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PAPER

The acid-mediated ring opening reactions of α-aryl-lactams†

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4-Aryl-azetidin-2-ones (β-lactams) undergo ring opening with triflic acid to give cinnamamides which, in benzene, react further to give 3-aryl-3-phenyl-propionamides. Prolonged reaction times in benzene give 3,3-diphenyl-propionamide *via* an aryl/phenyl exchange. Lactams of ring size 7 and higher also ring open, but only 7- and 8-membered rings give pure diphenylalkylamides. $AlCl_3$ only ring opens the 4-aryl-azetidinones.

Introduction

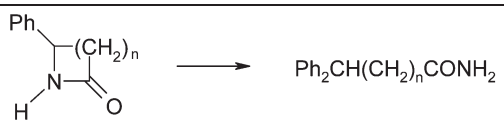
Triflic acid (TfOH) has been shown to protonate appropriately substituted amides to form reactive dications.[1,2] We have recently reported that TfOH induces ring opening of 4-phenylazetidin-2-one **1a** and 7-phenylazepin-2-one **1d** (Table 1, entries 1 and 4) to give dications, which react with benzene to give the diphenyl amides **2a** and **2d**, respectively.[3] However, neither the pyrrolidinone **1b** (entry 2) nor the piperidinone **1c** (entry 3) react, presumably due to the greater stability of the 5- and 6-membered rings. This result contrasts with our previously reported results with *N*-acyl derivatives of cyclic amines, for which TfOH-mediated ring opening/phenylation was observed for ring sizes 4–6.[4] With $AlCl_3$, **1a** also gave **2a**, but **1d** gave the isomeric 3-phenylazepin-2-one *via* a retro-Beckman rearrangement.[3]

In this paper we describe our results on investigating the ring-opening/phenylation reaction of lactams with increased ring size and on the utility of this reaction to the synthesis of 3-aryl-3-phenyl-propionamides. In addition we show that the reaction is also applicable to *N*-methyl lactams.

Results and discussion

Initially, we investigated the scope of the TfOH-mediated ring opening/phenylation reaction with respect to ring size. 8-Phenyl-azocin-2-one **1e** ring opened and phenylated to give the diphenyl compound **2e** in a good yield (entry 5). However, although 9-phenyl-azonan-2-one **1f** underwent ring opening, an inseparable mixture of compounds was obtained (entry 6). The NMR spectra and ms analysis of the mixture was consistent with a mixture of **2f**, $Ph(CH_2)_7CONH_2$ and other unidentified products. The formation of a mixture of phenylated and reduced products had also been observed in the TfOH-mediated ring-opening of *N*-acyl derivatives of homopiperidine.[4] Thus, it appears that the ring opening/phenylation of α-phenyl lactams is only synthetically useful for 4, 7 and 8-membered lactams. Interestingly, the ^{1}H-NMR spectrum of **1f** showed that it exists in two conformations at room temperature in a 1 : 1 ratio, probably a mixture of *cis*- and *trans*-amide conformers.[5]

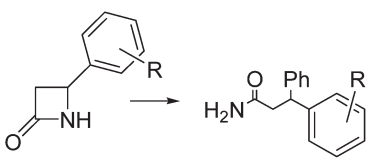
Table 1 Acid-mediated ring opening of α-phenyl-lactams **1a–f** in benzene with 10 equiv. TfOH



1a-f **2a-f**

Entry	Lactam	*n*	Product	Yield %
1	**1a**	1	**2a**	73
2	**1b**	2	**2b**	0
3	**1c**	3	**2c**	0
4	**1d**	4	**2d**	88
5	**1e**	5	**2e**	94
6	**1f**	6	**2f**	85[a]

[a] An inseparable mixture including **2f** and $Ph(CH_2)_7CONH_2$.



3a-i **4a-i**

Scheme 1 Synthesis of 3-aryl-3-phenyl-propionamides **4a–i** from 4-aryl-azetidin-2-ones **3a–i** (see Table 2).

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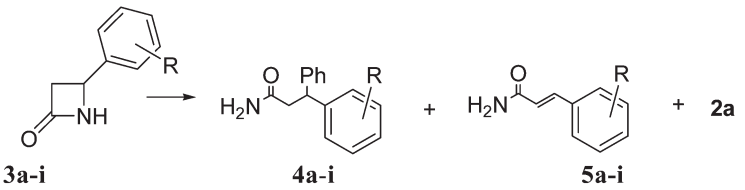
Table 2 The triflic acid-mediated synthesis of 3-aryl-3-phenyl-propionamides **4a–i**



3a-i **4a-i** **5a-i**

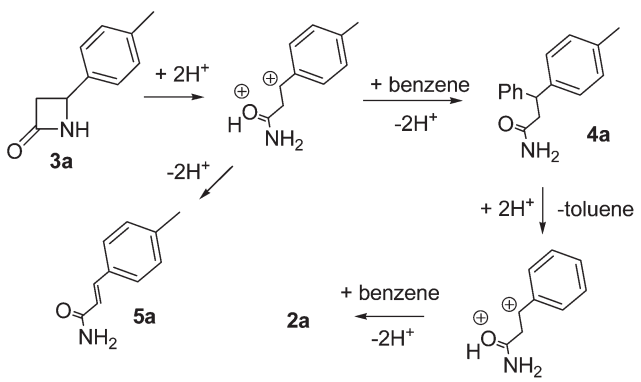
Entry	β-Lactam	R	TfOH equiv.	Solvent	C_6H_6 equiv.	Reflux time (h)	Amide (yield %)	Cinnamamide (yield %)	**2a** Yield %
1	**3a**	4-Me	10	C_6H_6	—	0.5	**4a** (72)	**5a** (0)	18
2	**3a**	4-Me	5	$CHCl_3$	2.5	0.5	**4a** (35)	**5a** (45)	0
3	**3a**	4-Me	5	$CHCl_3$	10	0.5	**4a** (91)	**5a** (0)	0
4	**3a**	4-Me	10	$CHCl_3$	0	0.5	**4a** (0)	**5a** (100)	0
5	**3b**	3-Me	5	$CHCl_3$	10	0.5	**4b** (81)	**5b** (6)	0
6	**3c**	4-Cl	10	C_6H_6	—	0.5	**4c** (51)	**5c** (28)	0
7	**3c**	4-Cl	10	C_6H_6	—	1	**4c** (87)	**5c** (0)	4
8	**3c**	4-Cl	10	$CHCl_3$	—	0.5	**4c** (0)	**5c** (100)	0
9	**3d**	3-Cl	10	C_6H_6	—	0.5	**4d** (55)	**5d** (27)	0
10	**3d**	3-Cl	10	C_6H_6		1	**4d** (92)	**5d** (0)	0
11	**3e**	2-Cl	5	C_6H_6		1.5	**4e**[a]	**5e** (0)	0
12	**3f**	4-Br	10	C_6H_6	—	0.5	**4f** (90)	**5f** (0)	5
13	**3f**	4-Br	5	C_6H_6	—	0.5	**4f** (55)	**5f** (22)	0
14	**3g**	4-F	10	C_6H_6	—	0.5	**4g** (73)	**5g** (10)	0
15	**3h**	3-CF_3	10	C_6H_6	—	1	**4h** (0)	**5h** (0)	0
16	**3i**	2-Naphthyl	10	C_6H_6	—	0.5	**4i** (30)	**5i** (0)	30
17	**3i**	2-Naphthyl	10	C_6H_6	—	1.5	**4i** (10)	**5i** (0)	50

[a] See text.

