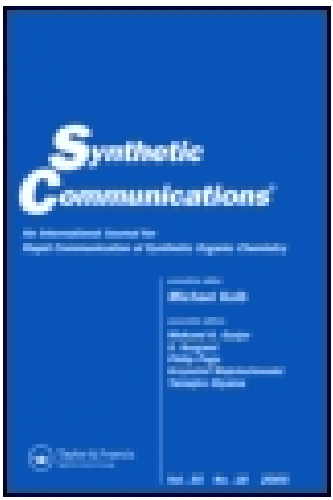

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Synthesis of Symmetrical and Unsymmetrical Ureas Using Unsymmetrical Diaryl Carbonates

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SYNTHESIS OF SYMMETRICAL AND UNSYMMETRICAL UREAS USING UNSYMMETRICAL DIARYL CARBONATES

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Abstract: Appropriately substituted unsymmetrical diaryl carbonates react smoothly with primary amines to give the carbamates derived by nucleophilic displacement of the less electron rich aromatic substituent. Subsequent treatment of the carbamates with primary and secondary amines gives either symmetrical or unsymmetrical ureas in excellent yield and the overall process can be carried out as a "one pot" operation. Acetonitrile is the preferred solvent and addition of DBU facilitates the carbamate → urea transformation.

As part of a drug development programme we required efficient, large scale access to a variety of unsymmetrical ureas of the type $R^1R^2NCONHR^3$, where R^1 and R^2 are alkyl and R^3 an alkyl substituent which contains a basic tertiary amine. Of particular interest were the ureas derived from *N*-methylbenzylamine (**1**) and 1-benzyl-4-aminopiperidine (**2**), *endo*-3-amino-8-methyl-8-azabicyclo[3.2.1]-octane (**3**) and 4-aminomethylpyridine (**4**).

A number of excellent methods is available for the synthesis of symmetrical ureas, especially those based on the use of phosgene, carbamates, dialkyl or diaryl

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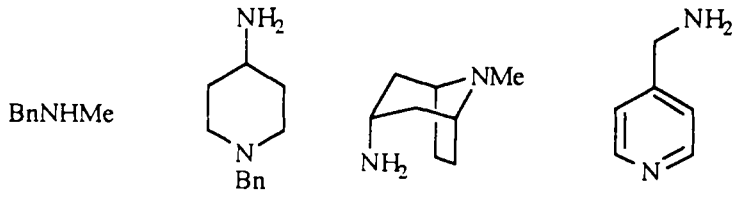


(1) (2) (3) (4)

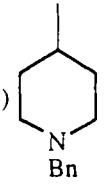
carbamates and isocyanates,[1-3] but, as pointed out recently,[2,3] the preparation of unsymmetrical ureas is more tedious and not always high yielding. Use of either phosgene or preformed isocyanates was prohibited in our work for operational reasons, and therefore we examined the diaryl carbonate → carbamate → urea approach[2] using commercially available bis-4-nitrophenyl carbonate (**5**) (Scheme 1, (**5**) → (**6**) → (**7**)). The results were not satisfactory, and were particularly poor with the aminotropane (**3**), an amine we were especially keen to incorporate into unsymmetrical ureas. The large amount of symmetrical urea (**8b**) formed in this

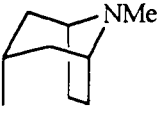
Scheme 1

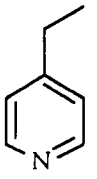
$(ArO)_2CO \xrightarrow[MeCN]{(2)\text{-}(4)} ArOCONHR \xrightarrow[MeCN]{(1)} RNHCONBnMe + RNHCONHR$

(**5**) (**6a-c**) (**7a-c**) (**8a,b**)

Ar = 4-$O_2NC_6H_4$

R = (**a**) 

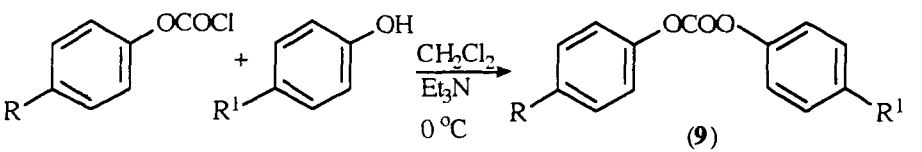
(**b**) 

(**c**) 

