Synthesis of 4-Substituted 5,6-Diphenylmorpholine-2,3-diones With Two or Three Chiral Centers

Benito Alcaide, Carmen López-Mardomingo, Berta López-Sáez, Rafael Pérez-Ossorio* and Joaquín Plumet

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense, Ciudad Universitaria, Madrid-3, Spain

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Chiral α-aminoalcohols obtained by stereoselective reduction of α-iminoketones have been condensed with oxalyl chloride to afford 4-substituted 5,6-diphenylmorpholine-2,3-diones having two or three chiral centers.

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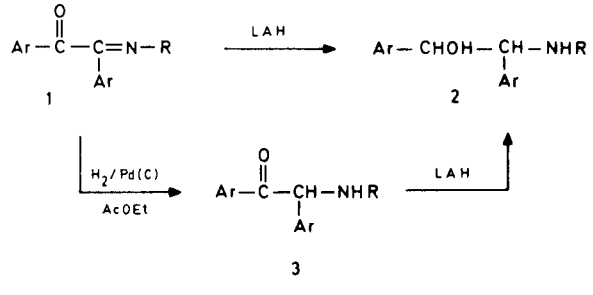
The monoimines **1** prepared from benzil and substituted benzils with primary amines are very versatile reagents for the stereoselective synthesis of α-aminoalcohols, **2**, (Scheme 1) [1,2]. When **1** was catalytically hydrogenated to aminoketones, **3**, and these were in turn reduced with lithium aluminium hydride (LAH) the *RS-SR* aminoalcohols were obtained with total stereoselectivity. On the other hand, direct LAH reduction of **1** afforded a mixture of **2** in which the *RR-SS* isomer predominates to an extension depending upon the nature of R. Both procedures allow the highly stereoselective preparation of α-aminoalcohols having two or three chiral centers, the latter being obtained when R is chiral.



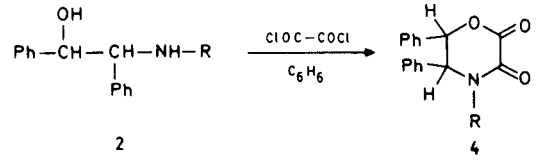
Scheme 1

It is of some interest to examine the behaviour of chiral **2** in the synthesis of heterocyclic systems particularly in what concerns the retention or alteration of the configuration at the chiral centers during the synthetic process. Also, the stereoselectivity of the formation of a new chiral center could be followed during the ring closure. In this connection, we have reported [3] the stereosepecific synthesis of substituted oxazolidines from **2** and benzaldehyde.

The interest in α-aminoalcohols resides partly in their β-adrenergic blocking properties. To study the conformational implications of their action as drugs some of these α-aminoalcohols have been transformed into the related morpholine derivatives [4,5]. In this way analogs of the drugs having a restricted conformational mobility can be studied and the conformational equilibria of the α-aminoalcohols can be deduced.

In the present paper we report the synthesis of some morpholinediones obtained from the aminoalcohols, **2**. With this synthesis we extended the use of **2** for the preparation of heterocyclic compounds carrying various chiral centers and provide new morpholine derivatives of **2** which, in our case, possessed a very limited conformational mobility. This rigidity extends, of course, to the configurations of some of the chiral centers and this may be convenient for pharmacological testing.

The reaction of aminoalcohols, **2**, (Ar = Ph) with oxalyl chloride yielded *N*-substituted, 5,6-diphenylmorpholine-2,3-diones **4** (Scheme 2).



Scheme 2

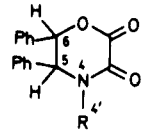
Oxalyl chloride has been allowed to react with alcohols to replace the hydroxyl by a chlorine atom [6,7], with phenols in the synthesis of *o*-hydroxybenzaldehydes [8,9] and with a variety of amino derivatives [10,11,12,13].

The reaction of oxalyl chloride with *o*-aminophenol has also been reported [14] but, to our knowledge, direct condensation with α-aminoalcohols has not received attention.

The starting aminoalcohols, **2**, were synthesized as reported above. The *RR-SS* diastereoisomers by direct LAH reduction of **1** followed by the appropriate isomers separation. The *RS-SR* diastereoisomers by the two-steps route **1** → **3** → **2**. The ir and ^{1}H nmr data of **4** are collected in Table 1.

Table 1

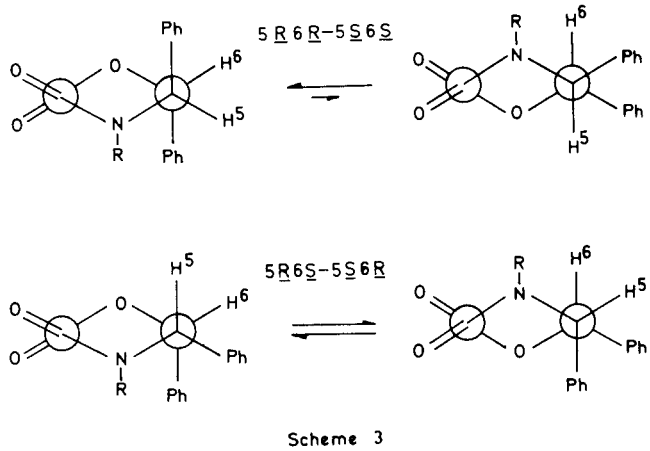
IR [a] and ^{1}H-NMR [b] data of Morpholinediones