TfOH-mediated synthesis of 3-aryl-3-phenyl-propionamides from 4-aryl-azetidin-2-ones

We then investigated whether this ring opening/phenylation reaction was suitable for the synthesis of substituted-phenyl-propionamides **4a–i** (Scheme 1) and the results are summarised in Table 2. The 4-aryl-azetidin-2-ones used in this study **3a–i** were prepared by the reaction of the appropriately substituted styrene with chloro-sulfonylisocyanate.[6]

The *p*-tolyl azetidinone **3a** with 10 equivalents of TfOH in benzene rapidly ring opened to give an inseparable mixture of 3-(*p*-tolyl)-3-phenyl-propionamide **4a** and 3,3-diphenyl-propionamide **2a** (Table 2, entry 1). As we wanted pure **4a**, and assuming that **2a** was formed due to the presence of an excess of benzene, the reaction was repeated in $CHCl_3$ with only 2.5 equivalents of benzene and 5 equivalents TfOH (entry 2). After 30 min reflux, TLC showed that all of **3a** had been consumed and a low yield of **4a** (35%) was obtained together with the readily separable cinnamamide **5a** (45% yield). Increasing the amount of benzene to 10 equivalents gave an excellent yield of **4a** (91%) with neither **2a** nor **5a** being detected (entry 3). Thus it would appear that ring opening of the azetidinone initially gives a cinnamamide, which subsequently reacts with benzene to give the 3-aryl-3-phenyl-propionamide. In support of this proposal, repeating the reaction in $CHCl_3$ gave a quantitative yield of **5a** (entry 4) and it has been reported that cinnamamide forms a dication with TfOH, which then reacts with benzene to give 3,3-diphenyl-propionamide.[1] Formation of **2a** from **4a** could be envisaged either *via* a methyl transfer reaction, known to occur with TfOH and polymethylated-benzenes in benzene,[7] or *via* protonation and elimination of ArH to form the 3-phenyl



Scheme 2 Proposed mechanism for the ring opening of **3a** to give **2a**, **4a** and/or **5a**.

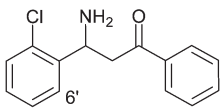
dication, which would then react with excess benzene to give **2a** (Scheme 2).

There is literature evidence for the mechanism of aryl elimination, for example in the TfOH induced elimination of ArH in the aromatization of 4-aryl-3,4-dihydro-quinolin-2-ones to quinolin-2-ones.[1] Acid-mediated displacement of aryls by benzene is also known to occur in the isolation of diphenylmethane from the alkylation of benzene by substituted arylmethanols[8] and substituted benzyl halides.[9–14] In addition, there are two reports of acid-mediated aryl–benzene exchange with diarylmethanes.[8,9]

Next we explored the reactions of other substituted azetidinones. Applying the optimized conditions for **3a** (entry 3) to the *m*-tolyl analogue **3b** (entry 5) gave a good yield of **4b** (81%) together with a small amount of the readily separable

cinnamamide **5b** (~6% yield). Reaction of the 4-chloro **3c** required the more forcing conditions described in entry 1 and gave ~2 : 1 mixture of **4c** and **5c** (entry 6). Comparing entries 1 and 6, it would appear that the phenylation reaction is slower for the less electron rich *p*-Cl substituted derivative. Extending the reaction time to 1 h (entry 7) completed the phenylation to give a 91% yield of **4c**, but with a small amount of **2a** (4%). However, the ring opening reaction of **3c** to give the cinnamamide **5c** (entry 8) required the same conditions as described for **3a** (entry 4). Similar results were obtained for the 3-chloro **3d** (entries 9 and 10), though in these cases no **2a** was detected.

In contrast, the 2-chloro analogue **3e** gave a product assigned as **6** in moderate yield (55%) (entry 11). Full NMR spectral assignments are given in the ESI.† However, key features in the ^{1}H-NMR spectrum were a broad singlet at δ = 1.88 for the NH_2 protons, two dds at δ = 3.19 and 3.41 for the CH_2 protons and a dd at δ = 5.05 for the CH proton. NOEs were observed between the NH_2 protons and the CH at δ = 3.19 and the aromatic *ortho* proton 6′ at δ = 7.67. NOEs were also observed between the 6′ proton and all three aliphatic protons. In the ^{13}C-NMR spectrum, the $CHNH_2$ carbon was observed at δ = 48.8 and a ketone carbon at δ = 199.2. In the IR spectrum, an aryl ketone C=O stretch at 1679 cm^{-1} and an N–H deformation at 1596 cm^{-1} were observed.



6

Unfortunately **6** did not appear to be stable and could only be obtained as an oil in *ca*. 95% purity. It would appear that in this case, the azetidinone cleaves the amide bond to form the acylonium ion, which then acylates benzene. However, we found this reaction to be capricious and non-reproducible.

The 4-bromo analogue **3f** (entry 12) reacted similarly to the 4-chloro **3c**, but the ring opening/phenylation was complete within 30 min (compare entries 7 and 12). Reducing the quantity of TfOH to 5 equivalents gave a readily separable mixture of **4f** (55%) and **5f** (22%) (entry 13). The 4-fluoro analogue **3g** appeared to be intermediate between **3c** and **3f**, giving a 7 : 1 mixture of **4g** and **5g** in an 83% overall yield (entry 14). However, **3h**, which contains a strong electron withdrawing group, gave no identifiable products (entry 15).

In order to gain further mechanistic insight into the unwanted formation of **2a**, the 2-naphthyl analogue **3i** was studied. If **2a** were formed from **3i**, this would support an ArH elimination pathway as substituent transfer is not possible. After 30 min reflux with 10 equivalents of TfOH in benzene, a 1 : 1 mixture of propionamide **4i** and **2a** was obtained (entry 16). Extending the reaction time to 1.5 h gave a 1 : 5 ratio of **4i** to **2a** (entry 17), and a similar result was obtained subjecting the 1 : 1 mixture of **4i** and **2a** to the same conditions. In all cases, naphthalene was isolated from the reaction mixture. Thus, we have compelling evidence that the mechanism for the formation of **2a** is likely to proceed *via* elimination of ArH.

In summary, we have shown that 4-aryl-azetidin-2-ones undergo ring opening with TfOH in benzene. The initial intermediate is a dication, which on neutralisation gives a substituted cinnamamide. The dication then reacts with benzene to give a 3-aryl-3-phenyl-propionamide, which subsequently undergoes an aryl exchange to give 3,3-diphenyl-propionamide. The ratio of products obtained depends upon the quantity of TfOH and benzene, the reaction time and the electronic properties of the substituent. Whereas we were unable to separate the 3-aryl-3-phenyl-propionamides and 3,3-diphenyl-propionamide by column chromatography, the cinnamamides were readily separable. Therefore, to obtain pure 3-aryl-3-phenyl-propionamides it is better to use the minimum amount of TfOH and benzene, and short reaction times.