(**5**)	20*	60*	10* %
(**7**)	72**		90** %
(**8**)	~8*	40*	0 %

*Determined by nmr **Yield of isolated product

Scheme 2



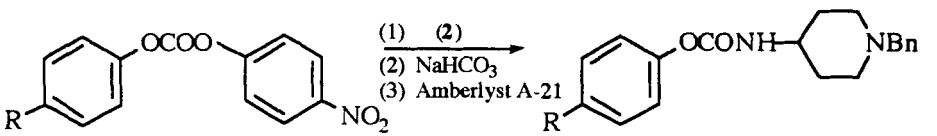
	R	R^1	Yield, %
(**9a**)	H	NO_2	77
(**b**)	MeO	NO_2	89
(**c**)	NO_2	CN	85
(**d**)	NO_2	MeS	70
(**e**)	NO_2	COOMe	76

case is presumably due to the intermediate carbamate (**6b**) being more reactive to the nucleophile than the carbonate (**5**).[4] To avoid this problem we investigated the use of unsymmetrical diaryl carbonates, $ArOCOOAr^1$, as starting materials, where the relative nucleofugacity of the phenolate leaving groups could be easily manipulated by appropriate substitution in the aromatic rings.

A series of unsymmetrical diaryl carbonates (**9a-e**) was prepared[5] (Scheme 2) and their reactivity towards 1-benzyl-4-aminopiperidine (**2**) examined with respect to formation of the carbamates (**10a-e**). Results are summarised in Table 1 and confirm that, as expected, selective and high yield displacement of 4-nitrophenol from unsymmetrical diaryl carbonates (**9**) is possible with appropriate choice of substituent R.

We examined next the conversion of the carbamates (**10a,b,d**) into ureas by reaction with *N*-methylaniline and with 1-benzyl-4-aminopiperidine (**2**). During this investigation we extended the range of carbamates (**10**) to include the sulfoxide (**10f**) and the sulfone (**10g**), which were prepared by oxidation of the sulfide (**10d**) with peracetic acid and sodium perborate respectively ((**10f**) could not be converted into (**10g**) with peracetic acid). There was virtually no reaction

Table 1. Synthesis of carbamates (**10**) by reaction of diaryl carbonates (**9**) with 1-benzyl-4-aminopiperidine (**2**)



(**9a-e**) (**10a-e**)

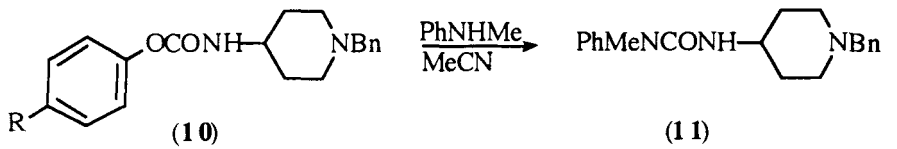
	R	Solvent	Conditions	Time, h	(**10**) Yield, %[a]
(**9a**)	H	$ClCH_2CH_2Cl$	RT	15	79
(**b**)	MeO	$ClCH_2CH_2Cl$	reflux	15	82
(**c**)	CN	CH_2Cl_2	RT	15	-[b]
(**d**)	MeS	CH_2Cl_2	RT	15	77
(**e**)	COOMe	$CHCl_3$	reflux	1	-[c]

[a] Refers to pure, isolated product. [b] A mixture of 4-cyanophenol, 4-nitrophenol and the symmetrical urea was obtained. [c] The carbamate (**10e**) was produced, but decomposed rapidly when isolated as the free base.

of the carbamates (**10a**,**b**,**d**,**f**,**g**) with either *N*-methylaniline or (**2**) at room temperature, irrespective of the solvent used, and use of halocarbon solvents or toluene or mesitylene at reflux temperatures gave only poor to moderate, and variable, yields of both the unsymmetrical (**11**) and symmetrical (**8a**) ureas. Use of acetonitrile, however, led to smooth reaction, and the variation in yield of the ureas (**11**) and (**8a**) with the nature of the substitution in the aromatic ring of the carbamates is clearly illustrated in the results summarised in Table 2.

