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Concise syntheses of bridged morpholines†

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Concise and practical syntheses of 8-oxa-3-aza-bicyclo[3.2.1]octane and 9-oxa-3-aza-bicyclo[3.3.1]nonane are described starting from furan-2,5-dicarboxylic acid and 4*H*-pyran-2,6-dicarboxylic acid, respectively, and using a solvent-free step for a key cyclisation.

Introduction

The morpholino unit is a privileged fragment[1] in numerous drugs[2] by virtue of its preferred chair conformation, oxygen lone pairs that can act as hydrogen bond acceptor(s) and a nitrogen atom that enables attachment to an aromatic or heteroaromatic scaffold. The importance of morpholino groups and especially their pseudoequatorial lone pair has recently been highlighted for inhibitors of phosphatidylinositol 3-kinases (PI3Ks) and phosphatidylinositol 3-kinase-related protein kinases (PIKKs).[3] The interaction of the morpholino group of an inhibitor with its target was described as 'representing a cornerstone in drug development of novel PI3K inhibitors'.[3] To modulate the properties of a morpholino unit in such inhibitors, one or more of the methylene groups may be substituted, which has enabled selectivity to be achieved amongst members of the PI kinase families. Thus, selectivity for mTOR (the mammalian target of rapamycin) over PI3Kα, was attained by replacing a morpholino unit in certain pyrazolopyrimidines with the bridged morpholine 8-oxa-3-aza-bicyclo[3.2.1]octane **1a**.[4] This morpholine analogue has also been used to introduce a bridged morpholino group into other compounds targeting mTOR,[5] as well as inhibitors of Aurora kinases[6] and glucokinase.[7] Such modifications permit the properties of inhibitors to be modulated, *e.g.* clog *P* is increased and a subtle structural feature is incorporated. For the mTOR pyrazolopyrimidine inhibitors with a bridged morpholine in place of the parent morpholine, hydrophobic interactions with the kinase's critical 'hinge' region were enhanced.[4]

Results and discussion

Owing to the current pharmaceutical interest in conformationally constrained ('bridged') morpholines, new synthetic methods to access these compounds have recently been developed.[8–10] Two exemplars are the bridged morpholines 8-oxa-3-aza-bicyclo[3.2.1]octane **1a** and 9-oxa-3-aza-bicyclo[3.3.1]nonane **2a**. The latter compound has only been described as *N*-substituted derivatives in patents.[11] Compared to **1a**, morpholine **2a** provides a significant increase in clog *P* (~0.4) and the possibility of an enhanced interaction at a hydrophobic binding site of a target protein.

The synthesis of **1a** has been previously achieved by reducing 5-hydroxymethyl-2-furfural to 2,5-bis-hydroxymethyl-tetrahydrofuran, the di-*p*-toluenesulfonate of which was treated with ammonia (under pressure at 170 °C) or benzylamine. These methods either afforded **1a** directly in very low yield[12–16] or in better yield (43–64%) *via* an intermediate *N*-benzyl compound, which was subjected to hydrogenolysis.[17] The latter synthesis was scalable, but required two high-pressure hydrogenations.

We have developed an efficient and rapid synthesis of 8-oxa-3-aza-bicyclo[3.2.1]octane **1a** (Scheme 1) from furan-2,5-dicarboxylic acid **3** *via* **4** and **5** that avoids high-pressure hydrogenation steps and is solvent-free for the key cyclisation step. The synthesis was inspired by Komppa's classical route[18] to 3-aza-bicyclo[3.3.1]nonane **2b**, whereby *cis*-cyclohexane-1,3-dicarboxylic acid **6b** was neutralised with aqueous ammonia and the solution evaporated presumably to give **7b**, which was heated at ~300 °C affording imide **8b**. Compound **8b** was

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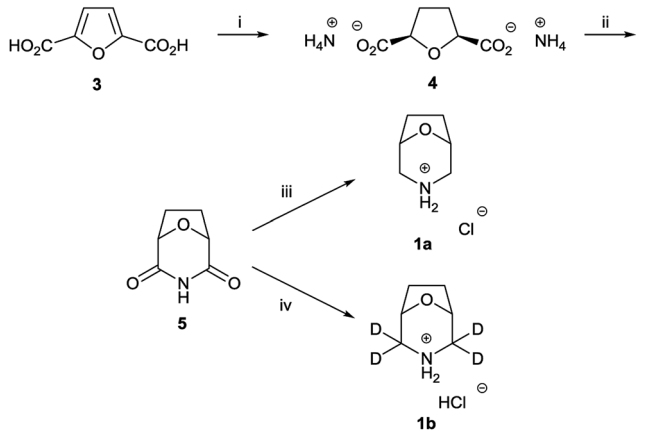
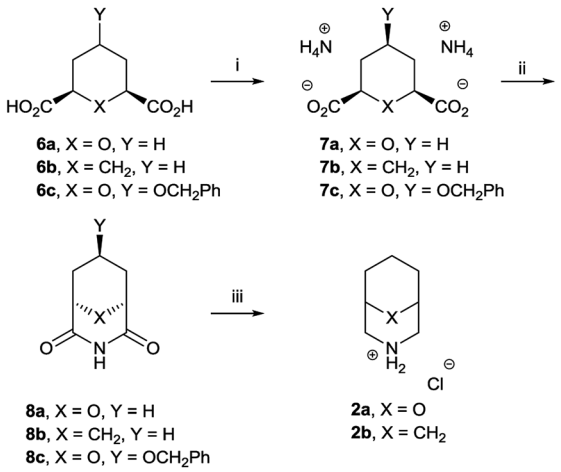