$AlCl_3$-mediated synthesis of 3-aryl-3-phenyl-propionamides from 4-aryl-azetidin-2-ones

We next turned our attention to investigating $AlCl_3$-mediated reactions. In our original protocol[3] for **1a** we employed 3 equivalents of $AlCl_3$ in benzene under reflux. However, further examination showed that the product **2a** is formed in quantitative yield at room temperature. We could find no evidence for the formation of the intermediate cinnamamide **5**. However, when employing $CHCl_3$ as solvent, we observed the formation of **5** (by TLC) but longer reaction time gave only insoluble material. Therefore, we believe that, by analogy with the TfOH-mediated reaction, **5** is an intermediate, but the subsequent reaction with benzene is fast. It has been reported that **5** readily reacts with $AlCl_3$ in benzene to give **2a** in a high yield[1] and we confirmed this by reacting **5** with 3 equivalents of $AlCl_3$ in benzene for 1 h to obtain **2a** in a quantitative yield (Table 3, entry 1).

For substituted-phenyl azetidinones, reaction of the *p*-tolyl **3a** with 3 equivalents of $AlCl_3$ in benzene at room temperature for 1 h gave a 75% yield of **2a** with no **4a** detected. However, the more forcing conditions of heating under reflux for 30 min were required for the 4-chloro **3c**, which gave a 95% yield of **2a** with only a trace (~2%) of **4c**. However, with 2 equivalents of $AlCl_3$, a 90% yield of a 2 : 1 mixture of **4c** and **2a** was obtained, whereas with 1.5 equivalents, **4c** was obtained in an 82% yield, though a longer reaction time was required (3 h heating under reflux).

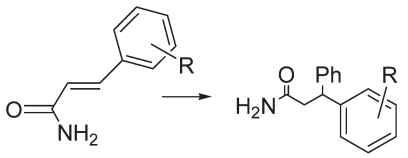
In spite of demonstrating that pure 3-aryl-3-phenyl-propionamides can be prepared from the acid-mediated ring opening of the α-aryl-azetidinones, we believed that a more useful procedure would be from the intermediate substituted cinnamamides, readily prepared from commercially available cinnamic acids. We therefore concentrated on optimising this reaction.

Acid-mediated synthesis of 3-aryl-3-phenyl-propionamides from substituted cinnamamides

The results from our studies on cinnamamides with $AlCl_3$ and TfOH are summarised in Table 3.

A previous study has described the reaction of the 4-methoxy analogue **5j**,[1] but a full study had not been carried out. The reaction of the *p*-tolyl analogue **5a** under standard conditions gave a good yield of the diphenyl **2a**, with no **4a** detected (Table 3, entry 2). Shorter reaction time (entry 3) or reducing the amount of $AlCl_3$ (entry 4) gave inseparable mixtures of **4a** and **2a**. Thus it would appear that, for $AlCl_3$ with an electron rich aromatic,

Table 3 The $AlCl_3$- and TfOH-mediated synthesis of 3-aryl-3-phenyl-propionamides **4a–j** from the cinnamamides **5a–j** in benzene



5a-j **4a-j**

Entry	Amide	R	Acid equiv.	Time (h)	Δ (°C)	Amide (yield %)	**2a** Yield %
1	**5**	H	3 $AlCl_3$	1	20	—	100
2	**5a**	4-Me	3 $AlCl_3$	1	20	**4a** (0)	85
3	**5a**	4-Me	3 $AlCl_3$	0.2	20	**4a** (12)	72
4	**5a**	4-Me	1.5 $AlCl_3$	0.2	20	**4a** (45)	50
5	**5a**	4-Me	5 TfOH	0.5	60[a]	**4a** (100)	0
6	**5c**	4-Cl	3 $AlCl_3$	1	20	**4c** (45)	45
7	**5c**	4-Cl	3 $AlCl_3$	0.5	20	**4c** (85)	5
8	**5c**	4-Cl	3 $SnCl_4$	1	80	**4c** (0)	0
9	**5c**	4-Cl	3 $TiCl_4$	1	80	**4c** (0)	0
10	**5c**	4-Cl	5 TfOH	1	80	**4c** (100)	0
11	**5e**	2-Cl	10 TfOH	1	80	**4e** (77)	0
12	**5f**	4-Br	3-$AlCl_3$	0.5	20	**4f** (87)	3
13	**5f**	4-Br	5 TfOH	1	80	**4f** (100)	0
14	**5h**	3-CF_3	5-$AlCl_3$	1	80	**4h** (0)	0
15	**5h**	3-CF_3	10 TfOH	1	80	**4h** (0)	0
16	**5i**	2-Naphthyl	3 $AlCl_3$	0.1	20	**4i** (20)	75
17	**5j**	4-MeO	5-$AlCl_3$	5	20	**4j** (95) [b]	
18	**5j**	4-MeO	5 TfOH	0.1	80	**4j** (10)	0

[a] In $CHCl_3$ with 10 equivalents of benzene. [b] Ref. 1.

the aryl exchange reaction is too rapid to be synthetically useful. However, the use of TfOH gave **4a** in a quantitative yield (entry 5).

The 4-chlorophenyl analogue **5c** with $AlCl_3$ for 1 h gave a 1 : 1 mixture of **4c** and **2a** in a 90% overall yield (entry 6). However, with a shorter reaction time an 85% yield of **4c** was obtained (entry 7). None of the other Lewis acids investigated, $BF_3{\cdot}OEt_2$, $SnCl_4$ and $TiCl_4$ induced the reaction, even when heated under reflux. The 4-Br-cinnamamide **5f** gave a mixture of **4f** (87%) and **2a** (3%) with $AlCl_3$ (entry 12), but the reaction was more effective when mediated with TfOH, whereupon we obtained a quantitative yield of **4f** (entry 13).

In contrast to **3e**, the 2-chloro-cinnamamide **5e** gave a good yield of **4e** (77%) with TfOH in benzene (entry 11). Again, however, no reaction was observed with the 3-trifluoromethyl analogue **5h**. We were also unable to get a selective reaction with the 2-naphthyl **5i**. With $AlCl_3$, after only 6 min, no **5i** remained and an inseparable ~ 4 : 1 mixture of **2a** and **5i** was obtained.

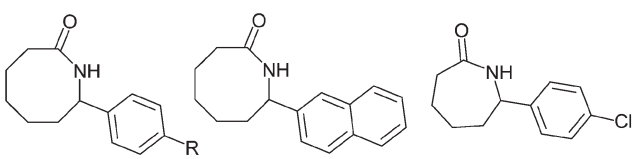
All of these reactions proceeded more rapidly and with less selectivity than the reported reaction with the 4-methoxycinnamamide **5j**.[1] On re-investigation, we confirmed the original report and found that the reaction of **5j** was, indeed, very much slower, requiring the reported 5 equivalents of $AlCl_3$ for 5 h to give a very good yield of **4j** (entry 17). It is tempting to speculate that this may be related to competition for the Lewis acid by the methoxy substituent. In contrast, the reaction of **5j** with TfOH (5 equiv.) gave only a poor yield of **4j** (11%, entry 18).

We then applied the optimised $AlCl_3$ conditions for **5c** (entry 7) to the azetidinone **3c** and obtained an 88% recovery of **3c** together with only a small quantity (12%) of **4c**. In contrast to the TfOH-mediated reactions, it would appear that with $AlCl_3$ ring opening is relatively slow and is likely to be rate limiting.

In summary, although we have shown that 4-aryl-azetidinones can undergo an $AlCl_3$-mediated ring opening, the most convenient synthesis of 3-aryl-3-phenyl-propionamides is from the cinnamamides. We also conclude that TfOH is probably the preferred reagent for the formation of 3-aryl-3-phenyl-propionamides.

