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The acid-mediated ring opening/cyclisation reaction of *N*-benzyl-α-aryl-azetidinones

Frank D. King *, Stephen Caddick

Dept. of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

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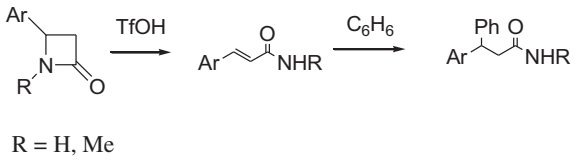
ABSTRACT

N-Benzyl-4-aryl-azetidinones undergo ring opening with triflic acid to form *N*-benzyl-cinnamamides, which either undergo cyclisation to give 5-aryl-benzazepin-3-ones or N-debenzylation to give cinnamamides.

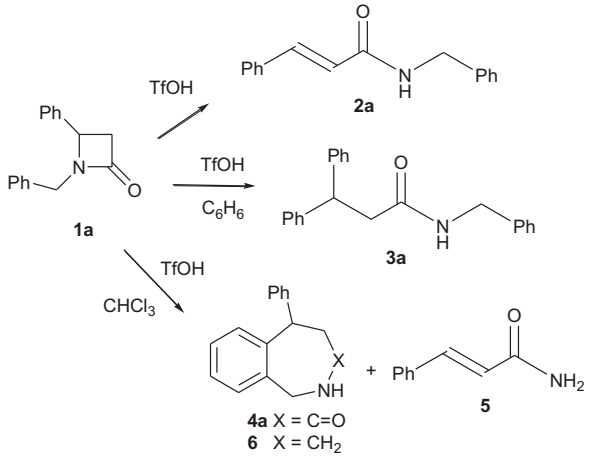
1. Introduction

We have recently shown that 4-aryl-azetidinones undergo ring opening with triflic acid (TfOH) in benzene to give cinnamamides, which undergo further reaction to give 3-phenyl-3-aryl propionamides (Scheme 1), most likely via a dication.[1,2]



Scheme 1.

During our further investigations on this reaction, we found that the *N*-benzyl derivative **1a** (Scheme 2) also rapidly underwent a TfOH-mediated ring opening to give *N*-benzylcinnamamide **2a** (85% yield). In benzene, **2a** reacted further to give *N*-benzyl-3,3-diphenylpropionamide **3a** (83% yield), together with a small amount (~5%) of a mixture of the benzazepinone **4a** and cinnamamide **5**. However, in $CHCl_3$, **1a** cyclised to give **4a** (65% yield) and **5** (7% yield).



Scheme 2.

The ability to produce benzazepinones and derivatives related to **4a** was intriguing because such structures have potential use as antiarrhythmics and memory enhancers,[3–5] and are intermediates to benzazepines **6**, which have been reported to have opioid receptor antagonist[6] and triple re-uptake inhibitor activity.[7] We were therefore interested in investigating this ring-opening/cyclisation reaction to synthesize novel analogues for biological evaluation.

* Corresponding author. E-mail address: fd.king@btinternet.com (F.D. King).

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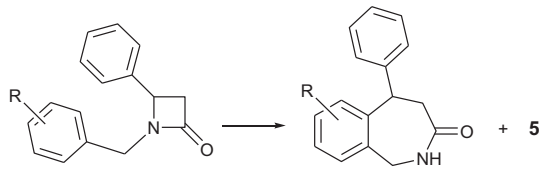
2. Results

Initially, we investigated what the effect of modifications of the *N*-benzyl group had on the ring-opening/cyclisation reaction (Table 1). The *N*-benzyl azetidinones were readily prepared from the azetidinones using KO*t*-Bu and benzyl bromide in THF. One equivalent of the benzyl bromide gave only moderate yields of the *N*-benzyl derivatives (35–60%), but 3 equiv gave much improved yields (>90%). In order to effect the ring-opening/cyclisation reaction, the *N*-benzyl-azetidinones were heated under reflux in $CHCl_3$ with 10 equiv of TfOH for 3 h.

Table 1
Acid-mediated ring opening of *N*-substituted-benzyl-α-phenyl-azetidinones **1a**–**e**



1a-e **4a-e**

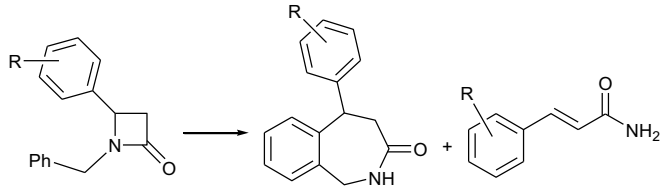
Entry	Lactam	R	Product	Yield %	**5** Yield %
1	**1a**	H	**4a**	60	20
2	**1b**	4-Me	**4b**	0	65
3	**1c**	3-Me	**4c**	24[a]	5
4	**1d**	4-Cl	**4d**	0	73
5	**1e**	4-F	**4e**	0	65

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

In cases where there was an electron rich 4-Me **1b** and electron deficient 4-Cl **1d** and 4-F **1e** substituent, only N-de-benzylation was observed with little or no evidence for cyclisation. However, the 3-Me substituted analogue gave a 24% yield of a 2:1 mixture of the 8- and 6-Me isomeric compounds along with **5** as a minor side-product. From this study it would appear that this method would be of little use for the synthesis of benzo-substituted analogues.

