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**PAPER**

# Triflic acid-mediated phenylation of *N*-acylaminoalkyl diethylacetals and *N*-acyl-2-phenyl cyclic amides†

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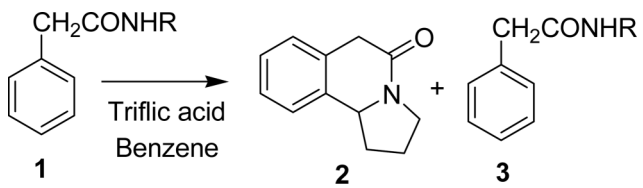
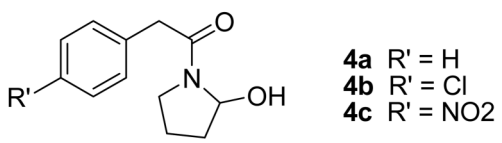
The reaction of *N*-acylaminoalkyl diethylacetals with triflic acid in benzene gave *N*-acylamino-diphenylalkyls. The proposed intermediates are the *N*-acyl-2-phenyl cyclic amides, which themselves are similarly converted to *N*-acylamino-diphenylalkyls.

## Introduction

We have been investigating the use of triflic acid in electrophilic iminium ion cyclisations and recently reported that treatment of **1** and **4a** with triflic acid and Lewis acids in $CHCl_3$ forms pyrrolo-tetra-hydroisoquinolinone, **2**.[1] In contrast, other *N*-acyl-2-hydroxypyrrolidines react with benzene in the presence of Lewis acids to form *N*-acyl-2-phenylpyrrolidines *via* an intermolecular Friedel Crafts reaction.[2] We therefore wished to compare the rates of the intramolecular cyclisation *versus* the intermolecular reaction with benzene and triflic acid. To our surprise, we found that the reaction of both **1** and **4a** gave a mixture of **2** (30% yield) and a second product, which proved not to be the expected *N*-acyl-2-phenylpyrrolidine, but 1-amido-4,4-diphenyl-butane, **3** (50% yield) (Scheme 1).



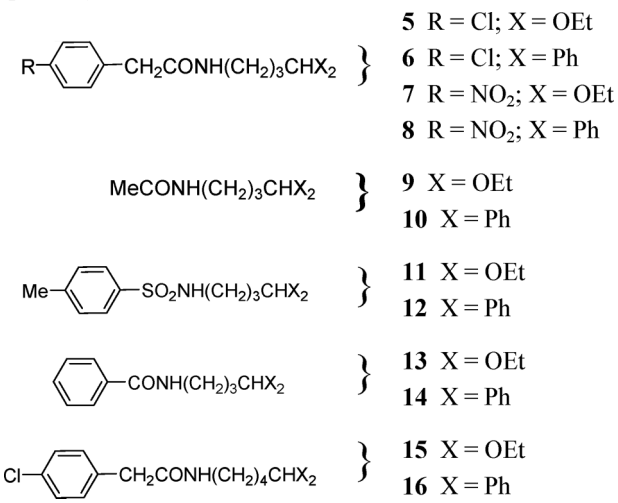




**Scheme 1** Reaction of **1** with triflic acid in benzene.

Although aminoacetals have been reported to undergo diphenylation *via* a dicationic intermediate,[3] that reaction was restricted to acetaldehyde and propionaldehyde derivatives and there have been no reports on the diphenylation of amido acetals. This paper describes the results of our investigation into the unexpected formation of **3**

## Results and discussion

The introduction of electron-withdrawing groups into the phenylacetyl ring would be expected to deactivate the ring to cyclisation and, consistent with this, we observed the exclusive formation of 4,4-diphenylbutanamides **6** (70% yield) and **8** (68% yield) from the respective 1-acylamido-4,4-diethoxybutanes **5** and **7**. Similarly yields of **6** (82% yield) and **8** (75% yield) were obtained from the appropriately substituted *N*-(phenylacetyl)-2-hydroxypyrrolidines **4b** and **4c**. This diphenylation reaction also worked for 1-acetamido-4,4-diethoxybutane **9** and 1-(*p*-toluenesulfonamido)-4,4-diethoxybutane **11** to give **10** (73% yield) and **12** (38% yield), respectively.




This transformation could be extended to the benzamide, with conversion of the diethylacetal **13** to the 4,4-diphenylbutylamide **14**, but only in a modest yield (36%). Improved yields were obtained when 1 equivalent of triflic anhydride (63% yield) or TMS triflate (61% yield) was added, which we believe limits the

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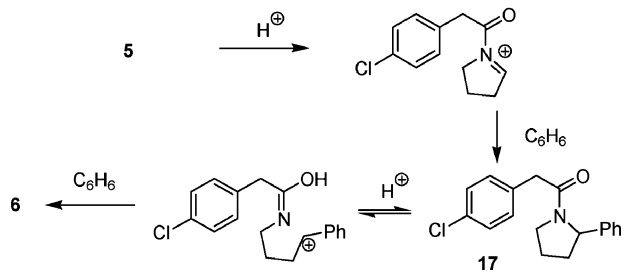
extent of amide hydrolysis. This protocol also worked well for the pentylamide **15**, which gave the 5,5-diphenyl-pentylamide **16** in a good yield (77%).

Scheme 2 illustrates our mechanistic hypothesis, which invokes phenylation of an iminium ion to form the 2-phenylpyrrolidine amide **17**, similar to the Lewis acid mediated reaction.[2] Amide **17** could then ring open to give a carbonium ion which would react further with benzene to form **6**. As no **17** was isolated, the formation of this intermediate must be slower than the conversion of **17** to **6**. In order to test this hypothesis, **17** was prepared from commercially available 2-phenylpyrrolidine and reacted with benzene and triflic acid to rapidly form **6** in high yield (87%), consistent with the mechanistic proposal. To the best of our knowledge, there is only one previous report of an amide group acting as a leaving group for a Friedel–Crafts alkylation of benzene.[4]

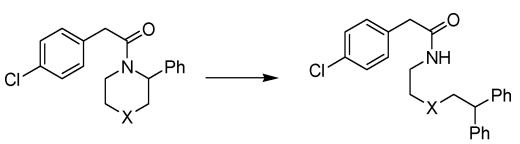



**Scheme 2** Proposed mechanism for the formation of **6**.

The facile ring-opening and phenylation of **17** prompted us to investigate the triflic acid-mediated ring opening/phenylation of other cyclic amides. The results are presented in Table 1.

