A Tandem Amination/Lactamisation Route to 2-Azabicyclo[2.2.2]octanones

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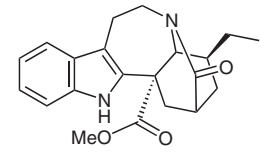
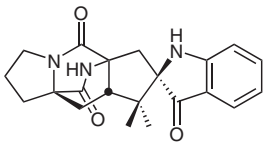
Abstract: An efficient one-pot amination/lactamisation sequence for the preparation of 2-azabicyclo[2.2.2]octanones from 6-carboalkoxycyclohex-2-enones and aqueous ammonia is described. Scope and limitation studies are reported for this tandem procedure and a range of bicyclic compounds have been prepared, two of which were characterised by X-ray crystallography.

Key words: amination, lactamisation, azabicyclo[2.2.2]octanones, bicyclic compounds, 6-carboalkoxycyclohex-2-enones

Functionalised 2-azabicyclo[2.2.2]octan-3-ones occur in a number of natural products such as 3-oxocoronaridine (**1**)[1] and brevianamide A (**2**; Scheme 1).[2] The best-described procedures for the preparation simple 2-azabicyclo[2.2.2]octan-3-ones involve the use of either Diels–Alder cycloaddition routes[3] or the thermal cyclisation of aminocyclohexane carboxylic acids.[4] We recently described an efficient method for preparing isoquinuclidinones from 6-acylcyclohex-2-enones using a tandem amination/imination sequence.[5] Herein we describe the application of a similar tandem procedure to prepare functionalised 2-azabicyclo[2.2.2]octane-3,5-diones **5** from 6-carboalkoxycyclohex-2-enones **3** as shown in Scheme 1. Thus, we envisaged that conjugate addition of ammonia into enones **3** would generate intermediate amino esters **4** which we expected to undergo intramolecular lactamisation to give the desired lactams **5**, possibly in a one-pot process.



1



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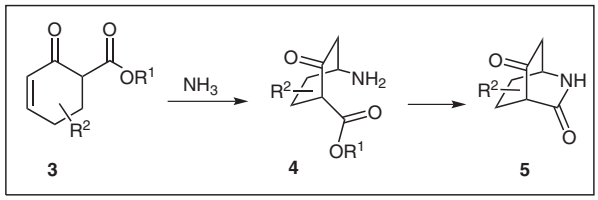
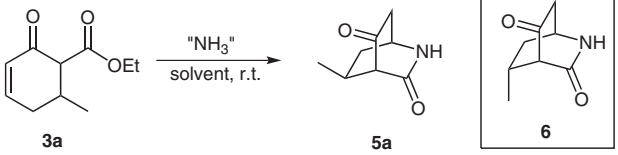


3 4 5

Scheme 1

In order to establish the viability of this approach, we initially decided to examine the cyclisation of the known[6] methyl-substituted cyclohexenone **3a** (Scheme 2 and Table 1).



3a 5a 6

Scheme 2

Table 1 Conversion of Enone **3a** into 8β-Methyl-2-azabicyclo-[2.2.2]octane-3,5-dione (**5a**)[a]

Entry	NH_3 source	Co-solvent	Time (h)	Conv.[b]
1	2.0 M in IPA	–	24	<5%
2	35% aq	THF[c]	24	100%
3	35% aq	MeCN	6	100%
4	35% aq	MeOH	2	100%
5	35% aq	–	1	100%

[a] All reactions were performed on a 0.1 mmol scale; entries 2–5 were carried out using 35% aq NH_3 (0.25 mL) and solvent (0.5 mL).
[b] Conversion estimated by ^{1}H NMR spectroscopy.
[c] A similar result was observed using CH_2Cl_2 as solvent.

The first attempt was carried out using ammonia in isopropanol (IPA) but only a trace amount of 8β-methyl-2-azabicyclo[2.2.2]octane-3,5-dione (**5a**)[7] was observed, even after extended reaction times. On changing to 35% aqueous ammonia, success was achieved under a range of conditions (entries 2–5). When THF or dichloromethane were employed as co-solvents (entry 2), quantitative conversions were observed with a reaction time of 24 hours but the use of acetonitrile or methanol as co-solvent gave full conversion in just a few hours (entries 3 and 4). The optimum procedure, however, used 35% aqueous ammonia without a co-solvent and under these conditions the conversion was complete after one hour at room temperature (entry 5). All of the aqueous ammonia examples resulted in the formation of a single diastereomeric product which was confirmed as the desired methylated 2-azabicyclo[2.2.2]octane-3,5-dione **5a** by ^{1}H NMR/^{13}C NMR spectroscopy [characteristic bridgehead proton signals at

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δ = 4.0 and 3.1 ppm; ^{13}C NMR signals at δ = 205.1 ppm (bridging ketone) and δ = 171.8 ppm (amide)]. This diastereomer was confirmed as the 8β-methyl isomer by NMR analysis and by X-ray crystallography of a crystalline derivative (see later), and the isomeric 8α-methyl isomer **6** was not observed; we assume that the 1,4-addition of ammonia occurs preferentially *anti* to the methyl substituent and that this is followed by in situ lactamisation.

