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The triflic acid-mediated cyclisation of *N*-benzyl-cinnamamides

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ABSTRACT

N-Benzyl-cinnamamides cyclise with triflic acid to form 5-aryl-benzazepinones and/or cinnamamides.
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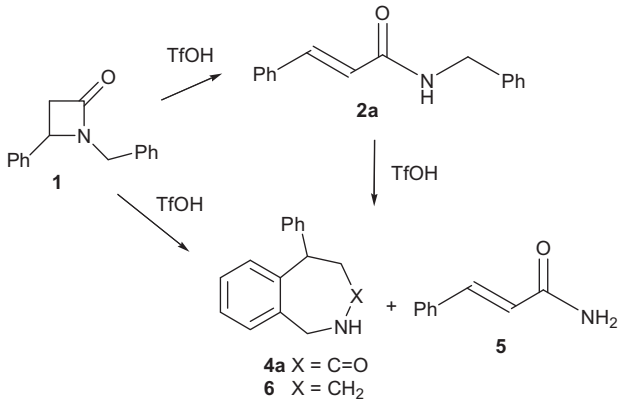
1. Introduction

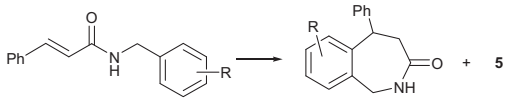
We have recently reported that *N*-benzyl-4-aryl-azetidinones (exemplified by **1** in Scheme 1) undergo ring opening with TfOH in $CHCl_3$ to give 5-phenyl-benzazepin-3-ones via *N*-benzyl-cinnamamides.[1]

Further investigation confirmed that **2a** underwent TfOH-mediated cyclisation to **4a** (Table 1, entry 1) together with the formation of a small amount of cinnamamide **5**. Previously cyclisation of *N*-benzyl-cinnamamides had been reported using polyphosphoric acid, but was restricted to *N*-methyl-*N*-3-methoxybenzyl derivatives.[2] 5-Phenyl-benzazepinones and derivatives related to **4a** have potential use as antiarrhythmics and memory enhancers[3,4] and are intermediates to 5-phenyl-benzazepines related to **6**, which have been reported to have opioid receptor antagonist[5] and triple re-uptake inhibitor activity.[2] Therefore, we were interested in investigating the scope of the TfOH-mediated cyclisation of *N*-benzyl-cinnamamides to produce novel analogues for biological testing.



Scheme 1.

Table 1
Yields of benzazepinones **4a–e**



Entry	Amide	R	Product	Yield %	**5** Yield %
1	**2a**	H	**4a**	69	7
2	**2b**	4-Me	**4b**	0	25
3	**2c**	3-Me	**4c**	37[a]	15
4	**2d**	4-Cl	**4d**	0	61
5	**2e**	3-MeO	**4e**	0	0
6[b]	**2e**	3-MeO	**4e**	28	3

[a] Mixture of the 8- and 6-Me isomers in a 2:1 ratio.
[b] See text.

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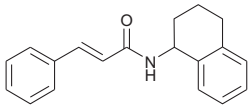
2. Results and discussion

2.1. Cyclisations of *N*-benzyl-cinnamamides—substituted benzyl

Previously we have shown that substitution on the *N*-benzyl group of the 4-phenyl-azetidinone considerably reduced the yield of 5-phenyl-benzazepin-3-one.[1] Similarly, in this study both the *N*-4-Me-benzyl **2b** (Table 1, entry 2) and the *N*-4-Cl-benzyl **2d** (entry 4) gave no cyclised products, only cinnamamide **5**. However, the 3-Me **2c** (entry 3) gave **4c** as a 2:1 mixture of the 8- and 6-isomers together with cinnamamide **5**, an improvement over the conversion of the azetidinone to **4c** (24% yield).[1] 3-MeO-benzyl analogues have been reported to cyclise in moderate yields using polyphosphoric acid to give the 8-methoxy isomer.[2] The 3-MeO compound **2e** (entry 5) rapidly reacted with TfOH (30 min) under reflux in $CHCl_3$ to give a complex mixture of products. However, with Eaton's reagent in 1,2-dichloroethane (DCE) at reflux overnight (entry 6), an inseparable mixture of the 6-MeO and 8-MeO isomers (ratio 2:1) was obtained.