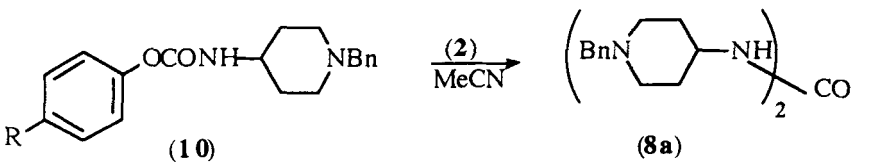
While these results were encouraging, the method was still unsatisfactory inasmuch that preparation of what appeared to be the most effective carbamate for urea formation, *viz.* the methanesulfonyl derivative (**10g**) was somewhat tedious, expensive and low yielding, and clearly inapplicable to larger scale operations. We therefore re-examined the overall process starting from the cheap easily accessible

Table 2. Reaction of the carbamates (**10a**,**b**,**d**,**f**,**g**) with *N*-methylaniline and *1-benzyl-4-aminopiperidine* (**2**)



(**10**) (**11**)

	R	Conditions	Time, h	(**11**) Yield, % [a]
(**10a**)	H	reflux	16	52
(**d**)	MeS	reflux	18	45
(**f**)	MeSO	reflux	16	72
(**g**)	$MeSO_2$	reflux	9	88



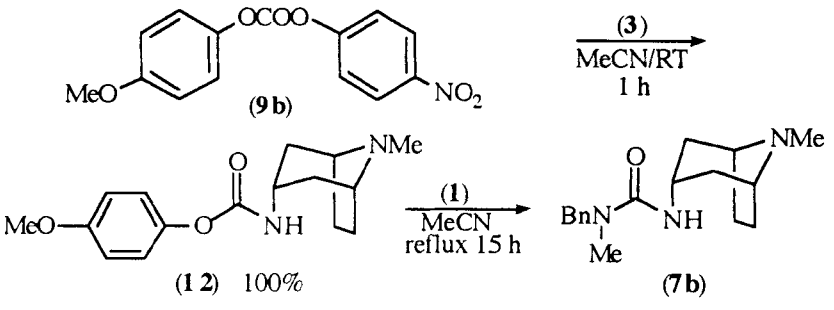
(**10**) (**8a**)

	R	Conditions	Time, h	(**8a**) Yield, % [a]
(**10a**)	H	reflux	16	52
(**b**)	MeO	reflux	16	49
(**d**)	MeS	reflux	7	65
(**f**)	MeSO	reflux	3	66
(**g**)	MeSO2	RT	15	74

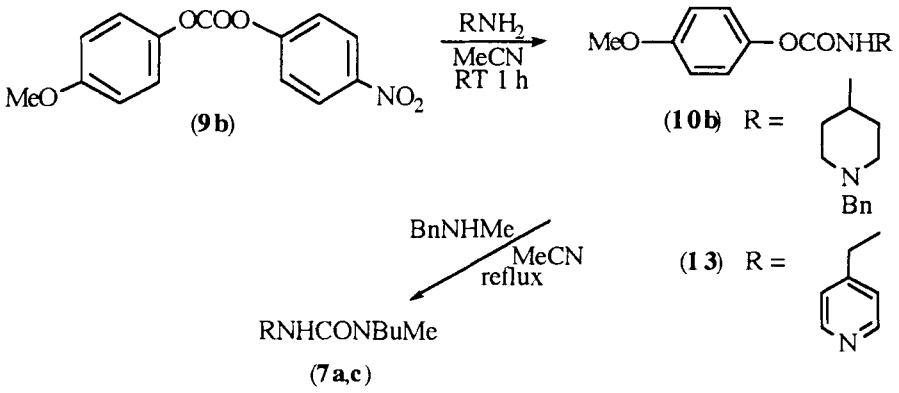
[a] Refers to isolated yields

4-methoxyphenyl 4-nitrophenyl carbonate (**9b**), and using acetonitrile as solvent. In contrast to the poor results obtained on reaction of the aminotropane (**3**) with bis-4-nitrophenyl carbonate (**5**) (Scheme 1), simply stirring a mixture of the unsymmetrical carbonate (**9b**) with the aminotropane (**3**) in acetonitrile at room temperature for one hour resulted in quantitative conversion (nmr) to the carbamate (**12**). Addition of *N*-methylbenzylamine (**1**) to the reaction mixture and heating for 15 hours at reflux gave a 92% yield of the pure urea (**7b**) after chromatography and crystallisation (Scheme 3).

