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Catalytic decomposition of enantiomerically pure 3-methyl and 3-phenyl-6-diazo-4-methyloxazepan-5,7-diones

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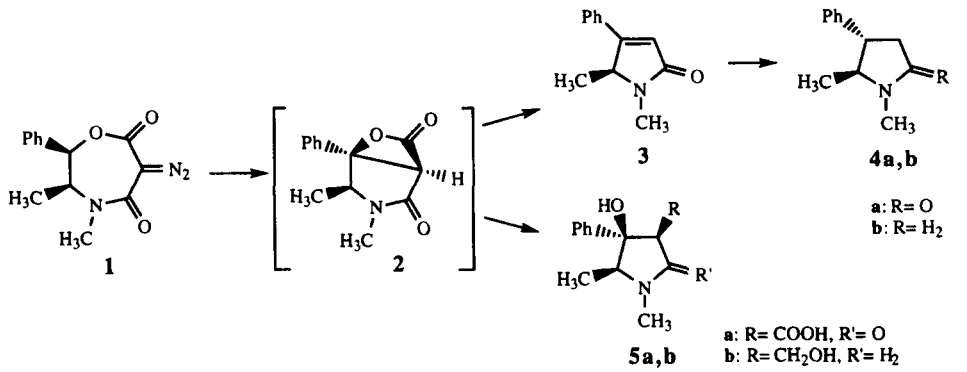
Abstract: The catalytic decomposition of enantiomerically pure 3-methyl and 3-phenyl-6-diazo-4-methyloxazepan-5,7-diones is reported. The preparation of some chiral β-lactams is described. © 1997 Published by Elsevier Science Ltd. All rights reserved.

We recently reported that the catalytic decomposition of the enantiopure diazoxazepanedione **1**, readily obtained from ephedrine, gave the homochiral unsaturated lactam **3** through the formation of the unisolable intermediate bicyclic lactone-lactam **2**.[1] From both compounds **2** and **3** a number of enantiopure pyrrolidinones and pyrrolidines were obtained (Scheme 1).[1,2] The global reaction involves an intramolecular carbenic C–H insertion followed by a ring contraction–decarboxylation step. The regiospecific carbenic insertion into the benzylic C–H bond of oxazepane **1** has been ascribed to the greater electron density of this bond: electronic activation by the lactone oxygen and by the phenyl group.



Scheme 1.

We have now undertaken work to define the role played by the phenyl group in the intramolecular carbenic attack, and to determine the possibility of transforming a substituted oxazepanedione into a four-membered β-lactam ring (by carbenic attack on the C_3–H bond) rather than the usual five-membered γ-lactam[3] (Scheme 2).

For this purpose the (S)-3,4-dimethyloxazepan-5,6-dione **6a** and (R)-3-phenyl-4-methyloxazepan-5,6-dione **6b** were synthesized according to a usual protocol[4] from (S)-3-methyl and (R)-3-phenylglycinol respectively, and transformed into the corresponding 6-diazo-derivatives **7a,b** under mild conditions by a 'diazo transfer' reaction with *p*-toluenesulfonyl azide (TsN_3).[5] The decomposition reactions of compounds **7a,b** were carried out in the presence of a catalytic amount of rhodium(II) acetate dimer in methylene chloride. The reaction was monitored by the disappearance of the diazo stretching band in the IR spectrum and by ^1H NMR spectra recorded at different reaction times.

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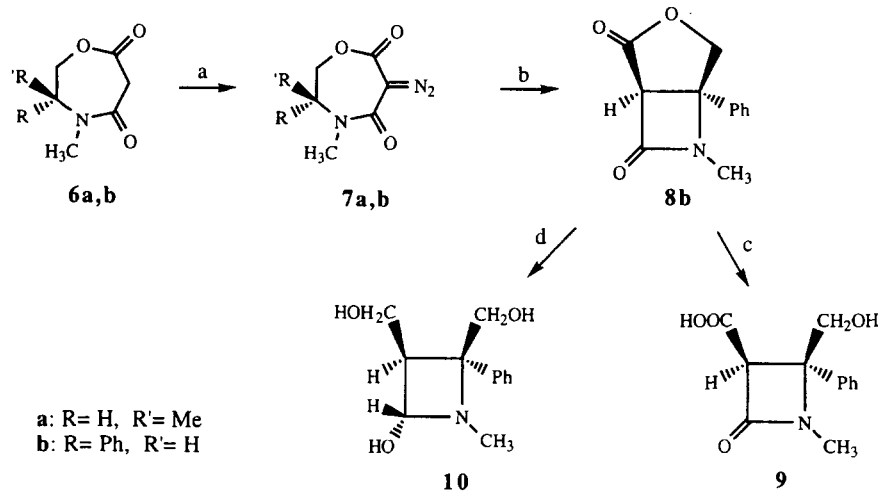

a: TsN_3, NEt_3, CH_3CN, r.t., 24 h; b: 5% rhodium (II) acetate dimer, CH_2Cl_2, r.t.,10 h, 27 %; c: 10% NaOH, r.t, 48 h, 51 %; d:$LiAlH_4$, Et_2O, r.t., 24 h, 76 %.