We then undertook an investigation on the effect of different substituents in the α-phenyl group on the ring-opening/cyclisation reaction and the results are summarised in Table 2.

Table 2
Acid-mediated ring opening of *N*-benzyl-α-substituted-phenyl-azetidinones **1f**–**j**

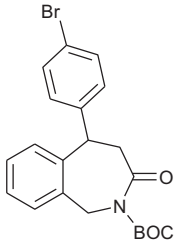


1f-j **4f-j** **5f-j**

Entry	Lactam	R	Product	Yield %	Amide	Yield %
1	**1f**	4-Me	**4f**	82	**5f**	5
2	**1g**	3-Me	**4g**	56	**5g**	<5
3	**1h**	4-Br	**4h**	78	**5h**	7
4	**1i**	2-Cl	**4i**	[a]	**5i**	[a]
5	**1j**	3,4-benzo	**4j**	0	**5j**	0

[a] See text.

We had previously shown that the *p*-methoxyphenyl azetidinone only gave a poor yield of ring-opened product, and phenyl groups containing strongly electron withdrawing groups, for example, CF_3, did not undergo the TfOH-mediated ring opening/phenylation reaction[2] and therefore these examples were eliminated from our investigation. For the α-substituted-phenyl derivatives, **1f**–**1h**, the TfOH-mediated cyclisation was much more successful. In most cases, moderate to good yields of cyclised products were obtained. For **4f** and **4g**, the cinnamamides could be separated by column chromatography. However, for **4h** we could not entirely remove all of the cinnamamide side-product. The impure **4h** was purified by conversion to the *N*-BOC derivative (65% yield) with BOC anhydride and DMAP,[8] the *N*-BOC derivative **7h** being readily purified by column chromatography. BOC cleavage with HCl regenerated pure **4h** in almost quantitative yield.



7h

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. In our previous study on the reaction with benzene, 4-(2-chloro-phenyl)azetidinone did not ring open to give the cinnamamide, but gave products derived from cleavage of the amide bond.[2] In this case, after 3 h reaction, the 2-chloro **1i** gave the *N*-benzylcinnamamide (23% yield) together with a more polar complex mixture, which from NMR spectroscopy and MS did appear to contain **4i** and **5i**. The 2-naphthyl **1j** gave only unidentified insoluble material.

3. Conclusion

In summary, *N*-benzyl-α-phenyl-azetidinone **1a** undergoes ring opening and cyclisation with TfOH in $CHCl_3$ to give 5-phenyl-benzazepin-3-one **4a**. A competing reaction is loss of the *N*-benzyl group to give cinnamamide **5**, which for substituted *N*-benzyl derivatives, **1b**, **1c** and **1d**, is the major pathway. In contrast, reaction of *N*-benzyl-α-substituted-phenyl-azetidinones **1f**–**i** gives moderate to good yields of 5-substituted-phenyl-benzazepin-3-ones **4f**–**i**. Occasionally it can be difficult to separate the cinnamamide side-product, in which case the benzazepinone can be purified by conversion to the *N*-BOC derivative, followed by acid cleavage. By this ring opening/cyclisation we have prepared novel 5-aryl-benzazepin-3-ones.

4. Experimental section

4.1. General

All reagents were commercially available, unless otherwise specified, and used without purification. The chloroform used was stabilized 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 FTIR spectrometer. Solution ^{1}H- and ^{13}C NMR spectra in $CDCl_3$, unless stated otherwise, were recorded on Bruker NMR spectrometer DRX500 equipped with z-gradient facilities. ^{1}H and ^{13}C chemical shifts are given relative to TMS. Mass spectra were run on a Thermo Mat900XP for EI and a Waters Micromaldi for TOF. Unless otherwise specified, spectra were recorded at 25 °C. Melting points were determined on a Sanyo-Gallenkamp capillary melting point apparatus and are uncorrected.

