Radical cyclization of *O*-trityl oximino esters: a ring closure that preserves the oxime function

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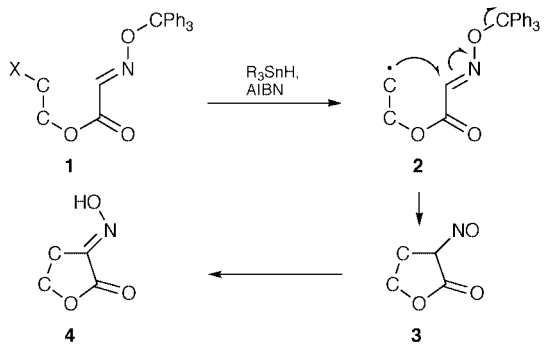
_O_-Trityl oximino esters 1 undergo stannane-induced radical cyclization to regenerate an oxime function, affording oximino lactones 4; these can be converted into enamides (*e.g.* 11b), and such a transformation was used to make the natural product 14c.

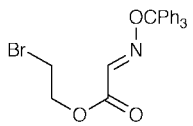
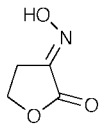
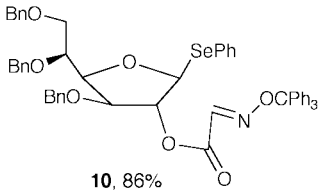
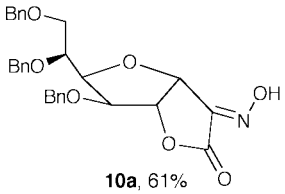
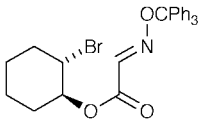
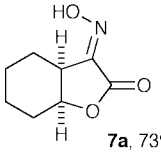
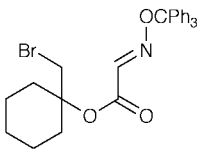
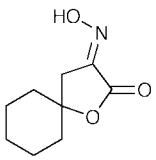
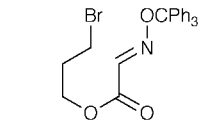
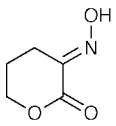
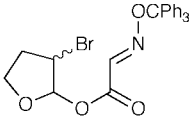
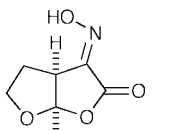
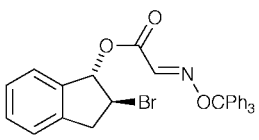
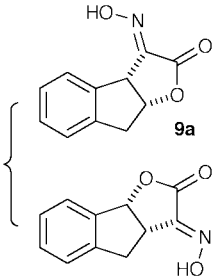
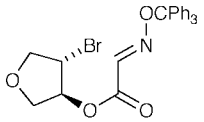
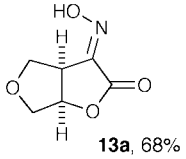
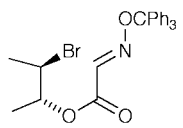
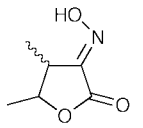
We report radical ring closures of the type summarized in Scheme 1 (X = homolyzable group).[1,2] The special feature of such reactions is that the sp^2 status of the acceptor carbon is preserved—a result that is different from the one seen in the classical cyclization of hexenyl radicals or the radical cyclization of *O*-alkyl oxime ethers.[3–5] Regeneration of the oxime function after the radical closure must involve[6] tautomerization of an intermediate nitroso compound, as shown in Scheme 1, **3** → **4**.†

The starting oximino esters (*cf.* **1**) are prepared using the crystalline reagent **5** (mp 165–166 °C), which is easily made (76%) by stirring equimolar amounts of *O*-trityl hydroxylamine and glyoxylic acid monohydrate in THF for 4 h. Evaporation of

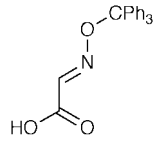


Scheme 1

Table 1 Esterification of various alcohols and subsequent radical cyclizations[a]

Entry	Ester	Lactone	Entry	Ester	Lactone
1	 **6**, 99%	 **6a**, 72%	5	 **10**, 86%	 **10a**, 61%
2	 **7**, 80%	 **7a**, 73%	6	 **11**, 68%	 **11a**, 80%
3	 **8**, 83%	 **8a**, 46%[b]	7	 **12**, 86%[d]	 **12a**, 41%
4	 **9**, 79%	 **9a** + **9b** 66%[c]	8	 **13**, 83%	 **13a**, 68%
			9	 **14**, 84%	 **14a**, 68%[e]

[a] Oxime geometries shown are arbitrary, except for **11** and **14a**. [b] A single product, which isomerizes on storage in MeOH. [c] Combined yield. Isomers **9a** and **9b** were obtained in a ratio of *ca.* 1:2. [d] Two isomers were isolated in yields of 61 and 25%. [e] A mixture (*ca.* 55:45) of two isomers was obtained.