Scheme 2.

Compound **7a** proved resistant to decomposition at room temperature, in fact after 48 h no reaction occurred. When the reaction was carried out at 40°C for 20 h only an unmanageable reaction mixture was obtained. On the other hand compound **7b** after 10 h at room temperature gave, though in low yield (27%), the β-lactam **8b** as a single diastereomer (by ^{13}C and ^{1}H NMR spectra).

Unlike the γ-lactam **2**, the β-lactam **8b** was a stable solid, but all attempts to obtain crystals suitable for X-ray analysis failed. However, since we have previously showed that the intramolecular carbene insertion on the asymmetric phenyl-substituted C–H bond of the diazoxazepanedione **1** proceeds with retention of configuration and the only possible stereochemical arrangement of the bicyclic lactone-lactam **8b** is a *cis*-fusion, it is reasonable to attribute to **8b** the 1R and 5S configurations as depicted in Scheme 2.

These results show that the intramolecular carbenic insertion on the C_2–H or C_3–H bond requires the presence on these carbon atoms of an electronically activating group such as the phenyl therefore, its presence on the diazepanedione ring governs the regiochemistry of the insertion.

Since the opening of the lactonic moiety of enantiopure bicyclic lactone-lactam **8b** could provide access to substituted β-lactams with defined configurations of the stereogenic centres, its transformation was planned. For this purpose, the hydrolytic opening of the lactonic moiety of **8b** was performed. Hydrolysis was carried out in basic conditions to give the (3S,4R)-3-carboxy-4-hydroxymethyl-1-methyl-4-phenyl-2-azetidinone **9** as a white solid (51%).

An alternative reaction involving the reductive lactonic ring opening of **8b** was also performed. Thus, the reduction carried out with lithium aluminium hydride afforded exclusively the 2-hydroxy-3,4-bis(hydroxymethyl)-4-phenylazetidine **10** as a single diastereoisomer. The assignment of the stereochemistry at the C_2 carbon was made on the basis of the lack of a coupling between the two C_2–H and C_3–H protons in the ^{1}H NMR spectrum, implying a dihedral angle close to 90°, which is only consistent with a *trans* orientation of two protons on the ring (Scheme 2).

In summary the present investigation demonstrates that the intramolecular carbene insertion in 2- and/or 3-substituted diazoxazepanediones requires the presence on these carbon atoms of an electronic activating group such as the phenyl group whose presence governs the regiochemistry of the insertion. Moreover this route opens the access to new chiral β-lactams.

Experimental

Melting points are uncorrected. ^1H (300 MHz) and ^{13}C NMR spectra were performed on a Varian VXR-300 spectrometer with TMS as the internal standard. The optical rotations were measured by a Perkin–Elmer 142 automatic polarimeter in a 1 dm tube. All reactions were carried out under argon atmosphere; all reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use.

Materials

(−)-(S)-3,4-Dimethyloxazepan-5,7-dione ***6a***

This compound was prepared from (S)-N-methyl alaninol[6] according to a reported procedure:[4] oil; $[\alpha]^{25}_D$ −39.1 (*c* 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 4.68 (d, 1H), 4.34 (dd, 1H), 3.95 (d, 1H), 3.79 (d, 1H), 3.68 (m, 1H), 2.95 (s, 3H), 1.34 (d, 3H).

(−)-(R)-4-Methyl-3-phenyloxazepan-5,7-dione **6b**: This compound was prepared from (R)-N-methylphenyl glycinol[6] according to a reported procedure:[4] m.p. 116–7°C; $[\alpha]^{25}_D$ −44.5 (*c* 0.40 $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.49–7.31 (m, 3H), 7.21 (d, 2H), 4.73 (dd, 1H), 4.59 (dd, 1H), 4.51 (dd, 1H), 4.17 (d, 1H), 3.88 (d, 1H), 2.78 (s, 3H).

(−)-(S)-6-Diazo-3,4-dimethyloxazepan-5,7-dione ***7a***

This compound was prepared from **6a** by reaction with *p*-toluenesulfonyl azide:[5] m.p. 74–5°C; $[\alpha]^{25}_D$ −46.7 (*c* 0.57, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 4.49 (d, 1H), 4.34 (dd, 1H), 3.61 (m, 1H), 3.09 (s, 3H), 1.34 (d, 3H).