4.2. General procedure for *N*-benzyl-4-arylazetidinones

To a stirred solution of the appropriate azetidinone[2] (10 mmol) and the benzyl bromide (30 mmol) in THF (100 mL) at 0 °C was added KO*t*-Bu (12 mmol) and the reaction stirred at room temperature for 1 h. 2 M aq HCl (20 mL) and water (50 mL) were added

and the THF removed by rotary evaporation. The product was extracted into DCM (3×50 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography on SiO_2, initially eluting with 1:1 petroleum ether/DCM to remove the excess benzyl bromide, then DCM to 1% MeOH/DCM to give the product.

*4.2.1. N-Benzyl-4-phenyl-azetidin-2-one (**1a**).* Colourless oil (93% yield); spectroscopically consistent with the literature data.[9] R_f (Et_2O) 0.5; ^{1}H NMR (500 MHz) δ=2.87 (1H, dd, J=2.2, 14.7 Hz), 3.34 (1H, dd, J=5.1, 14.7 Hz), 3.76 (1H, d, J=15.0 Hz), 4.40 (1H, dd, J=2.2, 5.1 Hz), 4.80 (1H, d, J=15.0 Hz), 7.14 (2H, d, J=7.2 Hz), 7.20–7.40 (8H, m); ^{13}C NMR+DEPT (125 MHz) δ=44.8 (CH_2), 47.0 (CH_2), 53.6 (CH), 126.6 (CH), 127.8 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 135.6 (C), 138.0 (C), 167.3 (C).

*4.2.2. N-(4-Methylbenzyl)-4-phenyl-azetidin-2-one (**1b**).* Colourless oil (85% yield); R_f (Et_2O) 0.5; ^{1}H NMR (500 MHz) δ=2.33 (3H, s), 2.86 (1H, ddd, J=0.8, 2.3, 14.7 Hz), 3.32 (1H, dd, J=5.2, 14.7 Hz), 3.71 (1H, d, J=14.9 Hz), 4.39 (1H, dd, J=2.3, 5.2 Hz), 4.78 (1H, d, J=14.9 Hz), 7.03 (2H, d, J=8.0 Hz), 7.10 (2H, d, J=8.0 Hz), 7.23–7.27 (2H, m), 7.30–7.40 (3H, m); ^{13}C NMR+DEPT (125 MHz) δ=21.2 (CH_3), 44.5 (CH_2), 46.9 (CH_2), 53.4 (CH), 126.6 (CH), 128.5 (CH), 128.6 (CH), 129.0 (CH), 129.5 (CH), 132.6 (C), 137.5 (C), 138.1 (C), 167.2 (C); ν_{max} (liquid film) 1743, 1455, 1387, 1359, 770, 750, 698 cm^{-1}; LRMS (EI) 251, 105, 104; HRMS (EI): M$^+$, found 251.1300. $C_{17}H_{17}NO$ requires 251.1305.

*4.2.3. N-(3-Methylbenzyl)-4-phenyl-azetidin-2-one **(1c)**.* Colourless oil (93% yield); R_f (Et_2O) 0.5; ^{1}H NMR (500 MHz) δ=2.30 (3H, s), 2.87 (1H, dm, J=14.6 Hz), 3.35 (1H, dd, J=5.2, 14.6 Hz), 3.72 (1H, d, J=14.9 Hz), 4.39–4.42 (1H, m), 4.80 (1H, d, J=14.9 Hz), 6.91–6.97 (2H, m), 7.08 (1H, d, J=7.6 Hz), 7.18 (1H, t, J=7.5 Hz), 7.24–7.27 (2H, m), 7.30–7.39 (3H, m); ^{13}C NMR+DEPT (125 MHz) δ=21.4 (CH_3), 44.7 (CH_2), 47.0 (CH_2), 53.6 (CH), 125.6 (CH), 126.6 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 129.3 (CH), 135.5 (C), 138.1 (C), 138.5 (C), 167.3 (C); ν_{max} (liquid film) 1743, 1386, 1349, 777, 699 cm^{-1}; LRMS (EI) 251, 105, 104; HRMS (EI): M$^+$, found 251.1300. $C_{17}H_{17}NO$ requires 251.1305.

*4.2.4. N-(4-Chlorobenzyl)-4-phenyl-azetidin-2-one (**1d**).* Colourless oil (87% yield); R_f (Et_2O) 0.5; ^{1}H NMR (500 MHz) δ=2.89 (1H, ddd, J=0.7, 2.3, 14.7 Hz), 3.35 (1H, dd, J=5.2, 14.7 Hz), 3.77 (1H, d, J=15.1 Hz), 4.39 (1H, dd, J=2.3, 5.2 Hz), 4.75 (1H, d, J=15.1 Hz), 7.07 (2H, d, J=8.4 Hz), 7.20–7.27 (4H, m), 7.31–7.39 (3H, m); ^{13}C NMR+DEPT (125 MHz) δ=44.2 (CH_2), 47.0 (CH_2), 53.8 (CH), 126.6 (CH), 126.7 (CH), 129.0 (CH), 129.1 (CH), 130.0 (CH), 133.7 (C), 134.2 (C), 137.8 (C), 167.2 (C); ν_{max} (liquid film) 1742, 1491, 1386, 1090, 1015, 804, 768, 753, 698 cm^{-1}; LRMS (EI) 273, 271, 192, 86; HRMS (EI): M$^+$, found 271.0753. $C_{16}H_{14}{}^{35}ClNO$ requires 271.0758; spectroscopically consistent with the literature material.[10]