Reaction of the tetrahydro-naphthalene **7** gave only cinnamamide **5**, probably due to the enhanced stability of the benzylic carbonium ion[6] facilitating N-debenzylation.



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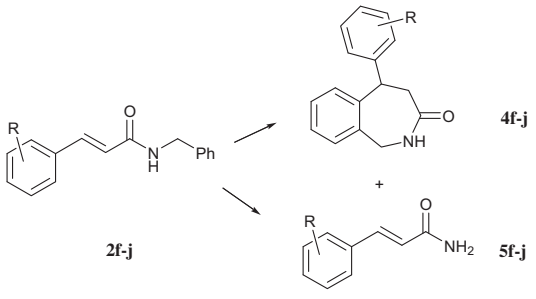
2.2. Cyclisations of *N*-benzyl-cinnamamides—substituted cinnamamides

The cyclisation reaction was much more successful for substituted cinnamamides (Table 2).

The 4-Me **2f** (entry 1) and 4-Br **2h** (entry 4) cyclised to give the benzazepinones **4f** and **4h**, respectively, together with small amounts of cinnamamides. However, the 3-Me **2g** (entry 2) cyclised to **4g** with no evidence of formation of the cinnamamide. Repeating the reaction of **2g** (entry 3) in the presence of 10% P_2O_5 (to remove any water present) increased the yield of **4g**.

Table 2
Yields of benzazepinones **4f**–**k**

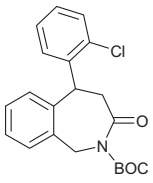


2f-j **4f-j** **5f-j**

Entry	Amide	R	Time h	Product	Yield %	**5f**–**j** yield %
1	**2f**	4-Me	3	**4f**	76	2
2	**2g**	3-Me	3	**4g**	50	0
3	**2g**	3-Me	3	**4g**	70[a]	0
4	**2h**	4-Br	3[b]	**4h**	85	7
5	**2i**	2-Cl	5[b]	**4i**	43	43
6	**2j**	3-Cl	3[b]	**4j**	11	38
7	**2k**	3,4-benzo	3	**4k**	0	0

[a] With 10% P_2O_5/TfOH.
[b] In 1,2-dichloroethane (DCE).

We were particularly interested in synthesizing the 2-Cl analogue **4i**, as the bulk of the *ortho* substituent should affect the preferred conformation of the molecule. However, we reported previously that the 4-(2-chlorophenyl)-azetidinone failed to give any **4i**.[1] In contrast, **2i**, heated under reflux in dichloroethane for 5 h (entry 5) gave an inseparable 1:1 mixture of **4i** and **5i**. Pure **4i** was obtained by formation[7] and purification of the *N*-BOC derivative **8** (overall 30% yield from **2i**) followed by BOC cleavage with HCl (90% yield).



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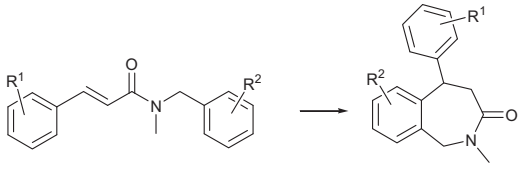
The reaction of 3-Cl **4j** (entry 6) was also slow and after 5 h reflux in DCE, 30% of starting material was recovered, together with a 49% yield of a 3.5:1 inseparable mixture of the cinnamamide **5j** and benzazepinone **4j**. Similarly to the 4-(2-naphthyl)-azetidinone,[1] the 2-naphthyl **2k** (entry 7) gave only insoluble, unidentified products.

2.3. Cyclisations of *N*-benzyl-cinnamamides—*N*-alkyl analogues

Unlike the azetidinones, the use of cinnamamides allowed us to investigate *N*,*N*-disubstituted derivatives. The *N*-methyl derivative **9a**[8] cyclised to give the benzazepinone **10a** in good yield (entry 1, Table 3), with no evidence of the formation of *N*-methyl-cinnamamide.