(−)-(R)-6-Diazo-4-methyl-3-phenyloxazepan-5,7-dione ***7b***

This compound was prepared from **6b** by reaction with *p*-toluenesulfonyl azide:[5] m.p. 113–5°C; $[\alpha]^{25}_D$ −51.1 (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.47–7.33 (m, 3H), 7.17 (d, 2H), 4.71–4.55 (m, 3H), 3.03 (s, 3H).

(−)-(1R,5S)-7-Aza-7-methyl-1-phenyl-3-oxa-4,6-dioxobicyclo[3.2.0.]heptane ***8b***

Rhodium(II)acetate dimer (74 mg) was added under argon to a solution of diazo compound **7b** (735 mg, 3 mmol) in CH_2Cl_2 (44 ml) and the mixture stirred at room temperature. After 10 h the solvent was evaporated and the residue purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 6/4) to give **8b** which was recrystallized from methylene chloride/petroleum ether: 176 mg (27%); m.p. 122–3°C; $[\alpha]^{25}_D$ −217.2 (*c* 0.83, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.55–7.40 (m, 3H), 7.33 (d, 2H), 4.82 (d, 1H), 4.76 (d, 1H), 4.06 (s, 1H), 2.74 (s, 3H). ^{13}H NMR ($CDCl_3$) δ: 168.7, 159.9, 133.4, 129.6, 129.5, 125.8, 70.2, 65.9, 62.4, 25.7. *Elem. anal.*, found % (calcd. for $C_{12}H_{11}NO_3$): C, 66.43 (66.35) H, 5.03 (5.10); N, 6.48 (6.45).

(+)-(3S,4R)-3-Carboxy-4-hydroxymethyl-1-methyl-4-phenyl-2-azetidinone ***9***

Compound **8b** (44 mg, 0.2 mmol) was added to a solution of KOH (179 mg) in H_2O (5 ml) and the resulting mixture stirred for 48 h at room temperature. The mixture was neutralized with 5% HCl and extracted with ethyl acetate. The separated organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a residue which after crystallization from chloroform gave pure **9**: 24 mg (51%); m.p. 150–1°C (dec.); $[\alpha]^{25}_D$ +179.2 (*c* 0.35, CH_3OH).^1H NMR ($CDCl_3$–$(CD_3)_2SO$) δ: 7.38 (m, 5H), 5.55 (broad, 2H), 4.33 (s, 1H), 4.26 (d, 1H), 3.96 (s, 1H), 2.94 (s, 3H). *Elem. anal.*, found % (calcd. for $C_{12}H_{13}NO_4$): C, 61.13 (61.27); H, 5.53 (5.57); N, 5.88 (5.95).

(+)-(2R,3S,4R)-2-Hydroxy-3,4-bis(hydroxymethyl)-1-methyl-4-phenylazetidine ***10***

A 1M solution of $LiAlH_4$ in THF (0.46 ml, 0.46 mmol) was added dropwise to a cooled (0°C) solution of **8b** (51 mg, 0.235 mmol) in anhydrous THF (5 ml). After 1h stirring at room temperature the reaction mixture was cautiously quenched with H_2O and extracted with CH_2Cl_2 (4 × 10 ml). The

combined organic phases were washed with brine, dried ($MgSO_4$) and the solvent removed to give a residue which after crystallisation from benzene/petroleum ether gave **10**: 40 mg (76%); m.p. 120°C (dec); $[\alpha]^{25}_D$ +10.0 (*c* 0.12, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.45–7.15 (m, 5H), 5.47 (s, 1H), 4.49 (d, 1H), 4.28 (d,1H), 3.49 (dd, 1H), 3.28 (dd, 1H), 3.05 (broad, 3H), 2.58 (dd, 1H), 2.08 (s, 3H).^{13}C NMR ($CDCl_3$) 137.8 (0), 128.8 (1), 127.7 (1), 127.1 (1), 102.1 (1), 71.3 (2), 69.0 (0), 60.7 (2), 57.7 (1), 28.9 (3). Ms *m/z* 223 (M^+, 2), 206 (2), 192 (7), 174 (5), 162 (100), 149 (92), 134 (16), 118 (51), 104 (53), 91 (43), 77 (65), 51 (30). *Elem. anal.*, found % (calcd. for $C_{12}H_{17}NO_3$): C, 64.33 (64.55); H, 7.61 (7.67); N, 6.48 (6.27).

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