Preparation of α-(2,2-diphenylhydrazino)- and α-(benzyloxyamino)-lactones by radical cyclization: use of glyoxylic acid diphenylhydrazone and glyoxylic acid *O*-benzyloxime

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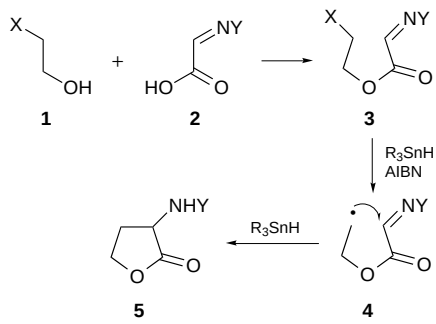
Glyoxylic acid diphenylhydrazone (2, Y = NPh_2) and the corresponding *O*-benzyloxime (2, Y = OBn) are easily esterified in high yield by β-bromo alcohols, and the resulting esters undergo radical cyclization to α-(2,2-diphenylhydrazino) or α-(benzyloxyamino) lactones on treatment with tributyltin hydride; the initial radical can be formed by homolysis of a carbon–selenium bond as well as a carbon–bromine bond and, when applied to appropriate alcohols, the esterification–radical closure sequence can also be used to make six- or seven-membered lactones.

We report here the synthesis of α-hydrazino lactones (**5**, Y = NPh_2) and the corresponding *O*-benzylhydroxylamines (**5**, Y = OBn) by the radical cyclization process summarized in Scheme 1 (X = Br, SePh). The radical precursors **3** are readily accessible by DCC-mediated coupling of glyoxylic acid diphenylhydrazone (**2**, Y = NPh_2)[1] or *O*-benzyloxime (**2**, Y = OBn)[2] with β-bromo or β-(phenylselanyl) alcohols (**1**, X = Br or SePh), themselves easily made from alkenes (NBS–H_2O,[3] PhSeX[4]) or epoxides (Me_2BBr,[5] PhSeNa[6]). The glyoxylic acids **2** (Y = NPh_2 or OBn) are stable, crystalline reagents, formed in high yield (90–96%) from glyoxylic acid.†

Both the coupling reaction (**1** + **2** → **3**) and the radical closure (**3** → **4** → **5**) generally proceed in good yield. Most of our work has been done with hydrazone acid **2** (Y = NPh_2), but related experiments with the *O*-benzyloxime acid **2** (Y = OBn) were also successful; however, we have not made a sufficiently extensive comparison to identify which series (hydrazone or oxime) is generally more efficient. Likewise, the superiority of bromides over selenides for the radical closure step has also not yet been firmly established.

Formation of carbocycles — specially five-membered rings — by radical closure onto a carbon–nitrogen double bond is well-established with oxime ethers,[7] but to a much lesser extent with diphenylhydrazones.[8,9] In the case of hydrazones there is evidence to suggest[8a] that hydrazone amides and semicarbazides **6** (Y = NHCOPh or $NHCONHNH_2$) close more efficiently than do the corresponding diphenylhydrazones; however, in this preliminary work we used diphenylhydrazones. The ring closure shown for **4** (Scheme 1) requires the indicated proximity of the carbon radical and the carbon–nitrogen double bond; this conformation is adequately accessible because of the sufficiently low rotational barrier about ester C(O)–O single bonds.[10]



X = Br, SePh, Y = NPh_2, OBn

Scheme 1

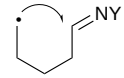
Our reaction produces lactones bearing an α-nitrogen substituent (Table 1). When the starting alcohol **1** is cyclic, the stereochemical outcome at the newly-created ring junction is determined by the stereochemistry of the original hydroxy-bearing carbon in **1**, but for both cyclic and non-cyclic starting alcohols the degree of stereoselectivity α to the lactone carbonyl is low,[11] at least under the thermal conditions we have used (see footnotes to Table 1).

Experiments with indane derivative **15a** (see Table 1) revealed the intervention of a 1,2-acyl migration[12] which, in this case, must be especially fast because of the fact that it leads—*via* a readily accessible and favourable geometry—to a benzylic radical. Entry 6 of Table 1 shows an application to carbohydrates, and also serves as an example of 7-*exo* closure. Presumably, favourable geometrical constraints are operating in this case, but are absent in **9a** (6-*exo* closure), where an appreciable amount of reduction occurs before cyclization.