Table 3
Yields of *N*-methyl-benzazepinones **10a**–**k**



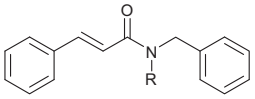
9a-k **10a-k**

Entry	Amide	R^1	R^2	Product	Yield %	*N*-methyl-cinnamamide yield %
1	**9a**	H	H	**10a**	83	0
2	**9c**	H	3-Me	**10c**	37[a]	5
3	**9e**	H	3-MeO	**10e**	64[b]	3
4	**9i**	2-Cl	H	**10i**	27	54
5	**9j**	3-Cl	H	**10j**	20	60
6	**9k**	3,4-benzo	H	**10k**	35	0

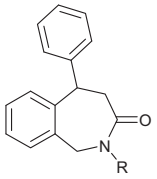
[a] 55:45 mixture of 8- and 6-isomers.
[b] 5:3 mixture of 6- and 8-isomers.

As cyclisation of the *N*-methyl derivative appeared to give a higher yield with reduced formation of the cinnamamide, we re-investigated the cyclisations of substituted cinnamamides, which had given poor yields with the NH amides. Thus, cyclisation of the 3-methylbenzyl **9c** (entry 2) gave a similar yield of benzazepinone, but as a 55:45 mixture of the 8- and 6-isomers together with a small amount of *N*-methyl-cinnamamide. Cyclisation of the 3-methoxy **9e** (entry 3) was very rapid (30 min) and gave a 5:3 mixture of the 6- and 8-isomers. Cyclisation of the 2-Cl **9i** (entry 4) gave a 2:1 mixture of the *N*-methyl-cinnamamide and **10i**. The cinnamamide was removed by conversion into its *N*-BOC derivative and separation using column chromatography to give the pure **10i** (overall yield 25% from **9i**). The ^{1}H NMR spectrum of **10i** at room temperature showed broadening of some of the peaks indicating a slow conformational change. Whereas cyclisation of the naphthyl

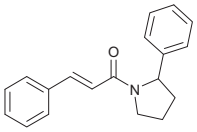
2k gave no cyclic product, the *N*-methyl analogue **9k** (entry 6) gave the desired benzazepinone **10k**.



11 R = CH_2Ph



12 R = CH_2Ph



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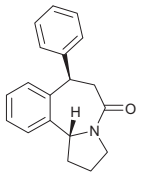
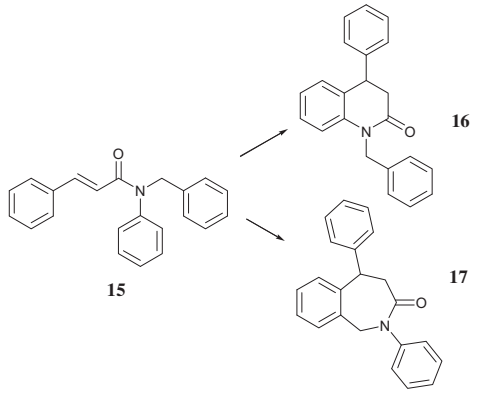


14 (±)

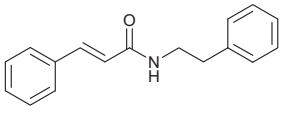
Cyclisation of the *N*-dibenzyl **11** gave the *N*-benzyl-benzazepinone **12** (68% yield) together with **4a** (12% yield). The TfOH-mediated cyclisation of the 2-phenylpyrrolidine derivative **13** gave **14** (35% yield). Although we obtained a lower yield than previously obtained by the iminium ion cyclisation,[9] this method could be applied to analogues with substituents on the 7-phenyl ring, as analogues of **13** can be prepared from readily available cinnamic acids.



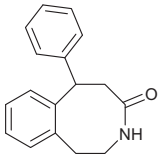
15 **16** **17**

We also found that the cyclisation of the *N*-phenyl-*N*-benzyl derivative **15**, gave the six-membered **16** (80% yield) with only a 7% yield of the seven-membered **17**. *N*-Phenyl-cinnamamide has previously been reported to undergo a facile TfOH-mediated cyclisation to give 4-phenyl-tetra-hydroquinolin-2-one.[10]

Previously, we have shown that appropriately substituted *N*-acyl-iminium ions cyclise with TfOH to give the eight-membered benzazocin-4-ones.[11] However, the *N*-phenethyl derivative **18**[12] with TfOH failed to give any benzazocin-4-one **19**, although with benzene the 3,3-diphenyl-propionamide **20** was formed. Thus it appears that **18** is protonated by the TfOH, but cyclisation to the eight-membered ring is not favoured.