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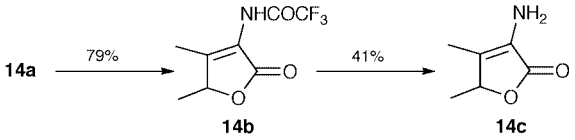
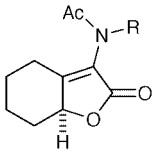


Scheme 2

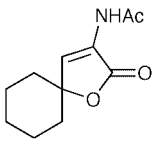
the solvent and column chromatography over silica gel (3:7 hexane–EtOAc) gives pure **5**, whose geometry in the solid state was established by X-ray analysis. The reagent (1 mmol) reacts smoothly with alcohols (1.1 mmol) in CH_2Cl_2 in the presence of DCC (1.1 mmol) and DMAP (1.1 mmol) to give the corresponding esters, after 1–26 h. Yields in these esterifications are generally high (see Table 1, entries 1–6 and 8–9). The parent alcohol for **11** is a known compound,[8,9] but one tentative structural assignment given[8] in the literature [(1-bromocyclohexyl)methanol] is incorrect; our X-ray analysis of **11** establishes the actual structure. In one case (Table 1, entry 7) we prepared the required starting ester by reaction of **5** (1.1 mmol) with a THF solution of the alkene (1.0 mmol) in the presence of NBS (1.1 mmol), and again the yield was high.

The radical cyclizations were done by slow addition (*ca*. 10 h, syringe pump) of separate toluene solutions of Bu_3SnH (0.17 M, 1.5–2.5 mmol per mmol ester) and AIBN (0.012 M, 0.1–0.2 mmol per mmol ester) to a refluxing toluene solution of the ester (1.0–1.8 mmol, 0.016 M). Refluxing was continued for an arbitrary period of 2 h after the end of the addition. The products were isolated in the yields indicated in Table 1, by evaporation of the solvent and flash chromatography. While the oxime geometry for **5**, **11** and **14a** was determined by X-ray analysis, the geometries shown for the other oximes are arbitrary assignments. All the cyclization products were single isomers, except for **14a**. In that example, the material was obtained crystalline, and X-ray analysis showed the crystals to be composed of the *trans,E* and *cis,E* isomers in a ratio of *ca*. 55:45; the same composition was evident from the ^{1}H NMR spectrum. During cyclization of **9** a 1,2-acyloxy rearrangement[10] occurs, driven by formation of a benzylic radical.

We have examined briefly the partial reduction of several of our α-oximino lactones. For example, treatment of **7a** with iron



7b R = H, 54%
7c R = Ac, 30%



11b, 80%

powder in Ac_2O[11] (room temperature, 14 h) gave a mixture of enamide **7b** (54%) and the doubly acetylated analog **7c** (30%). Under the same conditions, **11a** gave **11b** (80%), and no bis-acetylated product was isolated.

Treatment of **14a** with iron powder in TFAA gave enamide **14b** (Scheme 2), the fluorinated anhydride being used because we expected this choice to facilitate subsequent amide hydrolysis. In the event, treatment of **14b** with aqueous K_2CO_3 afforded enamine **14c**, which is a naturally-occurring substance[12,13] that is present in the flowers of the tree *Quararibea funebris* (Llave). Extracts of the flowers have been used[14] by the Zapotec Indians of Oaxaca, Mexico, to treat a number of disorders, including some of a psychological nature, but it is not known whether **14c** itself is biologically active. It has been suggested that the compound may be the biosynthetic precursor of several pyrrole alkaloids present in the flower extract.[14]

All new compounds were characterized spectroscopically, including high resolution mass measurements, except for **9b**, which was isolated as a mixture with **9a**.

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Notes and references

† No blue color was observed during the reaction. Tautomerization of a *C*-nitroso compound, as the terminating step of an intermolecular reaction, is known (see ref. 7)

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