*4.2.5. N-(4-Fluorobenzyl)-4-phenyl-azetidin-2-one (**1e**).* Colourless oil (88% yield); R_f (Et_2O) 0.5; ^{1}H NMR (500 MHz) δ=2.87 (1H, ddd, J=0.6, 2.3 14.7 Hz), 3.33 (1H, dd, J=5.2, 14.7 Hz), 3.78 (1H, d, J=15.0 Hz), 4.38 (1H, dd, J=2.3, 5.2 Hz), 4.68 (1H, d, J=15.0 Hz), 6.95 (2H, J=8.7 Hz), 7.10 (2H, dd, J=5.4, 8.6 Hz), 7.20–7.25 (2H, m), 7.30–7.38 (3H, m); ^{13}C NMR+DEPT (125 MHz) δ=44.1 (CH_2), 47.0 (CH_2), 53.7 (CH), 115.6 (CH, d, J=21.4 Hz), 126.6 (CH), 128.6 (CH), 129.1 (CH), 130.3 (CH, d, J=8.3 Hz), 131.5 (C, d, J=3.4 Hz), 137.9 (C), 162.3 (C, d, J=246 Hz), 167.2 (C); ^{19}F NMR (282 MHz) δ=114.9 (tt, J=8.5, 5.6 Hz); ν_{max} (liquid film) 1742, 1509, 1389, 1220, 1157, 840, 826, 753, 699 cm^{-1}; LRMS (EI) 255, 212; HRMS (EI): M$^+$, found 251.1056. $C_{16}H_{14}FNO$ requires 255.1054.

*4.2.6. N-(Benzyl)-4-(4-methylphenyl)-azetidin-2-one (**1f**).* Colourless oil (90% yield); R_f (DCM) 0.3; ^{1}H NMR (500 MHz) δ=2.36 (3H, s), 2.85 (1H, dm, J=14.7 Hz), 3.32 (1H, dd, J=5.2, 14.7 Hz), 3.73 (1H, d, J=15.0 Hz), 4.36–4.39 (1H, m), 4.80 (1H, d, J=15.0 Hz), 7.12–7.20 (6H, m), 7.24–7.33 (3H, m); ^{13}C NMR+DEPT (125 MHz) δ=21.3 (CH_3), 44.6 (CH_2), 46.9 (CH_2), 53.4 (CH), 126.6 (CH), 127.7 (CH), 128.6 (CH), 128.8 (CH), 129.7 (CH), 134.9 (C), 135.8 (C), 138.4 (C), 167.4 (C); ν_{max} (liquid film) 1743, 1387, 1352, 940, 822, 726, 715, 703 cm^{-1}; LRMS (EI) 251, 208, 119, 118; HRMS (EI): M$^+$, found 251.1307. $C_{17}H_{17}NO$ requires 251.1305.

*4.2.7. N-Benzyl-4-(3-methylphenyl)-azetidin-2-one (**1g**).* Colourless oil (92% yield); R_f (DCM) 0.3; ^{1}H NMR (500 MHz) δ=2.30 (3H, s), 2.87 (1H, dm, J=14.6 Hz), 3.35 (1H, dd, J=5.2, 14.6 Hz), 3.72 (1H, d, J=14.9 Hz), 4.39–4.42 (1H, m), 4.80 (1H, d, J=14.9 Hz), 6.91–6.97 (2H, m), 7.08 (1H, d, J=7.6 Hz), 7.18 (1H, t, J=7.5 Hz), 7.24–7.27 (2H, m), 7.30–7.39 (3H, m); ^{13}C NMR+DEPT (125 MHz) δ=21.4 (CH_3), 44.7 (CH_2), 47.0 (CH_2), 53.6 (CH), 125.6 (CH), 126.6 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 129.3 (CH), 135.5 (C), 138.1 (C), 138.5 (C), 167.3 (C); ν_{max} (liquid film) 1743, 1456, 1387, 1360, 939, 766, 739, 696 cm^{-1}; LRMS (EI) 251; HRMS (EI): M$^+$, found 251.1306. $C_{17}H_{17}NO$ requires 251.1305.