The piperidine **18a**, prepared from the commercially available 2-phenylpiperidine, rapidly ring opened with triflic acid in benzene to form the amide **16** in a very good yield. In contrast, azepine **18b** took much longer for all the starting material to be consumed and MS indicated that **19b** was formed together with other unidentified products. The structural elucidation was complicated by the presence of amide rotamers. Neither of the piperazine derivatives **18c** and **18d** reacted, the only starting material being present after 4 h reflux. **18d** was prepared by selective 4-*N*-acylation of 2-phenylpiperazine with 4-nitrophenylacetic acid O–N-hydroxysuccinimide ester, then 1-*N*-acylation with 4-chlorophenylacetyl chloride. In contrast, both the morpholine **18e** and thio-morpholine **18f** reacted rapidly, with the formation of a number of products, none of which were the amides **19e** or **19f**. The major product from both reactions was 1,1,2-triphenylethane (75% yield in both cases). We believe that this product is formed by reaction with 2 molecules of benzene, with elimination of $ArCH_2CONHCH_2CH_2XH$. Indeed, from the reaction of **18e**, *p*-$Cl–C_6H_4CH_2CONHCH_2CH_2OH$ was isolated in a 17% yield. The azetidine **20** also ring opened under these conditions to form the amide **21**, which has recently been described as a cannabinoid $CB_1$ receptor inverse agonist.[5]

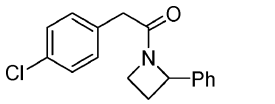
**Table 1** Investigation of the phenylation of cyclic amides **17a–g**



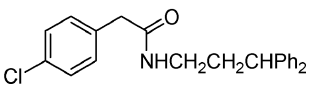

**18a-f** **16** and **19b-f**

| Cpd. No. | X | Cpd. No. | *T* (h) | Yield (%) |
|---|---|---|---|---|
| **18a** | $CH_2$ | **16** | 0.5 | 95 |
| **18b** | $(CH_2)_2$ | **19b** | 4 | [a] |
| **18c** | NMe | **19c** | 4 | 0 |
| **18d** | NR[b] | **19d** | 4 | 0 |
| **18e** | O | **19e** | 1 | 0 |
| **18f** | S | **19f** | 1 | 0 |

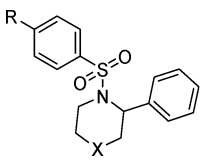
[a] See text. [b] R = *p*-$NO_2–C_6H_4–CH_2CO$-.




**20**




**21**

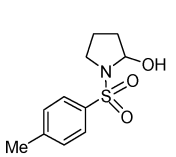



**22** R = Me, X = bond

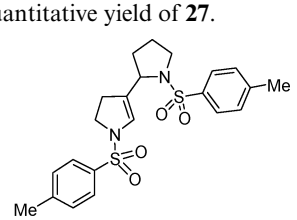
**23** R = Me, X = $CH_2$

**24** R = H, X = $(CH_2)_2$

We then investigated the ring opening/phenylation reaction of sulfonamides. The tosyl pyrrolidine **22** and piperidine **23** smoothly phenylated to give tosyl$NH(CH_2)_3CHPh_2$ **12** and tosyl$NH(CH_2)_4CHPh_2$ **25** in a 92% and 85% yield respectively. This result is in contrast to the poor yield of **12** from **11** and suggests that the proposed first step, the reaction of the tosyliminium ion with benzene, proceeds poorly. In order to investigate this further, **11** was hydrolysed to the 2-hydroxypyrrolidine **26**. This provides a simple alternative synthesis of **26** to that of either oxidation of *N*-tosyl-pyrrolidine[6] or *N*-tosyl-pyrrolidine-2-methanol,[7] or reduction of *N*-tosyl-2-pyrrolidinone.[8] Reaction of **26** with triflic acid in benzene gave both **12** (35% yield) and a compound which was spectroscopically consistent with the 'dimer' **27**. This compound is the *N*-di-tosyl analogue of the previously reported *N*-diacyl 'dimer', formed by treatment of the *N*-acyl-2-hydroxypyrrolidine with conc. $H_2SO_4$.[1] It was proposed that the 'dimer' was formed through reaction of the N-acyliminium ion with 1-acyl-2,3-dihydropyrrole, formed by loss of a proton from the iminium ion. Formation of the 'dimer' was suppressed by using triflic acid, which was believed to be acidic enough to keep the acyliminium ion fully protonated. However, it would appear that triflic acid is not a strong enough acid to keep the equivalent N-tosyliminium ion fully protonated, so that sufficient *N*-tosyl-2,3-dihydropyrrole is formed to react with the iminium ion. This is consistent with the *N*-tosyl group being a stronger electron withdrawing group that the *N*-acyl.[9] Heating **26** with trifilic acid in $CHCl_3$ gave an almost quantitative yield of **27**.




**26**




**27**

In a manner that was analogous to the observations with amide **18b**, the *N*-benzenesulfonylazepine **24** gave a mixture of

compounds which were inseparable by column chromatography. Both NMR and MS indicated that the product was a 3 : 2 mixture of tosyl-NH$(CH_2)_5CHPh_2$ **28** and tosyl-NH$(CH_2)_6$Ph **29**. Following this finding, a reinvestigation of the product from the reaction of **18b** by HRMS indicated that both **19b** and *p*-Cl–$C_6H_4$–$CH_2CONH$ $(CH_2)_6$Ph was present.