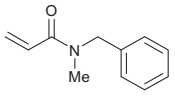
18



19

$Ph_2CHCH_2CONHCH_2CH_2Ph$ **20**

The acryloyl amide **21**[13] failed to give either the benzazepinone **22** or the 3-phenylpropionamide **23** with TfOH in benzene. Thus, we believe that the stabilisation of the carbonium ion by the phenyl of the cinnamoyl group assists in the protonation and subsequent cyclisation.



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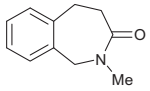

22

$PhCH_2CH_2CON(Me)CH_2Ph$ **23**

3. Conclusion

In summary, we have shown that *N*-benzyl-cinnamamides can undergo a TfOH-mediated cyclisation in an inert solvent to give 5-phenyl-benzazepin-3-ones. However, with substituted *N*-benzyl analogues, the major product is cinnamamide, resulting from *N*-debenzylation, exceptions being where the electronics of the substituent favours cyclisation. In contrast, good yields of benzazepinones can be obtained from cinnamamides with substituents in the phenyl ring. *N*-Benzyl-*N*-methyl-cinnamamides cyclise more rapidly and generally in higher yields. Seven-membered cyclisation is less favoured than six-membered.

4. Experimental section

4.1. General

All reagents were commercially available, unless otherwise specified, and used without purification. The chloroform used was stabilised with amylene. Commercial dry benzene was stored over molecular sieves. Petroleum ether was 40–60 °C fraction. Infrared spectra were run neat on a Perkin Elmer 100 FT IR spectrometer. Solution ^1H and ^{13}C NMR spectra, in $CDCl_3$ unless otherwise stated, were recorded on a Bruker NMR spectrometer DRX500 or Avance III 400, equipped with z-gradient facilities. ^1H and ^{13}C chemical shifts are given relative to TMS. Unless otherwise specified, spectra were recorded at 300 K. Mass spectra were run on a Thermo Mat900XP for EI and a Waters Micromaldi for TOF. Melting points were determined on a Sanyo-Gallenkamp capillary melting point apparatus and are uncorrected.

4.2. General procedure for the synthesis of the cinnamamides

A solution of the cinnamic acid (5.0 mmol) and oxalyl chloride (5.5 mmol) in DCM (50 mL) and 2 drops of DMF was stirred at room temperature for 2 h, until evolution of CO_2 had ceased. The DCM was removed by rotary evaporation, the residue dissolved in $CHCl_3$ (30 mL) and the $CHCl_3$ removed by rotary evaporation to remove any excess oxalyl chloride. The residue was dissolved in DCM (20 mL) and added to a stirred solution of the benzylamine (6.5 mmol) and triethylamine (7.0 mmol) in DCM (100 mL) at 0 °C. The reaction was stirred at room temperature for 1 h, washed with 2 M aq HCl (30 mL), water (30 mL) and 2 M aq K_2CO_3 (30 mL) and dried ($MgSO_4$). Removal of the solvent gave a solid, which was recrystallised from EtOAc/petroleum ether.

*4.2.1. (E)-N-(3-Methyl-benzyl)-3-phenyl-acrylamide (**2c**).* White solid (93% yield), mp 107–109 °C, ^1H NMR (500 MHz, $CDCl_3$) δ=3.45 (3H, s), 4.50 (2H, d, *J*=5.7 Hz), 5.93 (1H, br t), 6.41 (1H, d, *J*=15.6 Hz), 7.09–7.15 (3H, m), 7.24 (1H, t, *J*=7.6 Hz), 7.33–7.39 (3H, m), 7.47–7.51 (2H, m), 7.67 (1H, d, *J*=15.6 Hz); ^{13}C NMR+DEPT

(125 MHz, $CDCl_3$) δ=21.4 (CH_3), 43.9 (CH_2), 120.5 (CH), 125.1 (CH), 127.9 (CH), 128.4 (CH), 128.8 (CH), 128.8 (CH), 128.9 (CH), 129.8 (CH), 134.9 (C), 138.2 (C), 138.6 (C), 141.5 (CH), 165.8 (C); ν_{max} (solid) 3310, 1653, 1614, 1542, 1341, 1215, 987, 976, 769, 719, 689 cm^{-1}; HRMS (EI) M^+, found 251.1303, $C_{17}H_{17}NO$ requires 251.1305.