*4.2.8. N-(Benzyl)-4-(4-bromophenyl)-azetidin-2-one (**1h**).* Colourless oil (89% yield); R_f (DCM) 0.3; ^{1}H NMR (500 MHz) δ=2.82 (1H, dm, J=14.7 Hz), 3.34 (1H, dd, J=5.2, 14.7 Hz), 3.76 (1H, d, J=14.9 Hz), 4,35 (1H, dd, J=2.3, 5.2 Hz), 4.77 (1H, d, J=14.9 Hz), 7.09–7.13 (4H, m), 7.25–7.32 (3H, m), 7.48 (2H, d, J=8.4 Hz); ^{13}C NMR+DEPT (125 MHz) δ=44.9 (CH_2), 47.0 (CH_2), 53.0 (CH), 122.5 (C), 127.9 (CH), 128.3 (CH), 128.7 (CH), 129.1 (CH), 132.1 (CH), 135.4 (C), 142.6 (C), 167.0 (C); ν_{max} (liquid film) 1744, 1487, 1385, 1072, 1009, 938, 825, 717, 708, 695 cm^{-1}; LRMS (EI) 317, 315, 184, 182, 86; HRMS (EI): M$^+$, found 315.0255. $C_{16}H_{14}{}^{79}BrNO$ requires 315.0253.

*4.2.9. N-(Benzyl)-4-(2-chlorophenyl)-azetidin-2-one (**1i**).* Colourless oil (95% yield); R_f (DCM) 0.3; ^{1}H NMR (500 MHz) δ=2.79 (1H, dd, J=2.2, 14.7 Hz), 3.42 (1H, dd, J=5.4, 14.7 Hz), 3.92 (1H, d, J=14.9 Hz), 4.84 (1H, d, J=14.9 Hz), 4.87 (1H, dd, J=2.2, 5.4 Hz), 7.18 (2H, d, J=7.2 Hz), 7.22–7.37 (7H, m); ^{13}C NMR+DEPT (125 MHz) δ=45.5 (CH_2), 46.3 (CH_2), 50.4 (CH), 126.6 (CH), 127.5 (CH), 127.9 (CH), 128.6 (CH), 128.9 (CH), 129.3 (CH), 130.0 (CH), 133.3 (C), 135.4 (C), 136.0 (C), 167.4 (C); ν_{max} (liquid film) 1746, 1443, 1385, 1348, 1035, 754, 709, 696 cm^{-1}; LRMS (EI) 273, 271, 140, 138; HRMS (EI): M$^+$, found 271.0753. $C_{16}H_{14}ClNO$ requires 271.0758.

*4.2.10. N-(Benzyl)-4-(2-naphthyl)-azetidin-2-one (**1j**).* White solid (88% yield), mp 85–87 °C (Et_2O/petroleum ether); R_f (Et_2O) 0.5; ^{1}H NMR (500 MHz) δ=2.97 (1H, dd, J=2.2, 14.7 Hz), 3.42 (1H, dd, J=5.2, 14.7 Hz), 3.81 (1H, d, J=15.0 Hz), 4.58 (1H, dd, J=2.2, 5.2 Hz), 4.85 (1H, d, J=15.0 Hz), 7.16–7.19 (2H, m), 7.22–7.27 (3H, m), 7.38 (1H, dd, J=1.7, 8.5 Hz), 7.44–7.47 (2H, m), 7.69 (1H, s), 7.81 (1H, dd, J=3.4, 8.5 Hz), 7.81–7.85 (2H, m); ^{13}C NMR+DEPT (125 MHz) δ=44.9 (CH_2), 47.0 (CH_2), 53.8 (CH), 123.5 (CH), 126.3 (CH), 126.5 (CH), 126.7 (CH), 127.8 (CH), 127.9 (CH), 127.9 (CH), 128.6 (CH), 128.9 (CH), 129.2 (CH), 133.4 (C), 133.5 (C), 135.4 (C), 135.7 (C), 167.3 (C); ν_{max} (solid) 1740, 1380, 1307, 863, 829, 789, 751, 722, 703 cm^{-1}; LRMS (EI) 287, 154, 91; HRMS (EI): M$^+$, found 287.1301. $C_{20}H_{17}NO$ requires 287.1305.