## Conclusion

In conclusion, we have shown that the diphenylation of amino-acetals with triflic acid in benzene[3] can be extended to butanal and pentanal derivatives by using the amides or sulfonamides. Investigation of the possible mechanism of this reaction led to the novel finding that 2-phenyl-cyclic amides and sulfonamides can also be readily ring-opened to give diphenyl products in good yields.

## Experimental

All reagents were commercially available, unless otherwise specified, and used without purification. The chloroform used was stabilised with amylene. All non-crystalline final compounds were found to be >95% pure by HPLC, and all crystalline compounds >98% pure. Infrared spectra were run neat on a Perkin Elmer 100 FT IR spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on Bruker NMR spectrometers AMX300, Avance III 400, DRX500 and Avance III 600 equipped with *z*-gradient facilities. $^1$H and $^{13}$C chemical shifts are given relative to TMS.

### General procedure for the diphenylation reaction

Triflic acid (10 fold excess) was added to a stirred solution of the amide or sulfonamide (2 mmol) in benzene (20 ml) and the reaction mixture was heated under reflux until TLC showed no starting amide remaining. The reaction mixture was cooled to room temperature, water (50 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 $SiO_2$.

### Reaction of 1 with triflic acid in benzene

Following the general procedure, **1**[1] was heated under reflux for 1 h. Purification, initially eluting with DCM gave **3** (50% yield), mp 120–1 °C (EtOAc/petroleum ether). $^1$H-NMR (600 MHz) $\delta$ = 1.38–1.45 (2H, m), 1.96–2.02 (2H, m), 3.23 (2H, q, $J$ = 7.0 Hz), 3.54 (2H, s), 3.86 (1H, t, $J$ = 7.8 Hz), 5.52 (1H, brs), 7.15–7.40 (15H, m); $^{13}$C-NMR + DEPT (150 MHz) $\delta$ = 28.2 ($CH_2$), 32.9 ($CH_2$), 39.5 ($CH_2$), 44.0 ($CH_2$), 51.0 (CH), 126.4 (CH), 127.5 (CH), 127.9 (CH), 128.6 (CH), 129.2 (CH), 129.6 (CH), 135.2 (C), 144.8 (C), 171.1 (C), FT-IR (neat) 3269, 2935, 1638, 1556, 1494, 1454, 1435, 1344, 751, 716, 695 cm$^{-1}$, LRMS (EI) 343, 167, 92, 91, HRMS calcd for $C_{24}H_{25}NO$ 343.1931, found 343.1920. Further elution with DCM + 2% MeOH gave **2** (30% yield), identical to that previously reported.[1]

### 2-(4-Chlorophenyl)-*N*-(4,4-diphenylbutyl)acetamide, 6, from 4b

A solution of 2-(4-chlorophenyl)-1-(2-hydroxypyrrolidin-1-yl)ethanone[1] **4b** (0.88 g, 3.7 mmol) was stirred and heated under reflux in benzene (30 ml) with triflic acid (3.7 ml) for 1h. The reaction mixture was cooled to room temperature, water (50 ml) was added and the reaction carefully basified with solid $K_2CO_3$. The product extracted into ethyl acetate (2 × 50 ml) and the organic extract was dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by column chromatography on silica, eluting with DCM to give **6**, (1.13 g, 82% yield), mp 125–126 °C (EtOAC/petroleum ether). $^1$H-NMR (500 MHz) $\delta$ = 1.40 (2H, m), 1.98 (2H, q, $J$ = 7.9 Hz), 3.23 (2H, dt, $J$ = 6.9, 6.2 Hz), 3.49 (2H, s), 3.85 (1H, t, $J$ = 7.8 Hz), 5.27 (1H, brs), 7.11–7.21 (8H, m), 7.21–7.35 (6H, m).; $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 28.1 ($CH_2$), 32.8 ($CH_2$), 39.6 ($CH_2$), 43.2 ($CH_2$), 51.0 (CH), 126.3 (CH), 127.8 (CH), 128.6 (CH), 129.2 (CH), 130.8 (CH), 133.4 (C), 133.5 (C), 144.7 (C), 170.3 (C); FT-IR (neat) 3273, 2837, 1634, 1562, 1491, 1439, 1327, 1153, 1091, 809, 767, 749, 695 cm$^{-1}$; LRMS (EI) 377, 210, 167, 126, 91; HRMS calcd for $C_{24}H_{24}ClNO$ 377.1541, found 377.1543.