Having confirmed the viability of the one-pot amination/lactamisation sequence, the scope of the transformation was investigated using a range of substrates (Table 2). First the required β-ketoesters **3** were prepared; substrate **3b** was prepared using a literature[8] procedure and the remaining substrates were obtained from cyclohexenones **7** by treatment with LDA in THF–DMPU followed by trapping with ethyl cyanoformate.

As can be seen, the tandem amination/lactamisation sequence was applicable to a range of substituted β-keto esters. The reactions generally proceeded rapidly to give the expected 2-azabicyclo[2.2.2]octane-3,5-diones **5** in good to excellent yields. The initial example giving the 8β-methyl product **5a** proceeded in 93% isolated yield (entry 1) and the corresponding process with a phenyl substituent (**3b** → **5b**) also proceeded smoothly and stereoselectively (entry 2). However, cyclisation was not observed when 3-methyl-6-carboethoxycyclohexenone (**3c**) was employed as starting material (entry 3), presumably substitution at the β-position of the enone disfavours the initial 1,4-addition of ammonia. Moving on to disubstituted enones (entries 4–6), 2-azabicyclo[2.2.2]octane-3,5-diones **5d–5f** were obtained bearing 7,7-, 6,8- and 4,8- substitution patterns in good to excellent yields. The successful cyclisation of the carvone-derived cyclohexenone (**3e** → **5e**; entry 5) indicated that the tandem amination/lactamisation sequence is compatible with substitution at the α-position of the cyclohexenone. Similarly, the successful formation of azabicyclo[2.2.2]octane **5f** (entry 6; structure confirmed by X-ray crystallography, Figure 1) illustrates that ammonia addition/cyclisation can occur on same face as methyl substituent (cyclisation is not possible from the *anti*-addition product due to the presence of the α-methyl substituent preventing ester epimerisation). In both of the latter examples (entries 5 and 6) longer reaction times were required for cyclisation to go to completion. Finally, in this part of the study, we investigated cyclisation of the parent unsubstituted cyclohexenone **3g** (entry 7); in this case the unpurified reaction mixture was slightly more complex but the required 2-azabicyclo-[2.2.2]octane-3,5-dione **5g** was isolated by column chromatography in 60% yield.

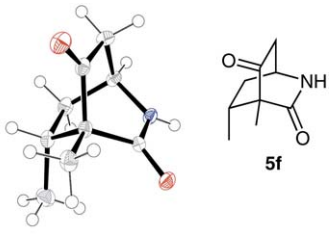
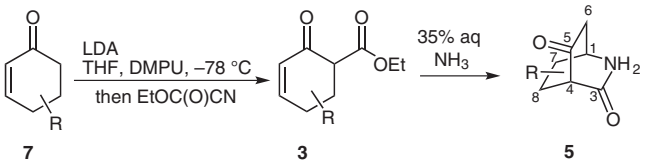
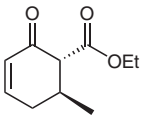
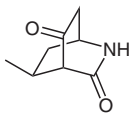
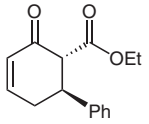
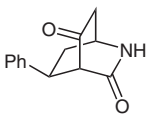
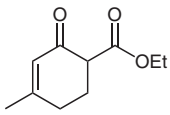
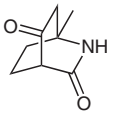
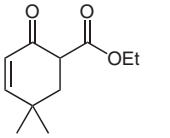
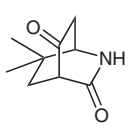
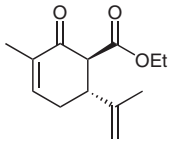
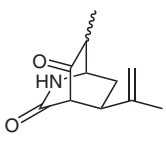
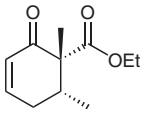
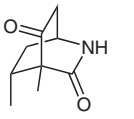
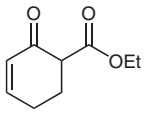
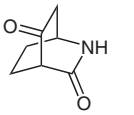


Figure 1 X-ray structure of compound **5f** depicted using ORTEP-3 (CCDC 789903)

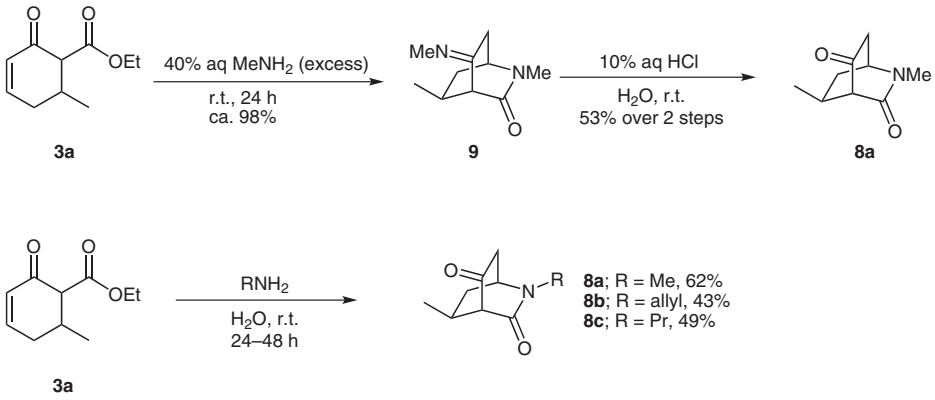
Table 2 Scope of Amination/Cyclisation Sequence[a]