Scheme 1 *Reagents and conditions* (i) Pd/C, H_2, AcOH, 60 °C, 69 h, then aq. NH_3, RT, 30 min, 100%; (ii) 230 °C (stirred solid), 6 h, 78%; (iii) BH_3 in THF, 67 °C, 2 h, then HCl in MeOH, 70 °C, 3 h, 70%; (iv) BD_3 in THF, 67 °C, 24 h; then HCl in MeOH, 70 °C, 3 h, 30%.

reduced to **2b**, either electrolytically under strongly acidic conditions[18] or with lithium aluminium hydride.[19] This route to **2b** was modified in the manner described below for **1a**, again starting from *cis*-cyclohexane-1,3-dicarboxylic acid and proceeding *via* **6b** and **7b** (see Scheme 2 and ESI†).

The route to **1a** parallels that for **2b** and is convenient on a laboratory scale, as well as being applicable to the synthesis of other bridged morpholines exemplified here by an analogous synthesis of **2a**. Catalytic hydrogenation of furan-2,5-dicarboxylic acid **3** was performed at atmospheric pressure in acetic acid at 60 °C to give (2*R*,5*S*)-tetrahydrofuran-2,5-dicarboxylic acid **4**, which was isolated as its crystalline di-ammonium salt in almost quantitative yield. The configuration of **4** was assigned by analogy with that of compound **6a** (see below). Thermolysis of the di-ammonium salt of **4** using either microwave or conventional heating gave 8-oxa-3-aza-bicyclo[3.2.1]octane-2,4-dione **5** (Scheme 1). Optimisation of



Scheme 2 *Reagents and conditions* (i) aq. NH_3, RT, 2 h, 98%; (ii) 230 °C (stirred solid heated), 6 h, 76%; (iii) BH_3 in THF, 67 °C, 2.5 h, then HCl in Et_2O, 70 °C, 3 h, 68% (yields are for the synthesis of **2a**; for **2b** and **8c** see ESI†).

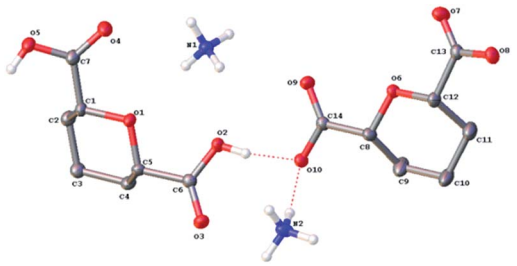


Fig. 1 The asymmetric unit of the crystal structure of **7a** (di-ammonium salt). Only the carboxylic acid protons with the highest occupancy are shown for clarity. Thermal ellipsoids are drawn at the 50% probability level.

the reaction conditions enabled imide **5** to be prepared in up to 78% yield, using conventional heating of **4**. A variety of solvents and conditions was explored for the conversion of **4** into **5**, but none provided a higher yield than heating at 230 °C, the melt derived from the neat solid of **4**. Finally, reduction of imide **5** with borane gave the desired bridged morpholine **1a**, which was isolated as its hydrochloride in 70% yield. None of the steps in this sequence required chromatographic purification.

In a similar manner (Scheme 2), the readily available 4*H*-pyran-2,6-dicarboxylic acid[20] was reduced (H_2, cat. Pd/C) to (2*R*,6*S*)-tetrahydro-2*H*-pyran-2,6-dicarboxylic acid **6a**, which was isolated as crystals of the di-ammonium salt **7a**. The configuration of the diacid was previously assigned by Cope and Fournier[20] and was confirmed by the crystal structure analysis (CCDC: 1471854; for data see Table 1, ESI†) of the di-ammonium salt **7a**, which showed a chair conformer with both carboxyl groups equatorial (Fig. 1). In this structure the protons of the acid groups have been modelled as disordered over two positions along the intermolecular hydrogen bond vectors in such a way that the structure with the highest occupancy is a co-crystal of both the deprotonated and doubly-protonated forms.

Thermolysis of **7a** gave 9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione **8a**, which was reduced with borane to afford 9-oxa-3-aza-bicyclo[3.3.1]nonane **2a**, isolated as its crystalline hydrochloride. A similar cyclisation of diammonium (2*R*,4*s*,6*S*)-4-(benzyloxy)-tetrahydro-2*H*-pyran-2,6-dicarboxylate **7c** gave (1*R*,5*S*,7*s*)-7-(benzyloxy)-9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione **8c** (see ESI† for the synthesis of **6c**).

Conclusions

Syntheses of 8-oxa-3-aza-bicyclo[3.2.1]octane **1a** and 9-oxa-3-aza-bicyclo[3.3.1]nonane **2a** were each rapidly and simply achieved with an overall yield of 50–55% without any hazardous steps, laborious purifications or costly reagents. The key cyclisation step is solvent-free. The developed methodology was also used to prepare [2,2,4,4-$^2H_4$]8-oxa-3-aza-bicyclo[3.2.1]octane **1b** (Scheme 1), which is potentially useful for metabolic studies of drugs containing the bridged morpholine unit derived from **1a**. The method described is versatile being applicable to both cycloalkane-1,3-dicarboxylates[18,19] and oxacycloalkane-1,3-dicarboxylates.

Contributions

B. T. G., R. J. G. and A. V. Z. conceived this study; A. V. Z. and J. E. P. contributed equally to the experimental work assisted by A. P. H. and M. A.; P. G. W. determined the crystal structure; B. T. G. wrote the paper assisted by A. V. Z., C. C., S. J. H. and J. E. P.

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