### 2-(4-Nitrophenyl)-*N*-(4,4-diphenylbutyl)acetamide 8 from 4c

A solution of 2-(4-nitrophenyl)-*N*-(4,4-diethoxybutyl)-acetamide[1] (3.2 g, 10 mmol) in THF (100 ml) and 2 M HCl (20 ml) was stirred at room temperature for 2 h, until all the starting material had been consumed (TLC). Water (50 ml) was added and the THF removed *in vacuo*. The 2-(4-nitrophenyl)-1-(2-hydroxypyrrolidin-1-yl)ethanone **4c** formed as a pale yellow solid, which was collected and dried (2.5 g, ~100% yield), pure by TLC and NMR showed it to be in equilibrium with the amido-aldehyde (~5%), and was used without further purification; $^1$H-NMR (500 MHz) $\delta$ = 1.80–2.15 (4H, m), 3.41–3.50 (1H, m), 3.55–3.68 (1H, m), 3.74 (2H, s), 4.10 (1H, brs), 5.65 (1H, dd, $J$ = 2.7, 6.1 Hz) 7.46 (2H, d, $J$ = 8.2 Hz), 8.19 (2H, d, $J$ = 8.2 Hz); $^{13}$C-NMR + DEPT (150 MHz) $\delta$ = 23.2 ($CH_2$), 32.1 ($CH_2$), 41.6 ($CH_2$), 46.9 ($CH_2$), 82.1 (CH), 123.8 (CH), 130.3 (CH), 141.7 (C), 147.2 (C), 169.9 (C); FT-IR (neat) 3356, 1608, 1514, 1444, 1421, 1343, 1318, 1263, 1172, 1154, 1106, 1040, 1016, 963, 859, 820, 727 cm$^{-1}$. Following the general procedure, **4c** (1 g, 4 mmol) was reacted for 1 h to give **8**, purified by column chromatography, eluting with DCM (1.2 g, 78% yield), mp 100–102 °C (EtOAc/petroleum ether). $^1$H-NMR (600 MHz) $\delta$ = 1.40–1.48 (2H, m), 1.98–2.05 (2H, m), 3.25 (2H, q, $J$ = 7.0 Hz), 3.53 (2H, s), 3.87 (1H, t, $J$ = 7.8 Hz), 6.20 (1H, t, $J$ = 5.5 Hz), 7.127.30 (10H, m), 7.38 (2H, d, $J$ = 8.6 Hz), 8.10 (2H, d, $J$ = 8.6 Hz); $^{13}$C-NMR + DEPT (150 MHz) $\delta$ = 28.2 ($CH_2$), 32.9 ($CH_2$), 39.8 ($CH_2$), 43.2 ($CH_2$), 51.0 (CH), 123.9 (CH), 126.5 (CH), 127.9 (CH), 128.7 (CH), 130.3 (CH), 143.1 (C), 144.8 (C), 147.0 (C), 169.5 (C), FT-IR (neat) 3281, 1637, 1557, 1516, 1493, 1345, 1254, 1110, 1030, 747, 697 cm$^{-1}$, LRMS (EI) 388, 221, 167, 137, 106, 91; HRMS calcd for $C_{24}H_{24}N_2O_3$ 388.1781, found 388.1777.

### *N*-(4,4-Diphenylbutyl)acetamide 10

Following the general procedure, *N*-(4,4-diethoxybutyl) acetamide **9**[10] gave **10**, purified by eluting with a solvent gradient, initially 1 : 1 petroleum ether/DCM to 1% MeOH/DCM mp 73–74 °C (EtOAc/petroleum ether), (lit. 76–78 °C [toluene/petroleum ether][11]). $^1$H-NMR (500 MHz) $\delta$ = 1.47 (2H, tt, $J$ = 6.9, 7.9 Hz), 1.92 (3H, s), 2.06 (2H, q, $J$ = 7.9 Hz), 3.16 (2H, q, $J$ = 6.9 Hz), 3.89 (1H, t, $J$ = 7.9 Hz), 5.43 (1H, brs), 7.19 (1H, tt, $J$ = 1.2, 7.2 Hz), 7.23 (2H, dd, $J$ = 1.2, 7.1 Hz), 7.27 (2H, t, $J$ = 7.5 Hz);

$^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 23.4 ($CH_3$), 28.3 ($CH_2$), 33.0 ($CH_2$), 39.6 ($CH_2$), 51.1 (CH), 126.4 (CH), 127.9 (CH), 128.6 (CH), 144.8 (C), 170.1 (C), FT-IR (neat) 3278, 2928, 2865, 1635, 1557, 1494, 1451, 1367, 1294, 1032, 745, 698 cm$^{-1}$, LRMS (EI) 267, 167, 100; HRMS calcd for $C_{18}H_{21}NO$ 267.1618, found 267.1609.

### *N*-(4,4-Diphenylbutyl)-4-methylbenzenesulfonamide 12 from 11

Tosyl chloride (3.8 g, 20 mmol) was added over 10 min. to a stirred solution of 4-amino-1,1-diethoxybutane (3.4 ml, 20 mmol) and triethylamine (3.5 ml, 25 mmol) in DCM (100 ml) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, then washed with saturated aqueous $NaHCO_3$ solution (100 ml). The DCM was separated, dried ($K_2CO_3$) and concentrated *in vacuo* to give 6.3 g of **11** (~100% yield) as an oil, pure by NMR and TLC and used without further purification. $^1$H-NMR (500 MHz) $\delta$ = 1.07 (6H, t, *J* = 7.0 Hz), 1.50–1.62 (4H, m), 2.32 (3H, s), 2.81–2.88 (2H, m), 3.27–3.37 (2H, m), 3.44–3.54 (2H, m), 4.30 (1H, t, *J* = 4.9 Hz), 4.84 (1H, brs), 7.20 (2H, d, *J* = 8.2 Hz), 7.64 (2H, d, *J* = 8.2 Hz). Crude **11** (1 g, 2.6 mmol) was reacted by the general procedure and the product was purified by column chromatography on silica, eluting with 3 : 1 DCM/petroleum ether to give **12** (38% yield) as a colourless oil which crystallized from $Et_2O$/petroleum ether, mp 119–120 °C; $^1$H-NMR (500 MHz) $\delta$ = 1.37–1.48 (2H, m), 1.97–2.05 (2H, m), 2.42 (3H, s), 2.94 (2H, q, *J* = 6.6 Hz), 3.80 (1H, t, *J* = 7.8 Hz), 4.81 (1H, brs), 7.14–7.20 (6H, m), 7.21–7.34 (6H, m), 7.73 (2H, d, *J* = 8.3 Hz), $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 21.6 ($CH_3$), 28.1 ($CH_2$), 32.5 ($CH_2$), 43.2 ($CH_2$), 50.9 (CH), 126.3 (CH), 127.2 (CH), 127.8 (CH), 128.6 (CH), 129.8 (CH), 137.0 (C), 143.4 (C), 144.6 (C), FT-IR (neat) 3223, 1494, 1446, 1315, 1163, 1066, 961, 812, 753, 696 cm$^{-1}$, LRMS (EI) 379, 224, 167, 129, 91; HRMS calcd for $C_{23}H_{25}NO_2S$ 379.1601, found 379.1595.

