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Synthesis of Some Substituted Adamantane-2,4-diones from 4,4-Disubstituted Cyclohexanone Enamines and α,β-Unsaturated Acid Chlorides

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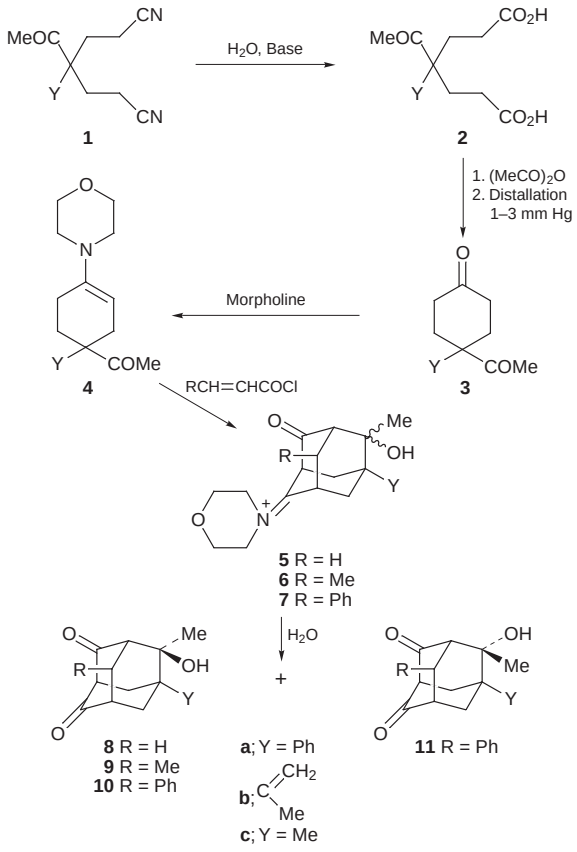
Following our previous report[7] on the synthesis of adamantane derivatives by condensation of 4,4-disubstituted cyclohexanone enamines with α,β-unsaturated acid chlorides, we now report the synthesis of seven new substituted adamantanediones from the reactions of three cyclohexanone enamines (**4**, Y = phenyl, isopropenyl, methyl) in which one of the substituents is an acetyl group.

The morpholine enamines **4a**, **4b** and **4c** (Scheme 1) of 4-acetyl-4-phenylcyclohexanone **3a**, 4-acetyl-4-isopropenylcyclohexanone **3b** and 4-acetyl-4-methylcyclohexanone **3c** respectively, were prepared following the procedure reported earlier.[7] The enamine **4a** reacted with acryloyl and crotonoyl chlorides to give (6*R*)-6-hydroxy-6-methyl-7-phenyladamantane-2,4-dione **8a** and (6*R*,9*R*)-6-hydroxy-6,9-dimethyl-7-phenyladamantane-2,4-dione **9a** respectively. The enamine **4a** was found to react with cinnamoyl chloride to produce two isomers, (6*R*,9*R*)-6-hydroxy-6-methyl-7,9-diphenyladamantane-2,4-dione **10a** and (6*S*,9*R*)-6-hydroxy-6-methyl-7,9-diphenyladamantane-2,4-dione **11a** which are epimeric at 6-C. In a similar manner the enamine **4b** reacted with cinnamoyl chloride to give (6*R*,9*R*)-6-hydroxy-7-isopropenyl-6-methyl-9-phenyladamantane-2,4-dione **10b** and (6*S*,9*R*)-6-hydroxy-7-isopropenyl-6-methyl-9-phenyladamantane-2,4-dione **11b** as isomers also epimeric at 6-C. From a reaction of the enamine **4c** with acryloyl chloride (6*R*)-6-hydroxy-6,7-dimethyladamantane-2,4-dione **8c** was obtained as the product. In our previous report[7] in the same reaction the presence of this adamantane-2,4-dione **8c** was detected in the ^{1}H NMR spectrum of the crude products. On repeating this reaction we have now isolated the compound **8c** in pure form.

All the aforementioned adamantane-2,4-diones are racemic, but only one enantiomer is shown (Scheme 1). The adamantanediones were obtained in stereochemically pure form with *R* configuration at C-6 in **8a**, **9a**, **10a**, **10b**, and **8c** and *S* in the compounds **11a** and **11b**. The configuration at C-9 in **9a**, **10a**, **10b**, **11a** and **11b** has been found to be *R*.

The structures of compounds **8a**, **9a**, **10a**, **11a**, **10b**, **11b** and **8c** were determined from their analytical data and spectral properties. Additional evidence for the structures of **11a** and **8c** was obtained from their ^{13}C–^{1}H NMR COSY and DEPT. The stereochemistry at positions 6-C and 9-C of **10a** and **11a** was further clarified with the help of NOESY. X-Ray crystallography afforded additional proof for the structures of **10a**, **11a** and **10b**. The presence of the hydroxy group in compounds **8a** and **9a** were further substantiated by the formation of their respective acetyl derivatives, the structures of which followed from their ^{1}H NMR spectra. The preparation and characterisation of the dioxime derivatives of compounds **8a**, **9a** and **10a** gave additional evidence for their structures.



Scheme 1

By running two-dimensional (^{1}H–^{1}H COSY) NMR spectra it was possible to assign all the protons in compound **8a**, **9a**, **10a**, **11a**, **10b**, **11b** and **8c** and the corresponding coupling constants were determined from one-dimensional ^{1}H NMR spectral data.