4.3. *N*-Benzyl-cinnamamide 2a from 1a

A stirred mixture of triflic acid (0.50 mL, 5 mmol) and **1a** (0.24 g, 1 mmol) in $CHCl_3$ (10 mL) was heated under gentle reflux for 30 min. The reaction mixture was cooled to room temperature, water (10 mL) was added and the mixture basified with an excess of solid K_2CO_3. 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, eluting with DCM—1% MeOH/DCM to give **2a** (0.21 g, 85% yield), mp 106–108 °C (EtOAc/petroleum ether) (lit. 108–110 °C[11]) identical to material prepared from cinnamoyl chloride and benzylamine by the literature procedure.[12] R_f (Et_2O)

0.5; ^{1}H NMR (500 MHz) δ=4.42 (2H, d, J=5.6 Hz), 6.36 (1H, brs), 6.52 (1H, d, J=15.6 Hz), 7.20–7.36 (8H, m), 7.40–7.50 (2H, m), 7.66 (1H, d, J=15.6 Hz); ^{13}C NMR+DEPT (125 MHz) δ=43.9 (CH_2), 120.6 (CH), 127.6 (CH), 127.9 (CH), 128.0 (CH), 128.8 (CH), 128.9 (CH), 129.8 (CH), 134.9 (C), 138.3 (C), 141.4 (CH), 166.0 (C).

4.4. *N*-Benzyl-3,3-diphenylpropionamide (3a)

A stirred mixture of triflic acid (1.0 mL, 10 mmol) and **1a** (0.24 g, 1 mmol) in dry benzene (10 mL) was heated under gentle reflux for 1 h. The reaction mixture was cooled to room temperature, water (10 mL) was added and the mixture basified with an excess of solid K_2CO_3. 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. Elution with DCM—0.5% MeOH/DCM gave the title compound **3a** (0.26 g, 83% yield), recrystallised from DCM/petrol, mp 142–144 °C (lit. 142–144 °C) and spectroscopically consistent with the literature material.[13] R_f (Et_2O) 0.5; ^{1}H NMR (500 MHz) δ=2.94 (2H, d, J=7.9 Hz), 4.29 (2H, d, J=5.7 Hz), 4.62 (1H, t, J=7.9 Hz), 5.68 (1H, brs), 6.86–6.92 (2H, m), 7.18–7.30 (13H, m); ^{13}C NMR+DEPT (125 MHz) δ=43.5 (CH_2), 43.5 (CH_2), 47.6 (CH), 126.6 (CH), 127.3 (CH), 127.5 (CH), 127.9 (CH), 128.6 (CH), 128.7 (CH), 138.1 (C), 143.7 (C), 171.0 (C). Further elution with 2% MeOH/DCM gave a product spectroscopically consistent with being a 1:1 mixture of 5-phenyl-benzazepin-3-one **4a** and **5** (10 mg ~5% yield).

4.5. General procedure for the TfOH-mediated ring opening/cyclisation

Triflic acid (20 mmol) was added to a stirred solution of the lactam or cinnamamide (2 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 and the mixture basified with an excess of solid K_2CO_3. 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 (0.5–1% MeOH/DCM).

*4.5.1. 5-Phenyl-1,2,4,5-tetrahydro-benzo[c]azepin-3-one (**4a**).* White solid (65% yield); mp 181–183 °C (EtOAc/petroleum ether) (lit. 182–3 °C)[3] and spectroscopically identical to the reported material.[6] R_f (Et_2O) 0.1; ^{1}H NMR (500 MHz) δ=3.02 (1H, dd, J=4.5, 14.4 Hz), 3.13 (1H, dd, J=10.2, 14.4 Hz), 4.31 (1H, dd, J=5.3, 16.1 Hz), 4.50 (1H, dd, J=5.3, 16.1 Hz), 4.54 (1H, dd, J=4.5, 10.2 Hz), 6.92–6.96 (1H, m), 7.08–7.30 (8H, m), 7.76 (1H, t, J=5.3 Hz); ^{13}C NMR+DEPT (125 MHz) δ=41.6 (CH_2), 44.6 (CH), 46.3 (CH_2), 126.6 (CH), 126.8 (CH), 128.0 (CH), 128.2 (CH), 128.6 (CH), 131.9 (CH), 136.0 (C), 141.0 (C), 145.2 (C), 175.2 (C).