*4.2.2. (E)-N-(3-Methoxy-benzyl)-3-phenyl-acrylamide (**2e**).* White solid (92% yield), mp 114–115 °C; ^1H NMR (500 MHz, $CDCl_3$) δ=3.79 (3H, s), 4.55 (2H, d, *J*=5.8 Hz), 5.98 (1H, br s), 6.42 (1H, d, *J*=15.6 Hz), 6.83 (1H, dd, *J*=2.1, 8.2 Hz), 6.86–6.88 (1H, m), 6.91 (1H, dd, *J*=0.5, 7.7 Hz), 7.26 (1H, t, *J*=7.7 Hz), 7.34–3.37 (3H, m), 7.46–7.50 (2H, m), 7.67 (1H, d, *J*=15.6 Hz); ^{13}C NMR+DEPT (125 MHz, $CDCl_3$) δ=43.9 (CH_2), 55.3 (CH_3), 113.2 (CH), 113.5 (CH), 120.2 (CH), 120.5 (CH), 127.9 (CH), 128.9 (CH), 129.8 (CH), 129.9 (CH), 134.8 (C), 139.8 (C), 141.5 (CH), 160.0 (C), 165.8 (C); ν_{max} (solid) 3233, 3061, 1651, 1610, 1584, 1489, 1438, 1265, 1223, 1157, 1146, 1045, 990, 873, 770, 739 cm^{-1}; LRMS (EI) 281, 204; HRMS (EI) M^+, found 267.1256, $C_{17}H_{17}NO_2$ requires 267.1254.

*4.2.3. (E)-3-Phenyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-acrylamide (**7**).* White solid (83% yield), mp 188–190 °C; ^1H NMR (500 MHz, $CDCl_3$) δ=1.80–1.95 (2H, m), 2.05–2.18 (1H, m), 2.75–2.87 (2H, m), 5.30–5.37 (1H, m), 5.90 (1H. br d), 6.39 (1H, d, *J*=15.6 Hz), 7.11 (1H, d, *J*=6.5 Hz), 7.14–7.21 (2H, m), 7.28–7.40 (4H, m), 7.49 (3H, d, *J*=6.2 Hz), 7.67 (1H, d, *J*=15.6 Hz); ^{13}C NMR+DEPT (125 MHz, $CDCl_3$) δ=20.0 (CH_2), 29.3 (CH_2), 30.2 (CH_2), 47.7 (CH), 120.9 (CH), 126.4 (CH), 127.4 (CH), 127.8 (CH), 128.9 (CH), 129.0 (CH), 129.3 (CH), 129.7 (CH), 134.9 (C), 136.7 (C), 137.7 (C), 141.3 (CH), 165.1 (C); ν_{max} (solid) 3263, 1650, 1615, 1540, 1350, 1218, 990, 976, 768, 748, 724, 671 cm^{-1}; LRMS (EI) 277, 146, 131, 130, 103, 91, 77; HRMS (EI) M^+, found 277.1464, $C_{19}H_{19}NO$ requires 277.1461.

*4.2.4. (E)-N-(3-Methyl-benzyl)-N-methyl-3-phenyl-acrylamide (**9c**).* To a stirred solution of *N*-methyl-cinnamamide[14] (0.65 g, 4.0 mmol) and 3-methyl-benzyl bromide (0.74 g, 4.4 mmol) in THF (20 mL) at 0 °C was added KO*t*-Bu (0.46 g, 4.0 mmol) and the solution stirred at room temperature for 1 h. The THF was removed by rotary evaporation and the residue partitioned between water (50 mL) and DCM (100 mL). The lower organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography, eluting with 0.5% MeOH/DCM to give the product, isolated as a colourless oil (88% yield); R_f (DCM) 0.43; NMR shows two rotamers about the amide bond in a 1:1 ratio, ^1H NMR (500 MHz, $CDCl_3$) δ=2.35, 2.35 (3H, 2s), 3.06 (1.5H, s), 3.08 (1.5H, s), 4.65 (1H, s), 4.69 (1H, s), 6.88 (0.5H, d, *J*=15.4 Hz), 6.95 (0.5H, d, *J*=15.4 Hz), 7.00–7.05 (1H, m), 7.06–7.12 (2H, m), 7.19–7.29 (1H, m), 7.30–7.42 (3H, m), 7.45–7.50 (1H, m), 7.55 (1H, m), 7.76 (0.5H, d, *J*=15.4 Hz), 7.79 (0.5H, d, *J*=15.4 Hz); ^{13}C NMR+DEPT (125 MHz, $CDCl_3$) δ=21.5 (CH_3), 34.5 (CH_3), 35.0 (CH_3), 51.3 (CH_2), 53.5 (CH_2), 117.5 (CH), 123.6 (CH), 125.3 (CH), 127.2 (CH), 127.9 (CH), 128.2 (CH), 128.8 (CH), 128.9 (CH), 128.9 (CH), 129.6 (CH), 129.7 (CH),135.4 (C), 135.4 (C), 136.8 (C), 137.3 (C), 138.4 (C), 138.8 (C), 143.0 (CH), 143.1 (CH), 166.7 (C), 167.3 (C); ν_{max} (film) 1648, 1603, 1397, 1114, 976, 762, 699, 684 cm^{-1}; LRMS (EI) 266, 134, 131, 105; HRMS (EI) M^+, found 266.1546, $C_{18}H_{20}NO$ requires 266.1545.