### *N*-(4,4-Diphenylbutyl)benzamide 14

*N*-(4,4-Diethoxybutyl)benzamide, **13**,[12] was reacted for 1 h following the general procedure and purified by column chromatography in $SiO_2$, eluting with a solvent gradient, initially 1 : 1 petroleum ether/DCM to 1% MeOH/DCM (36% yield), mp 102–103 °C (EtOAc/petroleum ether). $^1$H-NMR (500 MHz) $\delta$ = 1.55–1.66 (2H, m), 2.14 (2H, ddt, *J* = 1.9, 7.8, 9.8 Hz), 3.48 (2H, ddt, *J* = 1.9, 7.5, 8.9 Hz), 3.93 (1H, t, *J* = 7.2 Hz), 6.05 (1H, brs), 7.15–7.20 (2H, m), 7.21–7.30 (8H, m), 7.38–7.43 (2H, m), 7.46–7.51 (1H, m), 7.69–7.73 (2H, m); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 28.4 ($CH_2$), 33.0 ($CH_2$), 40.0 ($CH_2$), 51.1 (CH), 126.3 (CH), 126.9 (CH), 128.6 (CH), 131.4 (CH), 134.8 (C), 144.7 (C), 167.6 (C), FT-IR (neat) 3389, 1635, 1536, 1490, 1449, 1290, 716, 696 cm$^{-1}$, LRMS (EI) 329, 167, 149, 148, 105; HRMS calcd for $C_{23}H_{23}NO$ 329.1774, found 329.1765. Repeating the reaction with the addition of triflic anhydride (1 equiv.) also gave **14** (63% yield) and with trimethylsilyl triflate (2 equiv) gave **14** (61% yield).

**2-(4-Chlorophenyl)-*N*-(5,5-diphenylpentyl)acetamide 16 from 15.** Following the procedure described for **11**, 5-amino-1,1-diethoxypentane[13] (1.3 g, 7.4 mmol) was reacted with 4-chlorophenylacetyl chloride (1.3 g, 7.4 mmol) and triethylamine (1.4 ml, 10 mmol) to give **15** as an oil (2.6 g, ~100% yield) pure by NMR and TLC, and used without further purification, $^1$H-NMR (500 MHz) $\delta$ = 1.18 (6H, t, *J* = 7.1 Hz), 1.24–1.34 (2H, m), 1.40–1.50 (2H, m), 1.52–1.60 (2H, m), 3.20 (2H, quartet, *J* = 6.0 Hz), 3.40–3.50 (4H, m including 3.49, 2H, s). 3.55–3.63 (2H, m), 4.41 (1H, t, *J* = 5.6 Hz), 5.47 (1H, brs), 7.19 (2H, d, *J* = 8.3 Hz), 7.29 (2H, d, *J* = 8,3 Hz); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 15.4 ($CH_3$), 22.0 ($CH_2$), 29.3 ($CH_2$), 33.3 ($CH_2$), 39.7 ($CH_2$), 43.2 ($CH_2$), 61.2 ($CH_2$), 102.8 (CH), 129.1 (CH), 130.8 (CH), 133.1 (C), 133.6 (C), 170.4 (C). Following the general procedure, **15** (0.8 g, 2.4 mmol) was heated under reflux for 1 h to give **16** (0.67 g, 70% yield), purified by elution with DCM, mp = 75–77 °C (EtOAc/petroleum ether). $^1$H-NMR (500 MHz) $\delta$ = 1.27–1.35 (2H, m), 1.47 (2H, quintet, *J* = 7.4 Hz), 2.02 (2H, q, *J* = 7.8 Hz), 3.17 (2H, q, *J* = 6.8 Hz), 3.46 (2H, s), 3.84 (1H, t, *J* = 7.8 Hz), 5.29 (1H, brs), 7.11 (2H, d, *J* = 8.3 Hz), 7.14–7.35 (12H, m); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 25.3 ($CH_2$), 29.4 ($CH_2$), 35.2 ($CH_2$), 39.6 ($CH_2$), 51.3 (CH), 126.2 (CH), 127.9 (CH), 128.5 (CH), 129.2 (CH), 130.8 (CH), 133.3 (C), 133.5 (C), 145.0 (C), 170.3 (C), FT-IR (neat) 3287, 2936, 1645, 1543, 1493, 1092, 806, 754, 741, 696 cm$^{-1}$, LRMS (EI) 391, 167; HRMS calcd for $C_{25}H_{26}ClNO$ 391.1697, found 391.1689.

### 2-(4-Chlorophenyl)-*N*-(4,4-diphenylbutyl)acetamide, 6, from 17

Following the procedure described for **15**, 2-phenylpyrrolidine (0.87 g, 5.9 mmol) was converted to 2-(4-chlorophenyl)-1-(2-phenylpyrrolidin-1-yl) ethanone **17** (1.8 g, ~100% yield), mp 83–85 °C (EtOAc/petroleum ether). $^1$H-NMR (500 MHz) (two rotamers) $\delta$ = 1.80–2.00 (3H, m), 2.19–2.29 (0.25H, m), 2.31 0 2.41 (0.75H, m), 3.33 (0.75H, d, *J* = 15.1 Hz), 3.37 (0.75H, d, *J* = 15.1 Hz), 3.57–7.75 (1.25H, m), 4.93 (0.75H, dd, *J* = 2.3, 8.3 Hz), 5.22 (0.25H, dd, *J* = 2.8, 8.0 Hz), 6.97 (1.5H, d, *J* = 8.5 Hz), 7.06 (0.5H, d, *J* = 8.3 Hz), 7.14–7.31 (5.5H, m), 7.35 (1.5H, t, *J* = 7.6 Hz); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 21.7 ($CH_2$), 23.9 ($CH_2$), 34.0 ($CH_2$), 36.4 ($CH_2$), 40.9 ($CH_2$), 41.8 ($CH_2$), 47.4 ($CH_2$), 48.0 ($CH_2$), 60.8 (CH), 61.7 (CH), 125.5 (CH), 126.8 (CH), 127.5 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 129.0 (CH), 130.5 (CH), 130.6 (CH), 132.6 (C), 132.8 (C), 133.3 (C), 133.5 (C), 169.0 (C), 170.1 (C), FT-IR (neat) 1621, 1490, 1422, 1170, 1090, 810, 763, 751, 700 cm$^{-1}$, LRMS (EI) 299, 174, 131, 91; HRMS calcd for $C_{18}H_{18}ClNO$ 299.1071, found 299.0165. Following the general procedure, amide **17** was converted to **6** (87% yield), purified by elution with DCM, identical to that obtained.