TfOH-mediated ring opening of 7- and 8-membered lactams

We found that the TfOH-mediated ring opening/phenylation of the 8-membered analogues, **7–9**, gave good yields of the diphenyl-heptanoic acid amide **2e** (95%, 83% and 85% respectively) with only trace amounts of the substituted analogues observed. Similarly the 7-membered lactam **10** gave a good yield of **2d** (86%).



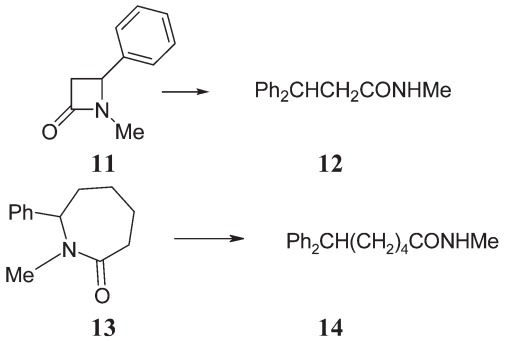
7 R = F
8 R = Br
9 **10**

Thus, for 7- and 8-membered lactams, the aryl replacement reaction is faster than the ring opening reaction. In order to assess the generality of the acid-mediated aryl replacement reaction, we studied 2-benzylnaphthalene,[15] which rapidly reacted with benzene and TfOH under reflux, or $AlCl_3$ at ambient

temperatures, both giving high yields of naphthalene (95%) and diphenylmethane (100%).

TfOH-mediated ring opening of *N*-methyl lactams

The *N*-substituted lactams **11** and **13** reacted with TfOH in benzene to give good yields of **12** (95% yield) and **14** (83% yield) respectively. Thus, the presence of an *N*-methyl group does not interfere with the ring-opening/phenylation reaction.



Conclusion

In summary, we have shown that TfOH promotes ring-opening of α-aryl lactams of a variety of ring sizes with cleavage of the N–CHAr bond. The presumed dications formed react with benzene to form aryl–phenyl alkylamides. For azetidinones, the intermediate dications, on basification, gave cinnamamides. For the 9-membered lactam, a mixture of products was obtained. With substituted-phenyl analogues, benzene subsequently displaces the substituted-phenyl group to give diphenyl amides. The products obtained were determined by the relative rates of the three sequential reactions; ring opening, phenylation and aryl exchange.

For azetidinones, the electronic properties of the substituent and the acid used determine the outcome of the reaction. With electron donating substituents, the aryl exchange reaction was relatively fast. For mildly electron withdrawing substituents, the aryl exchange reaction was relatively slow, with little difference in the ring opening and phenylation rates. However, with strongly electron withdrawing groups, the ring opening reaction failed. For the substituted-phenyl lactams of ring size 7 and 8, the ring opening reaction was slow compared to the aryl exchange, hence only the diphenyl compounds were obtained. With $AlCl_3$, only the azetidinones underwent ring-opening and the ring opening reaction was relatively slow compared with the phenylation and aryl exchange.

Investigations with substituted-cinnamamides, the presumed intermediates from the azetidinones, showed that the aryl-exchange reaction was fast, particularly for electron-donating substituents. For mildly electron withdrawing substituents, the 3-aryl-3-phenyl-propionamides could be obtained with reasonable selectivity. Previous work had concluded that $AlCl_3$ was superior to TfOH for the phenylation of α,β-unsaturated amides.[1] However, our work demonstrates that for substituted cinnamamides, TfOH is better.

In conclusion, we have demonstrated a synthetically useful method of synthesis of 3-aryl-3-phenyl-propionamides. The 3,3-diphenyl-propionyl and 3,3-diphenyl-proylamino groups appear in a wide range of pharmacologically active molecules,[16] and the methodology described here should facilitate the synthesis of novel analogues.

Experimental

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 the 40–60 °C fraction. Infrared spectra were run neat on a Perkin Elmer 100 FT IR spectrometer. Solution ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker NMR spectrometer DRX500 equipped with *z*-gradient facilities. ^{1}H and ^{13}C chemical shifts are given relative to TMS. Unless otherwise specified, spectra were recorded at 25 °C. Melting points were determined on a Sanyo-Gallenkamp capillary melting point apparatus and are uncorrected. The lactams **1a**,[17] **1b**,[18] **1c**,[19] **1d**,[20] **3a**,[21] **3c**,[6] **3d**,[6] **3e**,[6] **3f**,[6] **3g**,[6] **10**[22] and **11**,[23] and cinnamamides **5a**,[24] **5c**,[25] **5d**,[26] **5f**,[27] **5g**,[27] **5h**,[28] **5i**[29] and **5j**[1] were prepared by the literature methods.

8-Phenyl-azocan-2-one 1e

A solution of hydroxylamine hydrochloride (5 g) and sodium acetate trihydrate (12 g) in water (50 ml) was added to a stirred solution of 2-phenylcycloheptanone[30] (5.4 g, 28 mmol) in EtOH (200 ml) and the reaction heated under reflux for 2 h. On cooling, the ethanol was removed by rotary evaporation and the residue treated with water (200 ml). The solid was collected, dried and recrystallised from ether–petrol to give the oxime (5.5 g) mp 72–3 °C. A stirred suspension of the oxime (2.9 g, 14 mmol) in pyridine (20 ml) was cooled to 0 °C and *p*-toluenesulfonyl chloride (5 g) was added over 10 min. The reaction mixture was stirred at 0 °C for a further 2 h, then placed in a refrigerator at 4 °C for 2 days. The reaction mixture was then stirred with 2 M HCl (200 ml) for 30 min and the products extracted into DCM (2 × 100 ml), dried and evaporated. The residue was purified by column chromatography on silica, initially eluting with 1 : 1 DCM–petroleum ether to remove the non-polar impurities, then with 1% MeOH–DCM to give the product as a white solid (1.5 g, 52% yield) mp 101–2 °C (EtOAc–petroleum ether). ^{1}H-NMR (500 MHz) δ = 1.43–1.50 (2H, m), 1.72–2.00 (6H, m), 2.41 (1H, dt, J = 12.8, 3.9 Hz), 2.65 (1H, dt, J = 3.7, 13.0 Hz), 4.67 (1H, dt, J = 3.5, 11.4 Hz), 5.69 (1H, brd, J = 9.4 Hz), 7.20–7.42 (5H, m), ^{13}C-NMR + DEPT (125 MHz) δ = 24.7 (CH_2), 26.2 (CH_2), 28.4 (CH_2), 33.6 (CH_2), 38.7 (CH_2), 55.9 (CH), 126.3 (CH), 127.9 (CH), 129.0 (CH), 141.4 (C), 176.5 (C). LRMS (EI) 203, 106, 104; HRMS calcd for $C_{13}H_{17}NO$, 203.1305 found 203.1307. FT IR (neat) 3172, 3051, 2923, 2861, 1649, 1447, 1401, 1242, 1154, 821, 792, 745, 692 cm^{-1}.