4.3. General procedure for the TfOH-mediated ring cyclisation reactions

Triflic acid (20 mmol) was added to a stirred solution of the lactam or cinnamamide (2.0 mmol) in $CHCl_3$ (20 mL) and the reaction mixture was heated under gentle reflux for 3 h. The reaction mixture was cooled to room temperature, water (20 mL) was added followed by an excess of solid K_2CO_3 until CO_2 evolution ceased. The product was extracted into DCM (2×50 mL), dried ($MgSO_4$), concentrated in vacuo and the product purified by column chromatography on SiO_2.

*4.3.1. 5-(p-Tolyl)-1,2,4,5-tetrahydro-benzo[c]azepin-3-one (**4f**).* Following the general procedure for cyclisation, **2f** (0.45 g, 2 mmol) was converted into **4f** (0.34 g, 76% yield), R_f (Et_2O) 0.1, purified using 0.5% MeOH/DCM as eluant and isolated as a white solid, mp 190–191 °C, spectroscopically identical to that previously prepared from the azetidinone.[1]

*4.3.2. 5-(2-Chlorophenyl)-1,2,4,5-tetrahydro-benzo[c]azepin-3-one (**4i**).* Following the general procedure for cyclisation, but using DCE as solvent, **2i** (0.78 g, 2.9 mmol) was heated under reflux with TfOH (3.0 mL, 30 mmol) for 3 h. Purification by column chromatography on SiO_2, eluting with 2% MeOH/DCM gave a product (0.57 g), which, by NMR spectroscopy analysed for a 1:1 mixture of **4i** and **5i**. The impure product from two reactions (0.95 g) was dissolved in DCM (30 mL), treated with BOC anhydride (2.0 g, 8.5 mmol), Et_3N (2 mL, 14 mmol) and DMAP (1.0 g, 8 mmol) and stirred at room temperature for 2 days. The solvent was removed by rotary evaporation and the residue partitioned between EtOAc (50 mL) and 2 M aq H_2SO_4 (50 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by column chromatography on SiO_2, eluting with DCM—5% Et_2O/DCM to give the *N*-BOC derivative **8**, recrystallised from DCM/petroleum ether as a pale yellow solid (0.55 g, overall 30% yield from **2i**), mp 139–140 °C; ^1H NMR (500 MHz, $CDCl_3$) δ=1.49 (9H, s), 3.15–3.35 (2H, br m), 4.98 (1H, d, *J*=16.4 Hz), 5.02–5.09 (1H, br m), 5.14 (1H, d, *J*=16.4 Hz), 6.73–6.80 (1H, br m), 6.91 (1H, dd, *J*=4.4, 5.8 Hz), 7.09 (1H, t, *J*=7.5 Hz), 7.14 (1H, dt, *J*=1.7, 7.5 Hz), 7.17–7.20 (2H, m), 7.23–7.26 (1H, m), 7.37 (1H, dd, *J*=1.3, 7.9 Hz); ^{13}C NMR+DEPT (125 MHz, $CDCl_3$) δ=28.1 (CH_3), 42.1 (CH_2), 43.0 (CH), 49.3 (CH_2), 83.3 (C), 127.0 (CH), 127.3 (CH), 128.3 (CH), 128.7 (CH), 129.7 (CH), 129.9 (CH), 130.6 (CH), 131.8 (CH), 133.1 (C), 134.8 (C), 139.0 (C), 142.4 (C), 151.8 (C), 171.4 (C); ν_{max} (solid) 1728, 