Scheme 3



Scheme 4



R	Time, h	Added base[a]	(7) Yield, %
	15	-	16[b]
N Bn	30	Et_3N	65[b]
	48	DMAP	88[b]
	3.5	DBU	97[c]
N	3.0	DBU	96[c]

[a] 1 eq. [b] determined by nmr. [c] Yield of isolated product

Extension of this "one pot" procedure to the other primary amines in which we were particularly interested, *viz.* (**2**) and (**4**), was equally straightforward in terms of the reaction of the carbonate (**9b**) with the amines. In each case quantitative formation of the 4-methoxyphenyl carbamate was observed on mixing of the reagents in acetonitrile at room temperature for one hour. Subsequent reaction of the carbamates (**10b**, **13**) with *N*-methylbenzylamine (**1**), however, was slow and inefficient, even in refluxing acetonitrile, but this problem was easily circumvented by addition of one equivalent of a tertiary amine base (Scheme 4). DBU was most effective, and the two desired ureas (**7a**,**c**) were obtained in excellent yield.

In summary, the "one pot" preparation of ureas from 4-methoxyphenyl 4-nitrophenyl carbonate is a simple, straightforward and high yielding process. Acetonitrile is the preferred solvent, and addition of DBU can be beneficial for the second stage of the overall transformation, the carbamate to urea conversion.

Experimental

Carbonates

The following procedure for the preparation of 4-nitrophenyl phenyl carbonate is representative of the general method used for the synthesis of the carbonates (**9a-e**).

4-Nitrophenyl phenyl carbonate (9a). Phenyl chloroformate (0.7 ml, 0.0056 mol) and 4-nitrophenol (0.75 g, 0.0054 mol) were dissolved in dichloromethane (40 ml) and the solution cooled to 0 °C in an ice bath. A solution of triethylamine (0.75 ml, 0.0054 mol) in dichloromethane (10 ml) was added dropwise and the mixture was allowed to warm to room temperature and stirred for a further 2 h. Tlc analysis (silica; eluant:- dichloromethane) indicated that no 4-nitrophenol remained. The reaction mixture was transferred to a separating funnel and washed with water (2x25 ml) and brine (25 ml). The organic layer was

separated, dried (Na_2SO_4), filtered, and the solvent removed by evaporation *in vacuo* to leave a colourless solid (1.3 g). Recrystallisation from n-hexane (160 ml) gave pure (**9a**) (1.1 g, 77%) as a colourless solid, mp 128-130 °C. (Lit mp 128-129 °C[6] or 130-131 °C[7]; υ_{max} (KBr)/cm^{-1} 1764 (C=O); δ_H (270 MHz; $CDCl_3$) 7.30 (3H, m), 7.46 (4H, m), 8.32 (2H, half of AA'BB'); δ_C (270 MHz; $CDCl_3$) 120.73 (CH), 121.74 (CH), 125.42 (CH), 126.74 (CH), 129.76 (CH), 145.61, (C), 150.69 (C), 151.05 (C), 155.29 (C); *m/z* 259. Anal calcd for $C_{13}H_9NO_5$: C, 60.24; H, 3.50; N, 5.40. Found: C, 60.26; H, 3.57; N, 5.61.

4-Methoxyphenyl 4-nitrophenyl carbonate (**9b**). Obtained in 89% yield as a colourless solid (ex hexane), mp 143-144 °C; υ_{max} (KBr)/cm^{-1} 1761 (C=O); δ_H (270 MHz; $CDCl_3$) 3.82 (3H, s), 6.93 and 7.22 (4H, AA'BB'), 7.48 and 8.31 (4H, AA'BB'); δ_C (270 MHz; $CDCl_3$) 56.12 (CH_3), 115.11 (CH), 122.06 (CH), 122.20 (CH), 125.83 (CH), 144.74 (C), 146.03 (C), 151.89 (C), 155.82 (C), 158.32 (C); *m/z* 289. Anal calcd for $C_{14}H_{11}NO_6$: C, 58.14; H, 3.83; N, 4.84. Found: C, 58.04; H, 3.89; N, 5.04.

4-Cyanophenyl 4-nitrophenylcarbonate (**9c**). Obtained in 85% yield as a colourless solid (ex toluene), mp 157-159 °C; υ_{max} (KBr)/cm^{-1} 1762 (C=O); δ_H (270 MHz; $CDCl_3$) 7.45 and 7.49 (4H, AA'BB'), 7.76 and 8.34 (4H, AA'BB'); δ_C (270 MHz; $CDCl_3$) 110.86 (C), 117.80 (CN), 121.67 (CH), 121.89 (CH), 125.53 (CH), 134.02 (CH), 145.89 (C), 150.15 (C), 153.55 (C), 154.90 (C); *m/z* = 284. Anal calcd for $C_{14}H_8N_2O_5$: C, 59.16; H, 2.84; N, 9.86. Found: C, 61.18; H, 3.32; N, 9.33.