9-Phenyl-azonan-2-one 1f

Following the procedure described for **1e**, 2-phenylcyclooctanone[31] was converted into its oxime, isolated as an oil. Treatment of the oxime (2.7 g, 12 mmol) in pyridine (10 ml) and tosyl chloride (4.5 g) gave, after purification on silica, eluting with 1% MeOH–DCM, 2.5 g of a mixture of the 3- and 9-isomers. Crystallisation from 9 : 1 Et_2O–petroleum ether gave 0.5 g of the 3-isomer. Re-columning the mother liquors on silica, eluting with DCM plus increasing quantities of Et_2O to 1 : 1 DCM–Et_2O gave the pure 9-isomer (1.5 g, 55% yield), mp 112–3 °C (EtOAc–petroleum ether). ^{1}H-NMR (500 MHz) δ = 1.38–1.48 (0.5H, m), 1.50–2.30 (10H, m), 2.31–2.40 (0.5H, m), 2.44–2.58 (1H, m), 4.82 (0.5H, dt, J = 3.3, 11.5 Hz), 5.13 (0.5H, dt, J = 3.3, 10.3 Hz), 5.53 (0.5H, brd, J = 9.6 Hz), 5.74 (0.5H, brd, J = 10.0 Hz), 7.20–7.49 (5H, m). On heating to 60 °C, all of the peaks broadened. ^{13}C-NMR + DEPT (125 MHz) δ = 21.9 (CH_2), 22.9 (CH_2), 24.3 (CH_2), 25.3 (CH_2), 25.9 (CH_2), 27.4 (CH_2), 28.2 (CH_2), 29.7 (CH_2), 35.3 (CH_2), 36.5 (CH_2), 37.4 (CH_2), 38.9 (CH_2), 54.4 (CH_2), 56.6 (CH_2), 125.9 (CH), 126.3 (CH), 127.2 (CH), 127.7 (CH), 128.6 (CH), 128.9 (CH), 142.2 (C), 175.9 (C), 177.3 (C). LRMS (EI) 217, 189, 160, 106; HRMS calcd for $C_{14}H_{19}NO$, 217.1461 found 217.1467. FT IR (neat) 3333, 2927, 2889, 1650, 1543, 1523, 1453, 1282, 1237, 1146, 767, 751, 731, 713, 694 cm^{-1}.

4-(3-Trifluoromethyl-phenyl)-azetidin-2-one 3h

A solution of 3-trifluoromethylstyrene (1.0 g, 6 mmol) and chlorosulphonyl isocyanate (0.6 ml, 7 mmol) in toluene (40 ml) was allowed to stand at room temperature for 7 days. The reaction mixture was treated with a solution of sodium sulfite (2.4 g) and potassium carbonate (12 g) in water (100 ml) and stirred for 1 h. The product was extracted into Et_2O (100 ml), the organic layer separated and dried ($MgSO_4$). Evaporation and purification on silica, eluting initially with DCM, then 2% MeOH–DCM gave **3h** (0.27 g, 21% yield), mp 62–3 °C (EtOAc–petrol). ^{1}H-NMR (500 MHz) δ = 2.89 (1H, ddd, J = 0.8, 2.6, 15.0 Hz), 3.50 (ddd, J = 2.8, 5.4, 15.0), 4.80 (1H, dd, J = 2.6, 5.4 Hz), 6.27 (1H, brs), 7.52 (1H, t, J = 7.7 Hz), 7.59 (2H, t, J = 7.4 Hz), 7.63 (1H, s). ^{13}C-NMR + DEPT (125 MHz) δ = 48.3 (CH_2), 50.0 (CH), 122.6 (CH), 125.2 (CH), 129.0 (CH), 129.5 (CH), 131.4 (C, q, J = 33 Hz), 141.4 (C), 167.4 (C). (LRMS (CI) 216, 176, 172; HRMS calcd for $C_{10}H_9F_3NO$, 216.0636 found 216.0631. FT IR (neat) 3243, 1748, 1453, 1366, 1330, 1319, 1273, 1159, 1101, 1073, 802, 698, 672, 658 cm^{-1}.

General procedure for the TfOH-mediated phenylation reaction

Triflic acid (10 mmol) was added to a stirred solution of the lactam or cinnamamide (1 mmol) in dry benzene (20 ml) and the reaction mixture was heated under gentle reflux for the stated time. 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.

General procedure for the $AlCl_3$-mediated phenylation reaction

Aluminium chloride (3 mmol) was added to a stirred solution of the lactam or cinnamamide (1 mmol) in dry benzene and the reaction mixture stirred at room temperature for the stated time. Water (10 ml) and DCM (20 ml) was added and the reaction stirred until all solids had dissolved. The product was extracted with DCM (2 × 50 ml), dried ($MgSO_4$), concentrated *in vacuo* and the product purified by column chromatography on SiO_2.

3,3-Diphenyl-propionamide 2a

Prepared using TfOH in 73% yield from **1a** and purified on silica by elution with DCM + 1% MeOH; mp 125–7 °C (EtOAc–petroleum ether) lit. 127–8 °C.[1] ^{1}H-NMR (500 MHz) δ = 2.95 (2H, d, J = 7.8 Hz), 4.56 (1H, t, J = 7.8 Hz), 5.26 (1H, brs), 5.31 (1H, brs), 7.15–7.32 (10H, m), ^{13}C-NMR + DEPT (125 MHz) δ = 42.5 (CH_2), 47.3 (CH), 126.7 (CH), 127.8 (CH), 128.7 (CH), 143.6 (C), 173.4 (C).

3-Phenyl-3-*p*-tolyl-propionamide 4a from 3a

Prepared from **3a** (0.32 g, 2 mmol) as described in the general procedure, but using TfOH (1 ml, 10 mmol.) and benzene (2 ml, 20 mmol) in $CHCl_3$ (20 ml), reflux for 0.5 h, gave 0.4 g of **4a** (91% yield), purified on silica by elution with DCM + 1% MeOH; mp 122–4 °C (EtOAc–petroleum ether). ^{1}H-NMR (500 MHz) δ = 2.30 (3H, s), 2.89 (2h, d, J = 8 Hz), 4.51 (1H, t, J = 8 Hz), 5.28 (1H, brs), 5.39 (1H, brs), 7.09 (2H, d, J = 8.0 Hz), 7.14 (2H, d, J = 8.0 Hz), 7.18 (1H, t, J = 7.7 Hz), 7.21–7.30 (4H, m), ^{13}C-NMR + DEPT (125 MHz) δ = 21.1 (CH_3), 42.6 (CH_2), 46.9 (CH), 126.6 (CH), 127.6 (CH), 127.7 (CH), 128.7 (CH), 129.4 (CH), 136.2 (C), 140.6 (C), 143.9 (C), 173.6 (C). NMR consistent with literature.[32] LRMS (EI) 239, 194, 181, 165; HRMS calcd for $C_{16}H_{17}NO$, 239.1305 found 239.1305.

3-Phenyl-3-*p*-tolyl-propionamide 4a from 5a

Prepared from **5a** (0.18 g, 1 mmol) and TfOH (0.5 ml, 5 mmol) as described in the general procedure, heated under reflux for 1 h, to give **4a** (0.24 g, 100% yield) identical to that prepared above.