*4.5.2. Mixture of 6-methyl-5-phenyl-1,2,4,5-tetrahydro-benzo[c]azepin-3-one and 8-methyl-5-phenyl-1,2,4,5-tetrahydro-benzo[c]azepin-3-one (**4c**).* Elution with 1% MeOH/DCM gave the product mixture **4c**, as a colourless oil (24% yield); R_f (Et_2O) 0.1; ^{1}H NMR (500 MHz) δ=2.00 (1H, s), 2.29 (2H, s), 2.90–3.20 (2H, m), 4.19–4.60 (3H, m), 6.80–7.40 (9H, m), ^{13}C NMR+DEPT (125 MHz) δ=minor isomer, 20.7 (CH_3), 41.9 (CH_2), 42.5 (CH), 47.1 (CH_2); major isomer, 20.9 (CH_3), 41.7 (CH_2), 44.6 (CH), 46.5 (CH_2): unassigned—126.5 (CH), 126.7 (CH), 126.8 (CH), 127.0 (CH), 127.6 (CH), 128.2 (CH), 128.7 (CH), 128.7 (CH), 128.9 (CH), 129.4 (CH), 131.1 (CH), 131.9 (CH), 135.6 (C), 136.2 (C), 136.3 (C), 137.8 (C), 138.3 (C), 144.0 (C), 145.4 (C), 175.0 (C); ν_{max} (liquid film) 1164, 1649, 1488, 1446, 778, 743, 726, 710, 699, 682, 657 cm^{-1}; LRMS (EI) 251, 192, 86; HRMS (EI): M^+, found 251.1308. $C_{17}H_{17}NO$ requires 251.1305.

*4.5.3. 5-(p-Tolyl)-1,2,4,5-tetrahydro-benzo[c]azepin-3-one (**4f**).* White solid (82% yield); mp 190–191 °C; R_f (Et_2O) 0.1; ^{1}H NMR (500 MHz) δ=2.33 (3H, s), 3.01 (1H, dd, J=4.5, 14.4 Hz), 3.10 (1H, dd, J=10.0, 14.4 Hz), 4.31 (1H, dd, J=5.2, 16.0 Hz), 4.40–4.51 (2H, m), 6.92–6.96 (1H, m), 7.03 (2H, d, J=8.1 Hz), 7.08–7.18 (5H, m), 7.88 (1H, brt, J=5.4 Hz); ^{13}C NMR+DEPT (125 MHz) δ=21.2 (CH_3), 41.7 (CH_2), 44.3 (CH), 46.3 (CH_2), 126.5 (CH), 128.1 (CH), 128.7 (CH), 129.5 (CH), 131.8 (CH), 135.9 (C), 136.3 (C), 141.2 (C), 142.2 (C), 175.2 (C); ν_{max} (solid) 3270 (br), 1618, 1465, 1446, 1352, 1326, 1088, 818, 752, 721, 655 cm^{-1}; LRMS (EI) 251, 192, 86; HRMS (EI): M^+, found 251.1306. $C_{17}H_{17}NO$ requires 251.1305.

*4.5.4. 5-(m-Tolyl)-1,2,4,5-tetrahydro-benzo[c]azepin-3-one (**4g**).* White solid (56% yield); mp 158–160 °C; R_f (Et_2O) 0.1; ^{1}H NMR (500 MHz) δ=2.30 (3H, s), 2.95 (1H, dd, J=4.4, 10.3 Hz), 3.12 (1H, dd, J=10.3, 14.5 Hz), 4.27 (1H, dd, J=5.4, 16.0 Hz), 4.46–4.55 (2H, m), 6.88–6.95 (3H, m), 7.03 (1H, d, J=7.6 Hz), 7.08–7.21 (4H, m); ^{13}C NMR+DEPT (125 MHz) δ=21.6 (CH_3), 41.6 (CH_2), 44.8 (CH), 46.4 (CH_2), 125.3 (CH), 126.6 (CH), 127.6 (CH), 128.2 (CH), 128.7 (CH), 128.9 (CH), 131.9 (CH), 135.7 (C), 138.4 (C), 141.1 (C), 145.1 (C), 174.9 (C); ν_{max} (solid) 1665, 1487, 1403, 1358, 796, 778, 753, 710, 681, 657 cm^{-1}; LRMS (EI) 251, 192, 86; HRMS (EI): M^+, found 251.1306. $C_{17}H_{17}NO$ requires 251.1305.