### 1-{4-[2(4-Chlorophenyl)acety]-3-phenylpiperazin-1-yl}-2-(4-nitrophenyl)-ethanone 18d

A solution of 2-phenylpiperazine (1.6 g, 10 mmol) and 4-nitrophenylacetic acid O-*N*-hydroxysuccinimide ester (2.8 g, 10 mmol) in DCM (100 ml) was stirred at ambient temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue treated with EtOAc (150 ml), washed with 2 M NaOH (2 × 50 ml), brine (50 ml) and dried ($K_2CO_3$). Filtration and concentration *in vacuo* gave the 2-(4-nitrophenyl)-1-(3-phenylpiperazin-1-yl)ethanone as a pale yellow solid (2.8 g, 85% yield), mp 108–110 °C (EtOAc/petroleum ether). $^1$H-NMR (500 MHz) rotamer mixture $\delta$ = 1.98 (brs, 1H), 2.63 (0.4H, t, *J* = 12.5 Hz), 2.69–2.90 (1.6H, m), 3.00–3.19 (1.4H, m), 3.27 (0.4H, t, *J* = 12 Hz), 3.47 (0.6H, d, *J* = 10.5 Hz), 3.61–3.87 (3.6H, m), 4.61 (2H, d, *J* = 11 Hz), 7.16–7.50 (7H, m), 8.20 (2H, d, *J* = 8 Hz); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 40.4, 42.2, 45.9, 46.4, 46.5, 49.2, 53.7, 60.1, 61.1, 123.9, 126.9, 128.0, 128.3, 128.6, 128.8, 130.0, 140.5, 140.9, 142.8, 147.0, 167.8, FT-IR (neat) 3310, 2848, 1650, 1510, 1435, 1417,

1338, 1237, 1223, 1143, 1100, 1047, 816, 765, 740, 709, 700 $cm^{-1}$; LRMS (EI) 325, 282, 220, 161, 132, 118, 104, 91; HRMS calcd for $C_{18}H_{19}N_3O_3$ 325.1421, found 325.1425. Structural assignment was made from the NOESY spectrum which showed no NOE between the $ArCH_2CO$ and 3-CHPh protons, but did between the $ArCH_2CO$ and the 2-CH and 6-CH protons.

Following the general procedure described for **15**, 2-(4-nitrophenyl)-1-(3-phenylpiperazin-1-yl)ethanone (0.98 g, 3.0 mmol) was converted to **18d**, purified by column chromatography on $SiO_2$, eluting with 2% MeOH/DCM and isolated as a solid, m.pt 63–65 °C (1.3 g, 90% yield). $^1$H-NMR (400 MHz, d$^6$-DMSO, 373 K) $\delta$ = 3.21–3.37 (2H, brm), 3.48–3.90 (6H,m), 4.04–4.14 (1H, brm), 4.35–4.55 (1H, brm), 5.51 (1H, brs), 7.20–7.38 (11H, m), 8.06 (2H, d, $J$ = 8.5 Hz); $^1$H-NMR (600 MHz, d$^6$-DMSO, 298 K) $\delta$ = 37.2, 37.5, 38.6, 38.9, 40.1, 41.1, 41.2, 42.1, 42.5, 43.3, 44.7, 45.1, 47.5, 48.3, 51.7, 53.5, 56.1, 56.8, 65.0, 123.2, 126.2, 126.4, 127.0, 127.4, 128.2, 128.4, 128.7, 128.9, 130.4, 130.7, 130.9, 131.2, 134.7, 134.8, 138.4, 139.3, 143.9, 146.1, 146.2, 168.6, 169.5, 169.8, 170.0, FT-IR (neat) 1638, 1515, 1413, 1344, 1089, 1016, 857, 810, 732, 698 $cm^{-1}$, LRMS no molecular ion could be detected, (EI) and (CI), 267, 167, 100. Heating a solution of **18d** (0.75 g, 1.5 mmol) in benzene (15 ml) and triflic acid (1.5 ml) for 4 h showed only starting material by TLC.