3-Phenyl-3-*m*-tolyl-propionamide 4b

Prepared using TfOH in 81% yield from **3b** and purified on silica by elution with DCM + 10% Et_2O; mp 62–4 °C (EtOAc–petroleum ether). ^{1}H-NMR (500 MHz) δ = 2.31 (3H, s), 2.91 (2h, d, J = 8 Hz), 4.51 (1H, t, J = 8 Hz), 5.60 (1H, brs), 5.88 (1H, brs), 7.00–7.08 (3H, m), 7.16–7.22 (2H, m), 7.23–7.31 (4H, m), ^{13}C-NMR + DEPT (125 MHz) δ = 21.6 (CH_3), 42.4 (CH_2), 47.1 (CH), 124.7 (CH), 126.6 (CH), 127.5 (CH), 127.8 (CH), 128.6 (CH), 128.7 (CH), 138.3 (C), 143.7 (C), 143.9 (C), 174.1 (C). LRMS (EI) 239, 194, 181, 165; HRMS calcd for $C_{16}H_{17}NO$, 239.1305 found 239.1307. FT IR (neat) 3404, 3195, 1650, 1403, 1175, 786, 762, 717, 695 cm^{-1}. NMR consistent with literature.[31]

3-(4-Chlorophenyl)-3-phenyl-propionamide 4c

Prepared using TfOH in 87% yield from **3c** and purified on silica by elution with DCM + 1% MeOH; mp 110–2 °C (EtOAc–petroleum ether), lit. 112–3 °C.[33] ^{1}H-NMR (500 MHz) δ = 2.86 (1h, dd, J = 8.0, 14.7 Hz), 2.90 (1h, dd, J = 8.0, 14.7 Hz), 4.52 (1H, t, J = 8 Hz), 5.60 (1H, brs), 5.88 (1H, brs), 7.15 (2H, d, J = 8.4 Hz), 7.17–7.30 (7H, m). ^{13}C-NMR + DEPT (125 MHz) δ = 42.4 (CH), 46.5 (CH), 126.7 (CH), 127.7 (CH), 128.8 (CH), 129.2 (CH), 132.5 (C), 142.2 (C), 143.1 (C), 173.0 (C). LRMS (EI) 261, 259, 203, 201, 166, 165; HRMS calcd for $C_{15}H_{14}ClNO$, 259.0758 found 259.0764. FT IR (neat) 3394, 3182, 1654, 1629, 1490, 1412, 1092, 1013, 849, 816, 782, 757, 699 cm^{-1}.

3-(3-Chlorophenyl)-3-phenyl-propionamide 4d

Prepared using TfOH in 87% yield from **3d** and purified on silica by elution with DCM + 1% MeOH; mp 83–5 °C (EtOAc–petroleum ether), lit. 71–3 °C.[34] ^{1}H-NMR (500 MHz) δ = 2.89 (1h, dd, J = 8.0, 14.7 Hz), 2.94 (1h, dd, J = 8.0, 14.7 Hz), 4.55 (1H, t, J = 8 Hz), 5.40 (1H, brs), 5.53 (1H, brs), 7.10–7.30 (9H, m), ^{13}C-NMR + DEPT (125 MHz) δ = 42.1 (CH_2), 46.9 (CH), 126.1 (CH), 126.9 (CH), 127.0 (CH), 127.7 (CH), 127.9 (CH), 128.9 (CH), 130.0 (CH) 134.5 (C), 142.9 (C), 145.8 (C), 173.0 (C). LRMS (EI) 261, 259, 214, 179, 178, 166, 165; HRMS calcd for $C_{15}H_{14}ClNO$, 259.0758 found 259.0760. FT IR (neat) 3440, 3178, 1659, 1621, 1593, 1427, 1399, 1304, 1077, 862, 800, 785, 752, 692 cm^{-1}.

3-(2-Chlorophenyl)-3-phenyl-propionamide 4e

Prepared using TfOH in 77% yield from **5e** and purified on silica, eluting with DCM containing increasing quantities of Et_2O up to 3 : 1 DCM–Et_2O, mp 118–9 °C (EtOAc–petroleum ether). ^{1}H-NMR (500 MHz) δ = 2.92 (1h, dd, J = 8.0, 14.7 Hz), 2.96 (1h, dd, J = 8.0, 14.7 Hz), 5.02 (1H, t, J = 8 Hz), 5.50 (1H, brs), 5.70 (1H, brs), 7.10–7.30 (8H, m), 7.35 (1H, dd, J = 1.3, 7.9 Hz), ^{13}C-NMR + DEPT (125 MHz) δ = 41.7 (CH_2), 43.6 (CH), 126.8 (CH), 127.1 (CH), 128.0 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 130.1 (CH), 134.2 (C), 140.9 (C), 142.0 (C), 173.0 (C). LRMS (EI) 259, 224, 203, 201, 178, 166, 165; HRMS calcd for $C_{15}H_{14}ClNO$, 259.0758 found 259.0761. FT IR (neat) 3415, 3200, 1657, 1614, 1404, 1035, 747, 694 cm^{-1}.

3-(4-Bromophenyl)-3-phenyl-propionamide 4f

Prepared using TfOH in 90% yield from **3f** and purified on silica by elution with DCM + 1% MeOH; mp 122–3 °C (EtOAc–petroleum ether). ^{1}H-NMR (500 MHz) δ = 2.87 (1h, dd, J = 8.0, 14.7 Hz), 2.94 (1h, dd, J = 8.0, 14.7 Hz), 4.52 (1H, t, J = 8 Hz), 5.46 (1H, brs), 5.72 (1H, brs), 7.10 (2H, d, J = 8.3 Hz), 7.17–7.23 (3H, m), 7.28 (2H, t, J = 8.4 Hz), 7.39 (2H, d, J = 8.3 Hz), ^{13}C-NMR + DEPT (125 MHz) δ = 42.2 (CH2), 46.6 (CH), 120.5 (C), 126.9 (CH), 127.7 (CH), 128.6 (CH), 129.6 (CH), 131.8 (CH), 142.8 (C), 143.1 (C), 173.3 (C). LRMS (EI) 305, 303, 260, 258, 247, 245, 165; HRMS calcd for $C_{15}H_{14}BrNO$, 303.0253 found 303.0256. FT IR (neat) 3395, 3192, 1663, 1656, 1486, 1405, 1010, 818, 744, 698 cm^{-1}.

3-(4-Fluorophenyl)-3-phenyl-propionamide 4g

Prepared using TfOH in 73% yield from **3g** and purified on silica, eluting with 1%MeOH–DCM; mp 85–6 °C (EtOAc–petroleum ether). ^{1}H-NMR (500 MHz) δ = 2.87 (1h, dd, J = 8.0, 14.7 Hz), 2.94 (1h, dd, J = 8.0, 14.7 Hz), 4.54 (1H, t, J = 8 Hz), 5.49 (1H, brs), 5.78 (1H, brs), 6.95 (2H, t, J = 8.7 Hz), 7.15–7.24 (5H, m), 7.25–7.30 (2H, m); ^{13}C-NMR + DEPT (125 MHz) δ = 42.5 (CH_2), 46.4 (CH), 115.5 (CH, d, J = 21 Hz), 126.8 (CH), 127.7 (CH), 128.7 (CH), 129.3 (CH, d, J = 8 Hz), 139.5 (C), 143.5 (C), 161.6 (C, d, J = 245 Hz), 173.6 (C). LRMS (EI) 243, 185, 183; HRMS calcd for $C_{15}H_{14}FNO$, 243.1054 found 243.1056. FT IR (neat) 3432, 3353, 3208, 1653, 1604, 1507, 1402, 1221, 1159, 832, 799, 744, 701 cm^{-1}.