Entry	Substrate **3**	Product **5**	Time (h)	Yield[b] (%)
1	 **3a**	 **5a**	2	93%[9]
2	 **3b**	 **5b**	2	76
3	 **3c**	 **5c**	24	0
4	 **3d**	 **5d**	2	83
5	 **3e**	 **5e**	24	98[c]
6	 **3f**	 **5f**	6	83
7	 **3g**	 **5g**	4	60

[a] All reactions were performed on a 0.25 mmol scale using 35% aq NH_3 (1.0 mL) at r.t.
[b] Isolated yields.
[c] Diastereomeric ratio ca. 4:1

Finally, we briefly explored the use of substituted amines in this process in order to directly prepare *N*-substituted 2-azabicyclo[2.2.2]octane-3,5-diones **8** (Scheme 3). First, the readily available enone **3a** was treated with excess aqueous methylamine. This procedure generated the ex-



Scheme 3

pected bicyclic product but, somewhat surprisingly in view of the ammonia reactions, led to the formation of the unstable imine **9** (characterised by NMR spectroscopy only). However, imine **9** could be readily hydrolysed with 10% aqueous HCl to afford the desired 2-azabicyclo-[2.2.2]octane **8a** in 53% overall yield.

Subsequently, it was found that the unwanted imine formation could be precluded by the use of a stoichiometric amount of methylamine giving adduct **8a** directly in 62% yield (Scheme 3). Similar reactions using allylamine and propylamine gave the corresponding *N*-alkyl-2-azabicyclo-[2.2.2]octane-3,5-diones **8b** and **8c** in fair yields. This process is susceptible to steric effects, however, and no cyclisation was observed when cyclohexenone **3a** was treated with *tert*-butylamine, anisidine or benzylamine. The structure of *N*-methyl 8β-methyl-2-azabicyclo-[2.2.2]octane-3,5-dione (**8a**) was confirmed by X-ray crystallography (Figure 2).

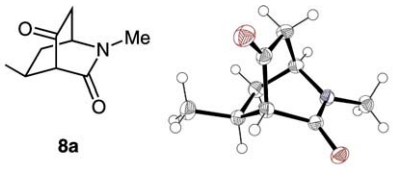


Figure 2 X-ray structure of compound **8a** depicted using ORTEP-3 (CCDC 789904)

In summary, an efficient tandem amination/lactamisation sequence has been developed for the preparation of 2-azabicyclo[2.2.2]octane-3,5-diones from 6-carboalkoxy-cyclohex-2-enones and aqueous ammonia. The scope and limitations of this methodology have been investigated and it has been extended to the direct preparation of some *N*-substituted 2-azabicyclo[2.2.2]octane-3,5-diones. Applications of the amination/lactamisation sequence in the synthesis of polycyclic alkaloids are currently under investigation.

Acknowledgment

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References and Notes

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(9) **Typical Procedure for the Synthesis of 8β-Methyl-2-azabicyclo[2.2.2]octane-3,5-dione (5a)**: A solution of β-keto ester **3a** (46 mg, 0.25 mmol) in 35% aq NH_3 (1 mL) was stirred at r.t. until consumption of starting material was observed by TLC analysis (CH_2Cl_2–MeOH, 9:1), ca. 2 h. The reaction mixture was then concentrated in vacuo and purified by column chromatography (SiO_2, CH_2Cl_2–MeOH, 98:2) to give the title compound **5a** as a colourless crystalline sold (36 mg, 93%); mp 135–137 °C; R_f 0.40 (CH_2Cl_2–MeOH, 9:1). IR (thin film): 3244, 2961, 1730, 1681, 1335, 1105 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (br s, 1 H, NH), 3.93–3.98 (m, 1 H), 3.03–3.11 (m, 1 H), 2.40–2.49 (m, 2 H), 2.28–2.37 (m, 1 H), 2.20 (dd, *J* = 18.5, 1.9 Hz, 1 H), 1.31 (ddd, *J* = 13.0, 4.6, 1.0 Hz, 1 H), 1.06 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1 (CO), 171.8 (CO), 64.4 (CH), 47.0 (CH), 43.8 (CH_2), 35.4 (CH_2), 29.4 (CH), 20.8 (Me). MS: *m*/*z* (ESI) = 154 $[MH]^+$. HRMS (ESI): *m*/*z* $[M + H^+]$ calcd for $C_8H_{12}NO_2$: 154.0863; found: 154.0864 (0.6 ppm error).