003, 1729.

6 F. Gagosz, C. Moutrille and S. Z. Zard, *Org. Lett.*, 2002, **4**, 2707.

7 J. Mihelcic and K. D. Moeller, *J. Am. Chem. Soc.*, 2004, **126**, 9106 and references there cited.

8 S. F. Martin and S. K. Bur, *Tetrahedron Lett.*, 1997, **38**, 7641.

9 P. Jarglis and F. W. Lichtenthaler, *Tetrahedron Lett.*, 1982, **23**, 3781.

10 J. A. Beutler, E. W. Karbon, A. N. Brubaker, R. Malik, D. R. Curtis and S. J. Enna, *Brain Res.*, 1985, **330**, 135.
11 For other syntheses of the tricyclic A,B,D system of securinine, see: (*a*) R. Kammler, K. Polborn and K. T. Wanner, *Tetrahedron*, 2003, **59**, 3359; (*b*) R. Alibes, P. Bayon, P. de March, M. Figueredo, J. Font, E. Garcia-Garcia and D. Gonzalez-Galvez, *Org. Lett.*, 2005, **7**, 5107.
12 H. Hayashi, Y. Nishimoto and H. Nozaki, *Tetrahedron Lett.*, 1997, **38**, 5655.