No	R	Isomer	ν (C=O)O	ν (C=O)N	δ H-5	δ H-6	$J_{5,6}$	δ R [c]
4a	Ph	*RR-SS*	1750	1675	5.30	5.83	3.0	
4b	Ph	*RS-SR*	1745	1680	5.06	6.33	3.0	
4c	CH_2Ph	*RR-SS*	1745	1670	4.76	5.60	3.5	δ CH_aH_b, δ H_a = 3.60, δ H_b = 5.30, J_{ab} = 15 Hz
4d	CH_2Ph	*RS-SR*	1735	1675	4.60	5.90	3.0	δ CH_aH_b, δ H_a = 3.00, δ H_b = 5.40, J_{ab} = 15 Hz
4e	CHMePh	6*R*5*R*4′*S*	1745	1665	4.70	[d]	1.5	δ Me = 1.00, J_{CH_3CH} = 7.0 Hz
4f	CHMePh	6*S*5*S*4′*S*	1740	1660	4.30	5.23	1.5	δ Me = 1.10, δ CH = 5.75, J_{CH_3CH} = 7.0 Hz
4g	CHMePh	6*S*5*R*4′*R*	1730	1675	4.33	5.60	3.0	δ Me = 1.20, δ CH = 6.20, J_{CH_3CH} = 8.0 Hz
4h	CHMePh	6*R*5*S*4′*R*	1735	1670	4.50	5.90	3.0	δ Me = 1.00, δ CH = 5.60, J_{CH_3CH} = 6.0 Hz

[a] Potassium bromide. [b] In deuteriochloroform at 60 MHz. Magnetic parameters were directly read on conveniently enlarged spectra. [c] Chemical shifts of aromatic protons not recorded. They appear as usual. [d] The signal of this proton appears together with that of N-C*H* quartet at 5.3-5.7 ppm.

Molecular models of **4** suggest a chair-type conformation with both keto groups in a non-planar arrangement (Scheme 3). For the 5*R*6*R*-5*S*6*S* isomer the conformer with H^5 and H^6 in a sinclinal arrangement should predominate for steric reasons. For the 5*R*6*S*-5*S*6*R* isomer both conformers may be nearly equally populated being H^5 and H^6 in a sinclinal arrangement in both. This conclusion is in agreement with the similar values of the coupling constants found for both isomers.



Scheme 3

EXPERIMENTAL

Melting points are uncorrected. The synthesis and assignment of configuration of aminoalcohols, **2**, have been reported previously [1,2].

Synthesis of 4-Substituted 5,6-Diphenylmorpholine-2,3-diones **4**.

To the aminoalcohol (400 mg, 1.26 mmoles) dissolved in benzene (15 ml) the oxalyl chloride (250 mg, 1.98 mmoles) was added. The mixture was stirred at room temperature for 4 days. The solvent was eliminated and the residue was crystallized several times from ethanol. Yields are referred to isolated pure products with correct analysis.

(5*R*6*R*-5*S*6*S*)-4,5,6-Triphenylmorpholine-2,3-dione (**4a**).

This compound was obtained in a yield of 42%, mp 195-196°.

Anal. Calcd. for $C_{22}H_{17}NO_3$: C, 76.96; H, 4.95; N, 4.08. Found: C, 76.61; H, 5.10; N, 4.35.

(5*R*6*S*-5*S*6*R*)-4,5,6-Triphenylmorpholine-2,3-dione (**4b**).

This compound was obtained in a yield of 59%, mp 214-215°.

Anal. Calcd. for $C_{22}H_{17}NO_3$: C, 76.96; H, 4.95; N, 4.08. Found: C, 77.32; H, 5.10; N, 4.27.

(5*R*6*R*-5*S*6*S*)-5,6-Diphenyl-4-benzylmorpholine-2,3-dione (**4c**).

This compound was obtained in a yield of 76%, mp 157-158°.

Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.31; H, 5.32; N, 3.92. Found: C, 77.06; H, 5.28; N, 4.04.

(5*R*6*S*-5*S*6*R*)-5,6-Diphenyl-4-benzylmorpholine-2,3-dione (**4d**).

This compound was obtained in a yield of 80%, mp 196-197°.

Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.31; H, 5.32; N, 3.92. Found: C, 77.12; H, 5.51; N, 3.86.

4-(*S*-1-Phenylethyl)-(5*R*6*R*)-diphenylmorpholine-2,3-dione (**4e**).

This compound was obtained in a yield of 62%, mp 238-239°; $[\alpha]_{578}^{20}$ +7.5 (c, 0.66 g/100 ml, chloroform).

Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.63; H, 5.66; N, 3.77. Found: C, 77.45; H, 5.85; N, 4.05.

4-(*S*-1-Phenylethyl)-(5*S*6*S*)-diphenylmorpholine-2,3-dione (**4f**).

This compound was obtained in a yield of 60%, mp 211-212°; $[\alpha]_{578}^{20}$ −105.8 (c, 4.50 g/100 ml, chloroform).

Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.63; H, 5.66; N, 3.77. Found: C, 77.58; H, 5.80; N, 3.69.

4-(*R*-1-Phenylethyl)-(5*R*6*S*)-diphenylmorpholine-2,3-dione (**4g**).

This compound was obtained in a yield of 60%, mp 168-169°; $[\alpha]_{578}^{20}$ +255.9 (c, 0.34 g/100 ml, chloroform).

Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.63; H, 5.66; N, 3.77. Found: C, 77.19; H, 5.82; N, 3.94.

4-(*R*-1-Phenylethyl)-(5*S*6*R*)-diphenylmorpholine-2,3-dione (**4h**).

This compound was obtained in a yield of 43%, mp 226-227°; $[\alpha]_{578}^{20}$ −164.3 (c, 1.73 g/100 ml, chloroform).

Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.63; H, 5.66; N, 3.77. Found: C, 77.25; H, 5.92; N, 3.87.

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