### 2-(4-Chlorophenyl)-*N*-(3,3-diphenylpropyl)acetamide, 21

Following the procedure described for **15**, 2-phenylazetidine[14] (0.41 g, 3.1 mmol) and triethylamine (0.7 ml) in DCM (50 ml) was cooled to 0 °C and 4-chlorophenylacetyl chloride (0.45 ml 3.1 mmol) in DCM (5 ml) was added dropwise and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was washed with 2 M NaOH (25 ml), water (25 ml) and 2 N HCl (25 ml), dried ($K_2CO_3$) and concentrated *in vacuo*. The residue was purified by column chromatography on silica, eluting with DCM to give 2-(4-chlorophenyl)-1-(2-phenylazetidin-1-yl)ethanone **20** (0.74 g, 83% yield), mp 88-89 °C (EtOAc/petroleum ether). $^1$H-NMR (500 MHz) (two rotamers in a 3 : 1 ratio) $\delta$ = 2.11–2.21 (2H, m), 2.66–2.76 (2H, m), 3.12 (1.5H, s), 3.49 (0.5H, d, $J$ = 2.5 Hz), 4.06–4.22 (2H, m), 5.26 (0.75H, dd, $J$ = 5.7, 8.8 Hz), 5.37 (0.25H, dd, $J$ = 6.0, 8.9 Hz), 6.90 (1.5H, d, $J$ = 8.4 Hz), 7.17 (1.5H, d, $J$ = 8.4 Hz), 7.22–7.43 (6H, m); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = major rotamer: 26.3 ($CH_2$), 38.5 ($CH_2$), 46.0 ($CH_2$), 65.7 (CH), minor rotamer: 25.0 ($CH_2$), 38.8 ($CH_2$), 48.4 ($CH_2$), 63.4 (CH); both rotamers: 125.7 (CH), 126.2 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 129.3 (CH), 130.5 (CH), 130.6 (CH), 132.6 (C), 132.9 (C), 133.1 (C), 141.5 (C), 170.8 (C), 171.3 (C), FT-IR (neat) 1626, 1489, 1455, 1425, 1089, 1015, 807, 772, 697 $cm^{-1}$; LRMS (EI) 285, 181, 160, 125, 91; HRMS calcd for $C_{17}H_{16}ClNO$ 285.0915, found 285.0905. Following the general procedure, **20** was converted to **21** (86% yield) purified by elution with DCM. mp = 103–104 °C. (lit. 107 °C[5]). $^1$H-NMR (500 MHz) $\delta$ = 2.22 (2H, q, $J$ = 7.8 Hz), 3.20 (2H, q, $J$ = 7.8 Hz), 3.43 (2H, s), 3.84 (1H, t, $J$ = 7.8 Hz), 5.25 (1H, brs), 7.12–7.19 (8H, m), 7.24–7.28 (4H, m), 7.32 (2H, d, $J$ = 8.4 Hz); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 35.1 ($CH_2$), 38.8 ($CH_2$), 43.2 ($CH_2$), 49.3 (CH), 126.5 (CH), 127.7 (CH), 128.7 (CH), 129.2 (CH), 130.8 (CH), 133.4 (C), 133.5 (C), 144.1 (C), 170.3 (C); FT-IR (neat) 3331, 1649, 1535, 1490, 1088, 1013, 806, 750, 693 $cm^{-1}$.

### *N*-(5,5-Diphenylpentyl)-4-methylbenzenesulfonamide 25

Following the procedure described for **11**, 2-phenylpiperidine (0.5 g, 3.1 mmol) was reacted with tosyl chloride (0.65 g, 3.4 mmol) and triethylamine (0.6 ml, 3.5 mmol) in DCM (50 ml) overnight at ambient temperature to give **23**, purified by column chromatography on $SiO_2$, eluting with 1 : 1 petroleum ether/DCM (0.88 g, 90% yield). $^1$H-NMR (500 MHz) $\delta$ = 1.28–1.55 (4H, m), 1.62–1.71 (1H, m), 2.20–2.27 (1H, m), 2.43 (3H, s), 2.99–3.06 (1H, m), 3.80–3.88 (1H, m), 5.26 (1H, d, $J$ = 4.3 Hz), 7.21–7.39 (7H, m), 7.76 (2H, d, $J$ = 8.3 Hz); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 19.0 ($CH_2$), 21.6 ($CH_3$), 24.4 ($CH_2$), 27.3 ($CH_2$), 41.9 ($CH_2$), 55.3 (CH), 126.9 (CH), 127.1 (CH), 127.1 (CH), 128.7 (CH), 129.8 (CH), 138.8 (C), 139.0 (C), 143.0 (C), FT-IR (neat) 2956, 2928, 2869, 1449, 1324, 1150, 1103, 1092, 1051, 948, 723, 663 $cm^{-1}$; LRMS (EI) 315, 238, 160, 159, 91; HRMS calcd for $C_{18}H_{21}NO_2S$ 315.1286, found 315.1281. Following the procedure, **16** (0.32 g, 1 mmol), with heating under reflux for 1 h, was converted into **25**, purified on a silica column, eluting with DCM (0.34 g, 85% yield) mp = 121–123 °C. $^1$H-NMR (500 MHz) $\delta$ = 1.18–1.26 (2H, m), 1.49 (2H, m), 1.98 (2H, q. $J$ = 7.6 Hz), 2.43 (3H, s), 2.89 (2H, q, $J$ = 6.6 Hz), 3.82 (1H, t, $J$ = 7.6 Hz), 4.65 (1H, t, $J$ = 5.5 Hz), 7.12–7.33 (12H, m), 7.74 (2H, d, $J$ = 8.3 Hz); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 21.9 ($CH_3$), 25.4 ($CH_2$), 30.0 ($CH_2$), 35.5 ($CH_2$), 43.4 ($CH_2$), 51.6 (CH), 126.6 (CH), 127.5 (CH), 128.2 (CH), 128.7 (CH), 128.9 (CH), 130.1 (CH), 137.4 (C), 143.8 (C), 145.2 (C), FT-IR (neat) 3265, 2925, 1598, 1493, 1448, 1427, 1316, 1149, 1092, 101, 815, 736, 699 $cm^{-1}$; LRMS (EI) 393, 238, 167, 91; HRMS calcd for $C_{24}H_{27}NO_2S$ 393.1757, found 393.1750.

### 1-(*p*-Toluenesulfonyl)-pyrrolidin-2-ol 26

A solution of **11** (4 g, 12.7 mmol) was dissolved in THF (50 ml) and 2 M HCl (25 ml) and was stirred for 4 h at ambient temperature until TLC showed that no **11** remained. The THF was removed *in vacuo* and the product extracted into DCM (3 × 50 ml), dried and concentrated to give **26** as an oil which solidified on standing and used without further purification. $^1$H-NMR (500 MHz) $\delta$ = 1.70–1.80 (2H, m), 1.85–1.94 (1H, m), 2.05–2.14 (1H, m), 2.42 (3H, s), 3.02–3.07 (1H, m), 3.10–3.17 (1H, m), 3.50–3.57 (1H, m), 5.42 (1H, m), 7.32 (2H, d, $J$ = 8.4 Hz), 7.72 (2H, d, $J$ = 8.4 Hz); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 21.6 ($CH_3$), 23.1 ($CH_2$), 33.9 ($CH_2$), 47.6 ($CH_2$), 84.0 (CH), 127.2 (CH), 129.9 (CH), 135.7 (C), 143.5 (C).