*4.5.5. 5-(4-Bromophenyl)-1,2,4,5-tetrahydro-benzo[c]azepin-3-one (**4h**).* Isolated as a mixture in 85% yield, which includes 7% cinnamamide, R_f (Et_2O) 0.1. The impure product (0.55 g, 1.8 mmol) was dissolved in DCM (30 mL), treated with BOC anhydride (0.50 g, 2.3 mmol), Et_3N (0.50 mL, 3.5 mmol) and DMAP (0.24 g, 2.0 mmol) and stirred at room temperature overnight. The solvent was removed by rotary evaporation and the residue portioned 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 **7h**, recrystallised from DCM/petroleum ether (0.44 g, 59% yield); R_f (Et_2O) 0.6; mp 133–5 °C; ^{1}H NMR (500 MHz) δ=1.51 (9H, s), 3.19–3.31 (2H, m), 4.56 (1H, dd, J=5.1, 9.6 Hz), 4.96 (1H, d, J=16.4 Hz), 5.11 (1H, d, J=16.4 Hz), 6.92 (2H, d, J=8.4 Hz), 6.93–6.96 (1H, m), 7.18–7.22 (2H, m), 7.23–7.26 (1H, m), 7.39 (2H, d, J=8.4 Hz); ^{13}C NMR+DEPT (125 MHz) δ=28.1 (CH_3), 45.0 (CH_2), 45.6 (CH), 49.2 (CH_2), 83.4 (C), 120.8 (C), 127.1 (CH), 128.7 (CH), 129.9 (CH), 132.0 (CH), 132.1 (CH), 134.6 (C), 138.8 (C), 144.3 (C), 151.7 (C), 171.5 (C); ν_{max} (solid) 1709, 1483, 1391, 1367, 1284, 1239, 1143, 1100, 1073, 1010, 851, 831, 771, 741, 721 cm^{-1}; LRMS (TOF ES$^+$) 440, 438, 381, 379, 259, 257, 178; HRMS (TOF ES$^+$):MNa^+, found 438.0679. $C_{21}H_{22}{}^{79}BrNNaO$ requires 438.0681. A solution of **7h** (0.40 g) in DCM (10 mL) and 4 M HCl in dioxan (1 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 pure **4h**, recrystallised from EtOAc/petroleum ether (0.28 g, 95% yield), mp 181–183 °C; ^{1}H NMR (500 MHz) δ=3.07 (2H, d, J=7.0 Hz), 4.39 (1H, dd, J=5.2,16.2 Hz), 4.50 (1H, dd, J=5.2, 16.2 Hz), 4.52 (1H, t, J=7.0 Hz), 6.60 (1H, brm), 6.85–6.88 (1H, m), 6.99 (2H, d, J=8.4 Hz), 7.09–7.13 (1H, m), 7.15–7.20 (2H, m), 7.40 (2H, d, J=8.4 Hz); ^{13}C NMR+DEPT (125 MHz) δ=41.3 (CH_2), 44.5 (CH), 46.5 (CH_2), 120.8 (C), 126.9 (CH), 128.4 (CH), 128.8 (CH), 129.9 (CH), 131.9 (CH), 132.0 (CH), 135.6 (C), 140.2 (C), 144.1 (C), 174.1 (C); ν_{max} (solid) 1666, 1486, 1407, 1353, 1329, 1072, 1011, 808, 771, 761, 738, 653 cm^{-1}; LRMS (EI) 317, 315, 258, 256, 88, 86; HRMS (EI): M^+, found 315.0254. $C_{16}H_{14}BrNO$ requires 315.0253.

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Supplementary data

Supplementary data contains NMR (^{1}H and ^{13}C) spectra for **1b**–**j**, **2a**, **3a**, **4a**, **4c**, **4g**, **4h** and **7h**. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.09.046.

References and notes

1. King, F. D.; Caddick, S. *Tetrahedron Lett.* **2011**, *52*, 6783–6784.
2. King, F. D.; Caddick, S. *Org. Biomol. Chem.* **2012**, *10*, 3244–3252.
3. Croisier, P.; Rodriquez, L. U.S. Patent 4,080,449A, 1978; *Chem. Abstr.* **1978**, *88*, 152456.
4. Johnson, R.E.; Busacca, C.A. U.S. Patent 5,098,901A, 1992; *Chem. Abstr.* **1992**, *117*, 7949.
5. Johnson, R. E.; Busacca, C. A. *Tetrahedron Lett.* **1992**, *33*, 165–168.
6. Wuensch, P.; Hasebein, P.; Schepmann, D.W.O. Patent 2010012812A1, 2010; *Chem. Abstr.* **2010**, *152*, 238800.
7. Molino, B.F.; Liu, S.; Sambandam, A.; Guzzo, P.R.; Hu, M.; Zha, C.; Nacro, K.; Manning, P.D.; Isherwood, M.L.; Fleming, K.N.; Cui, W.; Olson, R.E.W.O. Patent 2007011820A2, 2007; *Chem. Abstr.* **2007**, *146*, 184383.
8. Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424–2426.
9. Ahn, C.; Kennington, J. W.; DeShong, P. *J. Org. Chem.* **1994**, *59*, 6282–6286.
10. Elriati, A.; Loose, J.; Mayrhofer, R.; Bergmann, H. J.; Otto, H. H. *Monatsh. Chem.* **2008**, *139*, 835–846.
11. Roberts, B.; Liptrot, D.; Alcaraz, L.; Luker, T.; Stocks, M. J. *Org. Lett.* **2010**, *12*, 4280–4283.
12. Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14544–14545.
13. Watson, A. J. A.; Williams, J. M. J.; Maxwell, A. C. *Org. Lett.* **2009**, *11*, 2667–2670.