1698, 1367, 1300, 1281, 1236, 1145, 1099, 854, 776, 763, 740 cm^{-1}; LRMS (TOF) 396, 394, 337, 335, 215, 213, 178; HRMS (electrospray TOF) MNa^+, found 394.1183, $C_{21}H_{22}{}^{35}ClNNaO_3$ requires 394.1186. A solution of **8** (0.40 g, 1 mmol) in DCM (10 mL) and 4 M HCl in dioxan (1.0 mL) was stirred at room temperature for 1 h. The solvent was removed by rotary evaporation and the residue purified by column chromatography on SiO_2, eluting with 0.5% MeOH/DCM to give **4i** as an orange solid, recrystallised from EtOAc/petroleum ether (0.26 g, 90% yield), mp 160–162 °C; ^1H NMR (500 MHz, $CDCl_3$) δ=3.10 (2H, d, *J*=6.6 Hz), 4.47 (1H, dd, *J*=6.3, 16.3 Hz), 4.52 (1H, dd, *J*=4.6, 16.3 Hz), 5.06 (1H, t, *J*=6.6 Hz), 6.82–6.87 (1H, m), 6.93 (1H, d, *J*=7.6 Hz), 7.07–7.19 (5H), 7.25 (1H, br s), 7.39 (1H, dd, *J*=1.3, 7.9 Hz); ^{13}C NMR+DEPT (125 MHz, $CDCl_3$) δ=38.9 (CH_2), 41.4 (CH), 46.5 (CH_2), 126.7 (CH), 127.2 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 129.8 (CH), 130.5 (CH), 131.6 (CH), 133.3 (C), 135.9 (C), 140.1 (C), 142.4 (C), 174.5 (C); ν_{max} (solid) 1673, 1471, 1435, 1033, 769, 750, 725 cm^{-1}; LRMS (EI) 273, 271, 236, 214, 212, 193, 178, 165, 86, 84; HRMS (EI) M^+, found 271.0758, $C_{16}H_{14}{}^{35}ClNO$ requires 271.0752.

*4.3.3. 5-(2-Chlorophenyl)-N-methyl-1,2,4,5-tetrahydro-benzo-[c]azepin-3-one (**10i**).* Following the general procedure for cyclisation, **9i** (0.57 g, 2.0 mmol) was converted into a 2:1 mixture of the *N*-methyl cinnamamide and **10i** (0.37 g, 82% conversion). This mixture was reacted with BOC anhydride (1.0 g, 4.3 mmol) as described for **4i**. Column chromatography on SiO_2, eluting first with 1:1 DCM/petroleum ether to remove the BOC derivative of the cinnamamide, then DCM to give **10i**, isolated as an oil (0.15 g, 25% yield from **9i**). ^1H NMR (400 MHz, $CDCl_3$, 330 K) δ=3.05–3.11 (4H, m including 3.07, 3H, s), 3.29 (1H, dd, *J*=10.3, 13.8 Hz), 4.37 (1H, d,

J=16.2 Hz), 4.90 (1H, d, J=16.2 Hz), 5.05 (1H, dd, J=5.2, 10.3 Hz), 6.85–6.90 (1H, m), 6.90–6.93 (1H, m), 7.10–7.40 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 330 K) δ=34.8 (CH_3), 39.9 (CH_2), 42.6 (CH), 55.1 (CH_2), 126.6 (CH), 127.3 (CH), 128.1 (CH), 128.6 (CH), 128.9 (CH), 130.0 (CH), 130.7 (CH), 132.3 (CH), 133.4 (C), 135.1 (C), 140.1 (C), 143.5 (C), 171.7 (C); ν_{max} (film) 1643, 1475, 1395, 1103, 1035, 758, 745 cm^{-1}; LRMS (EI) 287, 285, 250, 214, 212, 193, 191, 178, 165, 110, 109, 97, 95; HRMS (EI) M^+, found 285.0919, $C_{17}H_{16}{}^{35}ClNO$ requires 285.0915.