### 1,1′-Bis-(toluene-4-sulfonyl)-2,2,4,5,4′,5′-hexahydro-1H,1′H-[2,3′]bipyrrolyl, 27

Following the general procedure, a solution of **26** (0.48 g, 2 mmol) was stirred and heated under reflux in $CHCl_3$ (30 ml) and triflic acid (2 ml, 20 mmol) for 1 h. Work-up and purification by column chromatography on silica, eluting with DCM gave **27** as an oil (0.45 g, ~100% yield), $^1$H-NMR (500 MHz) $\delta$ = 1.57–1.67 (3H, m), 1.70–1.82 (1H, m), 2.30–2.48 (8H, m including 2.42, 6H, s), 3.18–3.24 (1H, m), 3.33–3.39 (1H, m), 3.40–3.52 (2H, m), 4.22 (1H, dd, $J$ = 3.9, 6.8 Hz), 6.37 (1H, dd, $J$ = 1.8, 2.9 Hz), 7.26 (2H, d, $J$ = 7.9 Hz), 7.33 (2H, d, $J$ = 8.0 Hz), 7.63 (2H, dt, $J$ = 1.9, 8.4 Hz), 7.71 (2H, dt, $J$ = 2.1, 8.3 Hz); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 21.6 ($CH_3$), 21.7 ($CH_3$), 24.3 ($CH_2$), 29.5 ($CH_2$), 30.9 ($CH_2$), 47.9 ($CH_2$), 48.8 ($CH_2$), 57.9 (CH), 126.2 (C), 127.4

(CH), 127.5 (CH), 127.9 (CH), 129.7 (CH), 129.8 (CH), 133.0 (C), 134.9 (C), 143.5 (C), 143.9 (C); HRMS calcd for $C_{22}H_{27}N_2O_4S_2$ 447.1412, found 447.1390.

### Mixture of *N*-(6,6-diphenylhexyl)-benzenesulfonamide, 28, and *N*-(6-phenylhexyl)-benzenesulfonamide 29

By the method described for **11**, 2-phenylperhydroazepine[15] (0.7 g, 4 mmol) gave *N*-benzenesulfonyl-2-phenylperhydro-azepine **24**, purified by column chromatography on silica, eluting with DCM and isolated as a solid (1.1 g, 85% yield), mp 78–79 °C; $^1$H-NMR (500 MHz) $\delta$ = 1.21–1.33 (1H, m), 1.53 (1H, q, $J$ = 11.7 Hz), 1.62–1.74 (1H, m), 1.75–1.91 (4H, m), 2.20–2.30 (1H, m), 3.20–3.30 (1H, m), 3.95 (1H, dt, $J$ = 3.3, 15.4 Hz), 5.06 (1H, dd, $J$ = 6.0, 11.7 Hz), 6.98–7.02 (2H, m), 7.09–7.14 (3H, m), 7.21 (2H, t, $J$ = 7.9 Hz), 7.35 (1H, tt, $J$ = 1.1, 7.4 Hz), 7.43 (2H, d, $J$ = 7.4 Hz); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 25.8 ($CH_2$), 29.5 ($CH_2$), 31.0 ($CH_2$), 45.5 ($CH_2$), 61.7 (CH), 126.4 (CH), 127.0 (CH), 127.1 (CH), 128.4 (CH), 128.5 (CH), 131.8 (CH), 141.0 (C), 142.5 (C); FT-IR (neat) 2929, 1446, 1327, 1308, 1147, 1089, 1045, 936, 888, 780, 752, 723, 691 cm$^{-1}$; LRMS (EI) 315, 238, 174, 173, 145, 118, 117, 104, 91; HRMS calcd for $C_{18}H_{21}NO_2S$ 315.1288, found 315.1283. Following the general procedure, **24** (0.5 g, 1.6 mmol) was heated under reflux for 2 h until all the starting material had reacted by TLC. The product was purified by elution with 1 : 3 petroleum ether/DCM as an oil (0.26 g). NMR and MS showed it to be a 3 : 2 mixture of **28** and *N*-(6-phenylhexyl)-benzenesulfonamide, **29**. $^1$H-NMR (500 MHz), taking the NH multiplet at 4.75–4.72 as 1H $\delta$ = 1.12–1.35 (4H, m), 1.48–1.50 (2H, m), 1.51–1.62 (0.8H, m), 1.97 (1.2H, q, $J$ = 7.8 Hz), 2.56 (0.8H, t, $J$ = 7.6 Hz), 2.88–2.99 (2H, m), 3.83 (0.6H, t, $J$ = 7.8 Hz), 4.75–4.72 (1H, m), 7.12–7.31 (8H, m), 7.45–7.60 (3.2H, m), 7.83–7.91 (1.8H, m); $^{13}$C-NMR + DEPT (125 MHz) $\delta$ = 26.4 ($CH_2$), 26.5 ($CH_2$), 27.5 ($CH_2$), 28.7 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 31.3 ($CH_2$), 35.5 ($CH_2$), 35.9 ($CH_2$), 43.2 ($CH_2$), 43.3 ($CH_2$), 51.3 (CH), 125.7 (CH), 126.2 (CH), 127.1 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 129.2 (CH), 132.7 (C), 140.1 (C), 142.6 (C), 145.1 (C). LRMS for mixture: 393, 317, 252, 176, 170, 167, 141, 117, 104, 91. For **28**: HRMS calcd. for $C_{24}H_{27}NO_2S$ 393.1764, found 393.1767; for **29**: HRMS calcd. for $C_{18}H_{23}NO_2S$ 317.1450, found 317.1455.

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