4-Methylmercaptophenyl 4-nitrophenyl carbonate (**9d**). Obtained in 70% yield as a yellow solid (ex toluene), mp 141-142 °C; υ_{max} (KBr)/cm^{-1} 1763 (C=O); δ_H (270 MHz; $CDCl_3$) 2.50 (3H, s), 7.21 and 7.31 (4H, AA'BB'), 7.48 and 8.31 (4H, AA'BB'); δ_C (270 MHz; $CDCl_3$) 16.48 (CH_3,) 121.42 (CH), 121.96 (CH), 125.65 (CH), 128.10 (CH), 137.35 (C), 145.69 (C), 148.55 (C),

151.27 (C), 155.50 (C); *m/z* = 305. Anal calcd for $C_{14}H_{11}NO_5S$: C, 55.08; H, 3.63; N, 4.59. Found: C, 55.01; H, 3.69; N, 4.81.

4-Methoxycarbonylphenyl 4-nitrophenyl carbonate (9e). Obtained in 76% yield as a colourless solid (ex toluene), mp 179-181 °C, υ_{max} (KBr)/cm^{-1} 1763 (C=O), 1727 (COOMe); δ_H (270 MHz; $CDCl_3$) 3.94 (3H, s), 7.37 and 7.49 (4H, AA'BB'), 8.14 and 8.33 (4H, AA'BB'); δ_C (270 MHz; $CDCl_3$) 52.59 (CH_3), 120.97 (CH), 121.95 (CH), 125.79 (CH), 128.89 (C), 131.71 (CH), 146.01 (C), 150.69 (C), 154.19 (C), 155.32 (C), 166.22 (C); *m/z* = 317. Anal calcd for $C_{15}H_{11}NO_7$: C, 56.79; H, 3.49; N, 4.41. Found: C, 56.95; H, 3.70; N, 4.59.

Carbamates[8]

1-Benzyl-*N*-phenoxycarbonylpiperidine-4-amine (10a). 4-Amino-1-benzylpiperidine (**2**) (0.5 g, 0.0027 mol) was dissolved in 1,2-dichloroethane (15 ml) and the solution added dropwise over 15 min to a solution of 4-nitrophenyl phenyl carbonate (**9a**) (0.7 g, 0.0028 mol) in 1,2-dichloroethane (15 ml). The reaction mixture was stirred at room temperature for 15 h, then transferred to a separating funnel and washed with 10% w/v sodium hydrogen carbonate solution (3x15 ml), water (15 ml) and brine (15 ml). The organic solution was dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to leave a yellow solid (0.9 g). This was dissolved in acetone (30 ml) and the solution passed down an Amberlyst A-21 ion exchange column (*ca.* 30 ml of resin). Evaporation of the eluate *in vacuo* gave 0.66 g (79%) of (**10a**) as a light brown coloured solid, mp 130-133 °C, υ_{max} (KBr)/cm^{-1} 1697 (C=O); δ_H (270 MHz; $CDCl_3$) 1.63 (2H, br d, *J* 11), 2.03 (2H, br d, *J* 12), 2.21 (2H, br t, *J* 11), 2.88 (2H, br d, *J* 9), 3.57 (2H, s), 3.62 (1H, m), 4.94 (1H, br d, *J* 7), 7.12 (2H, d, *J* 8), 7.18 (1H, t, *J* 7), 7.31 (7H, m); δ_C (270 MHz; $CDCl_3$) 32.34 (CH_2), 48.44

(CH), 52.09 (CH_2), 63.01 (CH_2), 121.58 (CH), 125.22 (CH), 127.09 (CH), 128.24 (CH), 129.11 (CH), 129.25 (CH), 138.21 (C), 150.98 (C), 153.73 (C); *m/z* = 310. Anal calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.02. Found: C, 73.16; H, 7.07; N, 9.21.