All the coupling experiments to generate the radical precursors **3** were done by addition of DCC (5.5 mmol) and DMAP (0.5 mmol) to a solution of the appropriate alcohol (5.5 mmol) and reagent **2** (Y = NPh_2 or OBn) (5 mmol) in CH_2Cl_2. After 6–12 h at room temperature, the esters could be isolated in the yields shown. The radical cyclizations were conducted by simultaneously adding toluene solutions‡ (double syringe pump, 9-10 h) of Bu_3SnH (1.73 mmol, 0.173 m) and AIBN (0.12 mmol, 0.012 m) to a refluxing solution of the substrate (1.15 mmol, 0.016 m) in the same solvent. At the end of the addition refluxing was continued for an arbitrary period of 2–3 h (except for **8a**, where this period was 5 h).

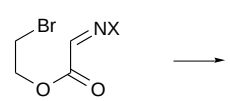
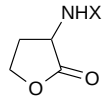
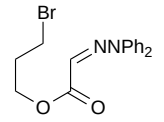
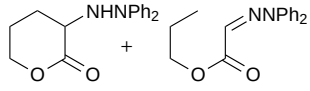
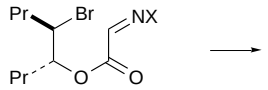
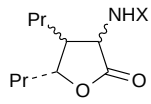
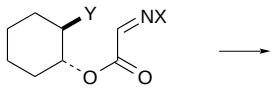
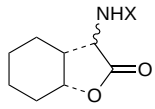
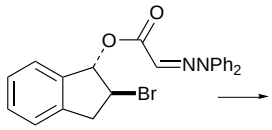
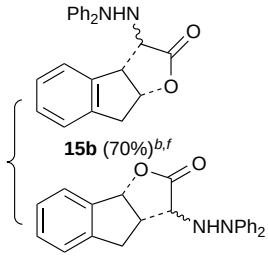
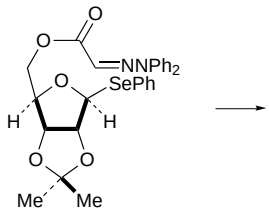
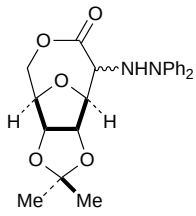
α-Hydrazino- and α-(hydroxyamino)-γ-lactones (*cf.* substructure **5**) are not well-known; neither are the corresponding δ-lactones.[13] In principle, these α-substituted lactones can be modified in various ways and, in the case of **7b** for example, hydrogenolysis (10% Pd–C, THF-aqueous HCl 6 m) gave homoserine γ-lactone hydrochloride[14] (81% after crystallization from acetone).

All new compounds were characterized by spectroscopic methods, including accurate mass measurements. The isomers of **11b** (four), **14b** (two) and **15b** (two) were chromatographic-



6 Y = NHCOPh, $NHCONHNH_2$

Table 1 Yields for coupling reaction to form hydrazones or oximes, and for radical cyclization

Hydrazone or oxime (yield)	Lactone (yield)
1  **7a** X = NPh_2 (80%) **8a** X = OBn (82%)	 **7b** X = NPh_2 (75%) **8b** X = OBn (51%)
2  **9a** (72%)	 **9b** (50%) **9b** (20%)
3  **10a** X = NPh_2 (98%) **11a** X = OBn (*ca.* 100%)	 **10b** X = NPh_2 (82%)[a] **11b** X = OBn (78%)[b,c]
4  **12a** X = NPh_2, Y = Br (90%) **13a** X = NPh_2, Y = SePh (85%) **14a** X = OBn, Y = Br (88%)	 **12b** X = NPh_2 (70%)[d] **13b** X = NPh_2 (*ca.* 20%)[d] **14b** X = OBn (64%)[b,e]
5  **15a** (82%)	 **15b** (70%)[b,f] **15c** (<10%)[g]
6  **16a** (92%)	 **16b** (64%)[d]

[a] Isomers not chromatographically separable; ratio (^{1}H NMR) *ca.* 2 : 3 : 2 : 3. [b] The individual isomers were separated and the relative stereochemistry of each was established by NOE measurements. [c] Taking the nitrogen function of C(2) to be on the α-face, the stereochemistry of the C(3) and C(4) substituents, in that order, can be defined as α (same face as the nitrogen function) and β. The isomer ratio (^{1}H NMR) was αα : αβ : ββ : βα : : 1 : 2 : 2.3 : 3. [d] Isomer ratio (^{1}H NMR) *ca.* 1 : 1. [e] Isomer ratio (isolation) 1 : 1. [f] Isomer ratio (isolation) 1 : 1.2. [g] Tentative structural assignment; the material was obtained mixed with **15b**. Isomer ratio (^{1}H NMR) *ca.* 1 : 1.

ally separable, and the relative stereochemistry of each was established by NOE measurements.

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Footnotes

† We used the procedure of ref. 2 for both reagents, but simply filtered off the product, without extraction into CH_2Cl_2, in the case of the hydrazone. ‡ For **16a** → **16b**, benzene was used, in order to demonstrate that the reaction works also at the reflux temperature of this solvent.

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