The signals for 1-H and 5-H overlapped at δ 2.80 for **8a** and at δ 2.66 for **9a**. The upfield shift in **9a** for both protons at positions 1 and 5 can be attributed to an anisotropic

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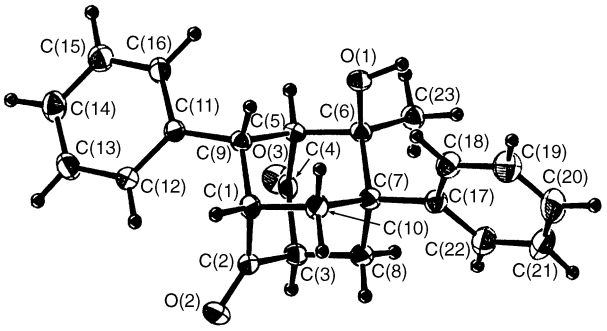

Fig. 1 Structure of **10a**

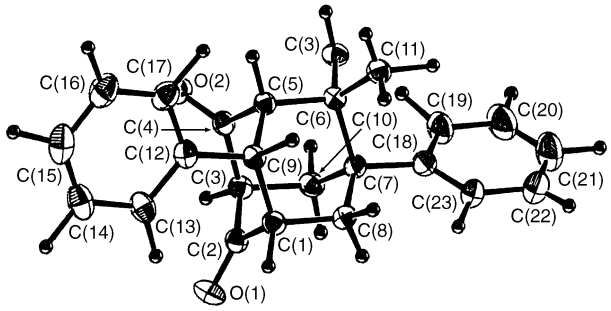

Fig. 2 Structure of **11a**

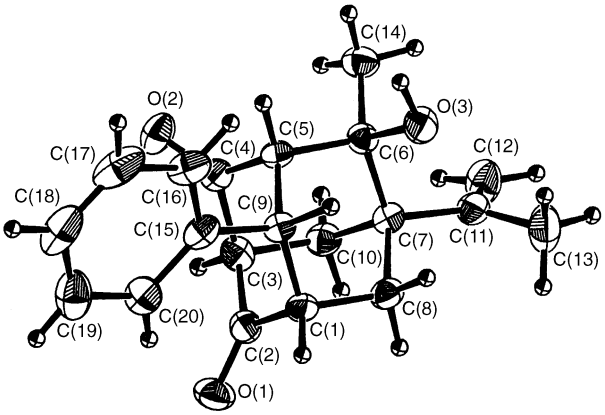

Fig. 3 Structure of **10b**

shielding effect of the methyl group at 9-C. However, the protons at 1-C and 5-C in **10a**, **11a, 10b** and **11b** experienced a deshielding effect by the 9-C_6H_5 group and were shifted downfield. Of the alicyclic part, 3-H resonated downfield considerably (δ 3.17–3 50) in all the compounds except for **8c**. This is because the protons at 3-C are α to two carbonyl groups. The 9-H protons in the compounds were shifted downfield[13,14] due to 1,3-diaxial interaction with the axial OH at position 6 in **8a**, **9a**, **10a**, **10b** and **8c**. Similar 1,3-interaction with the axial 6-CH_3 provides a smaller deshielding effect[15] in **11a** and **11b**.

In the ^{13}C NMR spectral data, the chemical shift values for 6-C and 6-CH_3 carbons of compounds **8a**, **9a**, **10a**, **11a**, **10b**, **11b** and **8c** compare well with the reported[16] values of δ 73.80 and 27.50 for 2-C and 2-CH_3 of 2-methyl-2-adamantanol where OH is axial and CH_3 is equatorial. 6-C of **10a** and **10b** resonated at δ 3.31 and 2.98, upfield from that of the corresponding epimers **11a** and **11b**, respectively, probably due to shielding operating in **10a** and **10b** resulting from the steric compression[17] between the axial OH at 6-C and equatorial phenyl and isopropenyl groups, respectively, at the adjacent bridgehead position (7-C). Evidence in support of the axial orientation of the OH group at position 6 in the relevant compounds is also provided by a downfield shift (1.38–3.05 ppm) of 10-C in comparison to 8-C in these compounds by the γ-*anti* effect.[18] This downfield γ-*anti* SCS (Substitution Chemical Shift) due to the OH substituent at 6-C increased by 3.36 ppm for **11a** and by 2.98 ppm for **11b** indicating their OH equatorial orientation where hetero atoms O, C_α, C_β, C_γ and H_δ are compressed in the same plane.[18] The CH_3 group (either axial or equatorial) would have very little SCS due to the γ-*anti* effect. A more downfield shift due to the γ-*anti* effect of 2.53 and 2.40 ppm of 9-C has been observed for **11a** and **11b** as compared to those in **10a** and **10b**, respectively.

From X-ray analysis crystallographic data and refinement details, bond lengths, bond angles, torsion angles and atomic coordinates provided informative additional evidence for the structures of **10a**, **11a** and **10b**. ORTEP drawings of **10a**, **11a** and **10b** are shown in Figs. 1, 2 and 3 along with their numbering systems.

Mass spectra of compounds **8a**, **9a**, **10a**, **11a**, **10b**, **11b** and **8c** gave moderately intense peaks for their molecular ions at *m/z* 270, 284, 346 (for isomers **10a** and **11a**), 310 (for isomers **10b** and **11b**) and 208, respectively.

Techniques used: IR, ^{1}H and ^{13}C NMR, ^{1}H–^{1}H NMR COSY, ^{13}C–^{1}H NMR COSY, DEPT, NOESY, mass spectra and X-ray diffraction

References: 25 Schemes: 2

Tables 1–3: NMR data

Tables 4–11: Crystallographic data

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