1-Benzyl-*N*-4-methoxyphenoxycarbonylpiperidine-4-amine (10b). 4-Amino-1-benzylpiperidine (**2**) (0.5 g, 0.0027 mol) and 4-nitrophenyl 4-methoxyphenyl carbonate (**9b**) (0.78 g, 0.0027 mol) were dissolved in dichloromethane (50 ml) and the solution was stirred at room temperature for 15 h. Tlc analysis (alumina; eluant:- dichloromethane : methanol : ammonia 95:5:2 drops) indicated mainly starting material. The reaction mixture was heated to reflux for 2h. Tlc analysis again indicated little change. The solvent was removed *in vacuo*, the residue was dissolved in 1,2-dichloroethane (50 ml) and the solution was heated to reflux for 15 h. Tlc analysis indicated that reaction was complete after this time. The reaction mixture was transferred to a separating funnel and washed with 10% w/v sodium hydrogen carbonate solution (3x15 ml), water (3x15 ml) and brine (15 ml). The organic solution was dried (Na_2SO_4), filtered, and the solvent was removed by evaporation *in vacuo* to leave a solid (1.0 g). This was dissolved in acetone (*ca.* 50 ml) and the solution passed down an Amberlyst-A21 ion exchange column (*ca.* 100 ml resin) using more acetone as eluent. Evaporation of the eluate *in vacuo* gave 0.75 g (82%) of (**10b**) as a light brown coloured solid, mp 129-131 °C, υ_{max} (KBr)/cm^{-1} 1696 (C=O); δ_H (270 MHz; $CDCl_3$) 1.61 (2H, dq, *J* 2, 11), 2.01 (2H, br d, *J* 11), 2.19 (2H, br t, *J* 11), 2.88 (2H, br d, *J* 11), 3.56 (2H, s), 3.61 (1H, m), 3.78 (3H, s), 4.91 (1H, d, *J* 8), 6.86 and 7.03 (4H, AA'BB'), 7.31 (5H, m); δ_C (270 MHz; $CDCl_3$) 32.32 (CH_2), 48.37 (CH), 52.09 (CH_2), 55.60 (CH_3), 62.99 (CH_2), 114.32 (CH), 122.45 (CH), 127.17 (CH), 128.27 (CH), 129.18 (CH), 137.88 (C), 144.51 (C), 154.16 (C), 156.89 (C); *m/z* = 340. Anal calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.40; H, 7.06; N, 8.35.

1-Benzyl-*N*-4-methylmercaptophenoxycarbonylpiperidine-4-amine (10d). 4-Amino-1-benzylpiperidine (**2**) (1.5 g, 0.0079 mol) was dissolved in dichloromethane (25 ml) and the solution added dropwise to a solution of 4-methylmercapto 4-nitrophenyl carbonate (**9d**) (2.4 g, 0.0079 mol) in dichloromethane (75 ml). The mixture was stirred at room temperature for 15 h, then transferred to a separating funnel and washed with 10% w/v sodium hydrogen carbonate solution (2x50 ml), water (2x50 ml) and brine (50 ml). The organic solution was dried (Na_2SO_4), filtered, and the solvent was removed by evaporation *in vacuo*. The residual solid was dissolved in acetone and the solution passed down an Amberlyst A-21 ion exchange column, to yield, after removal of solvent by evaporation *in vacuo*, 2.16 g (77%) of (**10d**) as a brown solid, mp 108-111 °C, υ_{max} (KBr)/cm^{-1} 1707 and 1736 (C=O); δ_H (400 MHz; $CDCl_3$) 1.53 (2H, dq, *J* 2, 12), 2.01 (2H, br d, *J* 12), 2.17 (2H, br t, *J* 11), 2.46 (3H, s), 2.85 (2H, br d *J* 13), 3.53 (2H, s), 3.61 (1H, m), 4.93 (1H, br d, *J* 10), 7.05 (2H, half of AA'BB'), 7.29 (7H, m); δ_C (400 MHz; $CDCl_3$) 16.96 (CH_3), 32.60 (CH_2), 48.77 (CH), 52.34 (CH_2), 63.30 (CH_2), 122.35 (CH), 127.37 (CH), 128.42 (CH), 128.51 (CH), 129.40 (CH), 135.09 (C), 138.45 (C), 149.10 (C), 153.93 (C); *m/z* = 356. Anal calcd for $C_{20}H_{24}N_2O_2S$: C, 67.39; H, 6.79; N, 7.86. Found: C, 66.59; H, 6.68; N, 7.41.