E-3-(2-Chlorophenyl)-acrylamide 5e

A suspension of *E*-3-(2-chlorophenyl)-acrylic acid (3.6 g, 20 mmol) in DCM (50 ml) was stirred at room temperature with oxalyl chloride (1.8 ml, 20 mmol) and 3 drops of DMF for 2 h. The solvent was removed by rotary evaporation and the residue was dissolved in THF (30 ml). This solution of the acid chloride was added over 5 min to a stirred solution of aqueous 0.88 NH_3 (50 ml) and IPA (50 ml) at 0 °C. After stirring to room temperature for 1 h, water (100 ml) was added and the mixture concentrated by rotary evaporation to ~100 ml. Another 100 ml of water was added and the solid collected and dried (3.4 g, 94% yield) mp 164–6 °C (lit. 166 °C).[33] ^{1}H-NMR (500 MHz) δ = 5.68 (2H, brs), 6.46 (1H, d, J = 15.8 Hz), 7.24–7.31 (2H, m), 7.41 (1H, dd, J = 1.7, 7.9 Hz), 7.59 (1H, dd, J = 2.0, 7.3 Hz), 7.99 (1H, d, J = 15.8 Hz); ^{13}C-NMR + DEPT (125 MHz) δ = 122.5 (CH), 127.1 (CH), 127.7 (CH), 130.3 (CH), 130.8 (CH), 132.9 (C), 134.9 (C), 167.3 (C).

8-(4-Fluorophenyl)-azocan-2-one 7

To a stirred solution of 4-fluorobenzaldehyde tosyl hydrazide[35] (5.8 g, 20 mmol) and cyclohexanone (10 g, mmol) in MeOH (100 ml) was added KBu^{t}O (2.2 g, 20 mol) and the reaction heated under reflux for 2 h, then left to cool to room temperature overnight. The MeOH was removed by rotary evaporation, water (50 ml) was added to the residue and the 2-(4-fluorophenyl) cycloheptanone was extracted into Et_2O (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), concentrated and the product purified by column chromatography on silica, eluting with toluene, isolated as an oil (3.0 g, 68% yield). ^{1}H-NMR (500 MHz) δ = 1.40–1.52 (2H, m), 1.60–1.73 (1H, m), 1.86–2.13 (5H, m), 2.49–2.55 (1H, m), 2.64 (1H, ddd, J = 3.4, 12.0, 13.9 Hz), 3.71 (1H, dd, J = 4.0, 11.4 Hz), 6.97 (2H, t, J = 8.7 Hz), 7.17 (2H, dd, J = 5.4, 8.6 Hz). ^{13}C-NMR + DEPT (125 MHz) δ = 25.0 (CH_2), 28.8 (CH_2), 29.9 (CH_2), 32.2 (CH_2), 35.4 (CH_2), 57.8 (CH), 115.3 (CH, d, J = 21 Hz), 129.4 (CH, d, J = 8Hz), 136.3 (C), 161.8 (C, d, J = 244 Hz), 213.2 (C). FT-IR (neat) 2935, 1704, 1681, 1597, 1508, 1225, 1188, 1157, 831, 821 cm^{-1}. LRMS (EI) 206, 138, 123; HRMS calcd for

$C_{13}H_{15}FO$, 206.1101 found 206.1104. Following the procedure described for **1e**, the ketone (3.0 g, 14.5 mmol) was converted into its oxime (3.1 g, 95% yield), mp 108–10 °C (EtOAc–petrol). The oxime (3.0 g, 13.5 mmol) was converted into **7** (1.4 g, 47% yield), purified by column chromatography on silica, eluting with 1% MeOH–Et_2O mp 112–4 °C (EtOAc–petroleum ether). ^{1}H-NMR (500 MHz) δ = 1.40–1.56 (2H, m), 1.70–2.00 (5H, m), 2.41 (1H, dt, J = 4.5, 12.8 Hz), 2.63 (1H, dt, J = 3.3, 12.7 Hz), 4.65 (1H, dt, J = 3.6, 11.2 Hz), 5.85 (1H, brd, J = 9.7 Hz), 7.04 (2H, t, J = 8.6 Hz), 7.30 (2H, dd, J = 5.2, 8.6 Hz). ^{13}C-NMR + DEPT (125 MHz) δ = 24.6 (CH_2), 26.1 (CH_2), 28.4 (CH_2), 33.6 (CH_2), 38.6 (CH_2), 55.2 (CH), 115.8 (CH, d, J = 21 Hz), 1281 (CH, d, J = 8 Hz), 137.2 (C, d, J = 3 Hz), 162.1 (C, d, J = 247 Hz), 176.6 (C). LRMS (CI) 222; HRMS calcd for $C_{13}H_{17}FNO$, 222.1294 found 222.1294. FT IR (neat) 3198, 2944, 2925, 1648, 1602, 1516, 1453, 1404, 1228, 1151, 837, 812, 798, 782, 754 cm^{-1}.

N-Methyl-3,3-diphenyl-propionamide 12

Following the general procedure, **11**[23] (0.32 g, 2 mmol) was heated with TfOH (1 ml, 10 mmol) in benzene (15 ml) under reflux for 1 h. A solid was obtained from rotary evaporation of the extraction solvent which was recrystallised from EtOAc–petroleum ether (0.45 g, 95% yield) mp 76–7 °C. ^{1}H-NMR (500 MHz) δ = 2.64 (1.5H, s), 2.65 (1.5H, s), 2.88 (2H, d, J = 7.8 Hz), 4.58 (1H, t, J = 7.8 Hz), 5.25 (1H, brs), 7.17–7.32 (10H, m), ^{13}C-NMR + DEPT (125 MHz) δ = 26.4 (CH_3), 43.4 (CH_2), 47.4 (CH), 126.6 (CH), 127.8 (CH), 128.7 (CH), 143.8 (C), 171.8 (C). LRMS (EI) 239, 167, 165; HRMS calcd for $C_{16}H_{17}NO$, 239.1305 found 239.1302. FT IR (neat) 3329, 1640, 1555, 1491, 760, 745, 699 cm^{-1}.

1-Methyl-7-phenyl-azepin-2-one 13

NaH (60% dispersion in oil, 0.22 g, 5.5 mmol) was added to a stirred solution of **1d** (0.84 g, 4.4 mmol) in dry THF (50 ml) under argon and the reaction stirred for 15 min to form a thick slurry. MeI (0.55 ml, 9 mmol) was then added and the solution stirred at room temperature for 4 h. Water (50 ml) was carefully added and the product extracted into EtOAc (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), concentrated and purified by column chromatography on silica, eluting with 1%MeOH–DCM to give **13** as an oil (0.77 g, 85% yield). ^{1}H-NMR (500 MHz) δ = 1.57–1.75 (4H, m), 1.95–2.11 (2H, m), 2.27–2.40 (2H, m), 2.03–2.11 (1H, m), 2.95 (3H, s), 4.71 (1H, dd, J = 3.2, 7.3 Hz), 7.18 (2H, d, J = 8.3 Hz), 7.22–7.29 (1H, m), 7.36 (2H, t, J = 8.3 Hz), ^{13}C-NMR + DEPT (125 MHz) δ = 22.8 (CH_2), 24.4 (CH_2), 31.3 (CH_2), 36.0 (CH_3), 36.9 (CH_2), 63.0 (CH), 126.5 (CH), 127.2 (CH), 129.0 (CH), 139.4 (C), 176.0 (C). LRMS (EI) 203, 174, 118. HRMS calcd for $C_{13}H_{17}NO$, 203.1305, found 203.1308. FT IR (neat) 2930, 1628, 1445, 1393, 750, 700 cm^{-1}.