*4.3.4. N-Benzyl-5-phenyl-1,2,4,5-tetrahydro-benzo[c]azepin-3-one (**12**).* Following the general procedure for cyclisation, **11**[15] (0.66 g, 2.0 mmol) was converted into **12** (0.16 g, 35% yield) by heating under reflux with TfOH (2.0 mL, 20 mmol) in $CHCl_3$ (10 mL) for 1 h, purified using 1:1 Et_2O/petroleum ether as eluant and isolated as a white solid, mp 130–131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=3.07 (1H, dd, J=5.1, 13.8 Hz), 3.38 (1H, dd, J=11.5, 13.8 Hz), 4.14 (1H, d, J=16.3 Hz), 4.43 (1H, d, J=14.9 Hz), 4.57–4.58 (1H, m), 4.91 (1H, d, J=14.9, 16.3 Hz), 6.91 (1H, d, J=7.6 Hz), 6.96 (1H, d, J=7.7 Hz), 7.05 (1H, t, J=7.5 Hz), 7.08–7.15 (2H, m), 7.19–7.35 (9H, m); ^{13}C NMR+DEPT (125 MHz, $CDCl_3$) δ=42.9 (CH_2), 45.8 (CH), 50.0 (CH_2), 52.0 (CH_2), 126.2 (CH), 126.7 (CH), 127.6 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 132.7 (CH), 134.7 (C), 137.2 (C), 140.4 (C), 146.4 (C), 172.1 (C); ν_{max} (solid) 1640, 756, 735, 695 cm^{-1}; LRMS (EI) 327, 194, 179, 178; HRMS (EI) M^+, found 327.1620, $C_{23}H_{21}NO$ requires 327.1618.

*4.3.5. N-Benzyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one (**16**) and 2,5-diphenyl-1,2,4,5-tetrahydro-benzo[c]azepin-3-one (**17**).* Following the general procedure for cyclisation, **15** (0.62 g, 2 mmol) was converted into **16** (0.50 g, 80% yield) and **17** (0.04 g, 7% yield) by heating under reflux with TfOH (2.0 mL, 20 mmol) in $CHCl_3$ (10 mL) for 1 h. Elution with 3:1 DCM/petroleum ether gave **16** as a white solid, R_f (DCM) 0.42, spectroscopically identical to the literature material.[16] Elution with DCM gave **17** as a white solid, mp 197–198 °C; R_f (DCM) 0.10; ^{1}H NMR (500 MHz, $CDCl_3$) δ=3.18 (1H, dd, J=4.9, 13.6 Hz), 3.46 (1H, dd, J=11.2, 13.6 Hz), 4.61–4.70 (2H, m), 5.41 (1H, d, J=16.4 Hz), 7.03 (1H, d, J=7.3 Hz), 7.10–7.39 (13H, m); ^{13}C NMR+DEPT (125 MHz, $CDCl_3$) δ=43.4 (CH_2), 45.9 (CH), 56.5 (CH_2), 125.8 (CH), 126.7 (CH), 126.8 (CH), 128.3 (CH), 128.6 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 132.9 (CH), 135.2 (C), 140.3 (C), 143.4 (C), 146.4 (C), 171.5 (C); ν_{max} (solid) 1663, 1596, 1491, 1438, 1399, 1206, 1101, 1076, 787, 758, 739, 697 cm^{-1}; LRMS (EI) 313, 265, 201, 192, 179, 178; HRMS (EI) M^+, found 313.1458, $C_{22}H_{19}NO$ requires 313.1458.

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Supplementary data

Supplementary data contains experimental procedures and characterizing data for **2a**, **2b**, **2d**, **2h**, **2i**, **2f**, **2g**, **2k**, **2j**, **4a**, **4e**, **4g**, **4h**, **9a**, **9e**, **9i**, **9j**, **9k**, **10a**, **10c**, **10e**, **10j**, **10k**, **13**, **14** and **20**. NMR (^{1}H and ^{13}C) spectra are included for the novel compounds **2c**, **2e**, **2f**, **2g**, **4i**, **7**, **8**, **9c**, **9i**, **10c**, **10i**, **10k**, **12**, **13**, **15**, **17**, and **20**. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.11.035.

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