6,6-Diphenylhexanoic acid methylamide 14

Following the general TfOH procedure, **13** (0.4 g, 2 mmol) was converted into **14**, purified by column chromatography on silica, eluting with 2% MeOH–Et_2O (0.46 g, 83% yield) mp 93–5 °C (EtOAc–petroleum ether). ^{1}H-NMR (500 MHz) δ = 1.24–1.33 (2H, m), 1.67 (2H, quintet, J = 7.7 Hz), 2.05 (2H, quartet, J = 7.8 Hz), 2.12 (2H, t, J = 7.5 Hz), 2.75 (3H, d, J = 3.7 Hz), 3.88 (1H, t, J = 7.8 Hz), 5.59 (1H, brs), 7.16 (2H, t, J = 7.1 Hz), 7.20–7.30 (8H, m), ^{13}C-NMR + DEPT (125 MHz) δ = 25.8 (CH_2), 26.4 (CH_3), 27.7 (CH_2), 35.4 (CH_2), 36.5 (CH_2), 51.2 (CH), 126.2 (CH), 127.9 (CH), 128.5 (CH), 145.1 (C), 173.8 (C). LRMS (EI) 281, 167; HRMS calcd for $C_{19}H_{23}NO$, 281.1774 found 281.1773. FT IR (neat) 2927, 1633, 1572, 1492, 1452, 1443, 1156, 760, 747, 706, 693 cm^{-1}.

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References

1 K. Y. Koltunov, S. Walspurger and J. Sommer, *Eur. J. Org. Chem.*, 2004, 4039.
2 D. A. Klump, R. Rendy, Y. Zhang, A. Gomez and A. McElrea, *Org. Lett.*, 2004, **6**, 1789.
3 F. D. King and S. Caddick, *Tetrahedron Lett.*, 2011, **52**, 6783.
4 F. D. King and S. Caddick, *Org. Biomol. Chem.*, 2011, **9**, 4361.
5 K. L. Williamson and J. D. Roberts, *J. Am. Chem. Soc.*, 1976, **98**, 5082.
6 E. Forro, T. Paal, G. Tasnadi and F. Fueloep, *Adv. Synth. Catal.*, 2006, **348**, 917.
7 M. Farcasiu and T. R. Forbus, US4454364, 1984, CA 101, 90555, 1984.
8 S. Shinichi, O. Tomohiko and S. Koichi, *J. Org. Chem.*, 1996, **61**, 8089.
9 Y. V. Pozdnyakovich, R. P. Savyak and S. M. Shein, *Zh. Org. Khim.*, 1986, **22**, 584.
10 M. Hannoun, N. Blazevic, D. Kolbah, Z. Mihalic, M. Mladen and F. Kajfez, *J. Heterocycl. Chem.*, 1982, **19**, 1131; T. Yamato and N. Sakaue, *J. Chem. Res., Miniprint*, 1997, 2614.
11 F. Huston, *J. Am. Chem. Soc.*, 1916, **38**, 2530.
12 D. V. Apte and K. D. Deodhar, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1980, **19**, 758.
13 S. Reindel, *Chem. Ber.*, 1923, **56**, 1553.
14 E. Connerade, *Bull. Soc. Chim. Belg.*, 1935, **44**, 411.
15 J. H. P. Utley and G. G. Rozenberg, *Tetrahedron*, 2002, **58**, 5251.
16 For example: J. J. Cumming, A. E. Cooper, K. Grime, C. J. Logan, S. McLaughlin, J. Oldfield, J. S. Shaw, H. Tucker, J. Winter and D. Whittaker, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5012; E. Carceller, C. Almansa, M. Merlos, M. Giral, J. Bartroli, J. Garcia-Rafanell and J. Forn, *J. Med. Chem.*, 1992, **35**, 4118; L. Diaz, J. Casas, A. Llebaria, A. Delgado and J. Bujons, *J. Med. Chem.*, 2011, **54**, 2069; R. E. Mewshaw, R. G. Sherrill, R. M. Mathew, C. Kaiser, M. A. Bailey and E. W. Karbon, *J. Med. Chem.*, 1993, **36**, 343; S. K. Sharma, M. L. Crowley, A. S. Hanson, P. M. Woster, Y. Wu, N. Steinbergs and R. A. Casero, *J. Med. Chem.*, 2010, **53**, 5197.
17 L. Crombie, R. C. F. Jones and D. Haigh, *Tetrahedron Lett.*, 1986, **27**, 5147.
18 B. Rigo, D. Fasseur, N. Cherepy and D. Couturier, *Tetrahedron Lett.*, 1989, **30**, 7057.
19 Adapted from: B. M. Nilsson, H. M. Vargas, B. Ringdahl and U. Hacksell, *J. Med. Chem.*, 1992, **35**, 285.
20 J. A. Lowe III, US5484917 1996, CA 124, 317009, 1996.
21 E. Forro and F. Fueloep, *Tetrahedron: Asymmetry*, 2001, **12**, 2351.
22 A. C. Huitric and S. D. Nelson Jr., *J. Org. Chem.*, 1969, **34**, 1230.
23 H.-J. Bergmann, R. Mayrhofer and H.-H. Otto, *Arch. Pharm.*, 1986, **319**, 203.
24 A. Tasaka, T. Hitaka and E. Matsutani, WO 2001077107, CA 135, 303897, 2001.
25 V. N. Rondestvedt, *J. Am. Chem. Soc.*, 1955, **77**, 4878.
26 J. A. Claisse, G. I. Gregory and W. K. Warburton, USP4012377, *Chem. Abstr*, 1977, **87**, 39491.

27 K. Fujimura, J. Matsumoto, M. Niwa, T. Kobayshi and Y. Kawashima, *et al.*, *Bioorg. Med. Chem.*, 1997, **5**, 1675.
28 W. J. Houlihan, J. H. Gogerty, E. A. Ryan and G. Schmitt, *J. Med. Chem.*, 1985, **28**, 28.
29 K. W. Gopinath, T. R. Govindachari, K. Nagarajan and K. K. Purushothaman, *J. Chem. Soc.*, 1957, 1144.
30 C. E. Sacks and P. L. Fuchs, *J. Am. Chem. Soc.*, 1975, **97**, 7373.
31 L. Lezhen, C. Peijie, G. Qingxiang and X. Song, *J. Org. Chem.*, 2008, **73**, 3516.
32 J. Lee, S.-U. Kang, J.-O. Lim, H.-K. Choi, M.-K. Jin, A. Toth, L. V. Pearce, R. Tran, Y. Wang, T. Szabo and P. M. Blumberg, *Bioorg. Med. Chem.*, 2004, **12**, 371.
33 Z. Zhuangyu, P. Yi, H. Honwen and K. Tsi-yu, *Synthesis*, 1991, 539B.
34 B. Blank, W. A. Zuccarello, S. R. Cohen, G. J. Frishmuth and D. Scaricaciottoli, *J. Med. Chem.*, 1969, **12**, 271.
35 L. A. Adams, V. K. Aggarwal, R. V. Bonnert, B. Bressel, R. J. Cox, J. Shepherd, J. de Vicente, M. Walter, W. G. Whittingham and C. L. Winn, *J. Org. Chem.*, 2003, **68**, 9433.