1-Benzyl-*N*-4-methylsulfinylphenoxycarbonylpiperidine-4-amine (10f). 1-Benzyl-*N*-4-methylmercaptophenoxycarbonylpiperidine-4-amine (**10d**) (0.5 g, 0.0014 mol) was dissolved in glacial acetic acid (5 ml), peracetic acid solution (4.87M, 3 ml, 0.0146 mol) was added, and the mixture was stirred at room temperature for 15 h. It was then transferred to a separating funnel and chloroform (30 ml) added. The solution was washed with sodium thiosulphate (3 g) in water (10 ml) and 10 w/v sodium hydrogen carbonate solution added until the pH was 7. The chloroform layer was separated, dried (Na_2SO_4), filtered, and the solvent removed by evaporation *in vacuo* to leave a solid (0.5 g). This was

slurried with ether to give 0.42 g (79%) of (**10f**) as a yellow solid, mp 117-121 °C, υ_{max} (KBr/)/cm^{-1} 1739; δ_H (400 MHz; $CDCl_3$) 1.62 (2H, dq. *J* 2, 11), 2.02 (2H, br d, *J* 11), 2.19 (2H, br t, *J* 10), 2.71 (3H, s), 2.89 (2H, br d, *J* 13), 3.56 (2H, s), 3.63 (1H, m), 5.07 (1H, br d, *J* 8), 7.30 (7H, m), 7.64 (2H, half of AA'BB'); δ_C (400 MHz; $CDCl_3$) 32.30 (CH_2), 44.07 (CH_3), 48.67 (CH), 52.07 (CH_2), 63.01 (CH_2), 122.60 (CH), 124.82 (CH), 127.09 (CH), 128.24 (CH), 129.09 (CH), 138.25 (C), 141.84 (C), 153.03 (C), 153.14 (C); *m/z* = 372. Anal calcd for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N, 7.52. Found: C, 64.78; H, 6.62; N, 6.68.

1-Benzyl-*N*-4-methylsulfonylphenoxycarbonylpiperidine-4-amine (**10g**). 1-Benzyl-*N*-4-methylmercaptophenoxycarbonylpiperidine-4-amine (**10d**) (0.5 g, 0.0014 mol) was dissolved in glacial acetic acid (5 ml). Sodium perborate tetrahydrate (0.65 g, 0.0042 mol) was added and the reaction mixture was stirred for 15 h at room temperature. It was then transferred to a separating funnel with chloroform (40 ml) and the mixture was washed with sodium thiosulphate solution (1.0 g) dissolved in water (15 ml). The organic layer was separated, dried (Na_2SO_4), filtered, and the solvent was removed by evaporation *in vacuo* to leave a pale yellow oil (1.0 g). This crude product was purified by column chromatography on neutral alumina (eluant:- chloroform : acetonitrile 1:1 v/v) to give 0.15 g (28%) of (**10g**) as a colourless solid, mp 138-140 °C, υ_{max} (KBr)/cm^{-1} 1742 (C=O); δ_H (400 MHz; $CDCl_3$) 1.61 (2H, dq, *J* 2, 11), 2.02 (2H, br d, *J* 11), 2.18 (2H, br t, *J* 11), 2.88 (2H, br d, *J* 12), 3.04 (3H, s), 3.54 (2H, s), 3.63 (1H, m), 5.07 (1H, br d *J* 8), 7.30 (7H, m), 7.94 (2H, half of AA'BB'); δ_C (400 MHz; $CDCl_3$) 32.53 (CH_2), 44.94 (CH_3), 49.00 (CH), 52.26 (CH_2), 63.26 (CH_2), 122.55 (CH), 127.39 (CH), 128.52 (CH), 129.31 (CH), 129.35 (CH), 137.21 (C), 138.43 (C), 152.73 (C), 155.42 (C); *m/z* = 388. Anal calcd for $C_{20}H_{24}N_2O_4S$; C, 61.84; H, 6.23; N, 7.21. Found: C, 61.85; H, 6.33; N, 7.11.

Ureas

***N*-(1-Benzylpiperidin-4-yl)-*N*'-benzyl-*N*'-methylurea (7a).** 4-Amino-1-benzylpiperidine (**2**) (0.665 g, 0.0035 mol) and 4-methoxyphenyl 4-nitrophenyl carbonate (**9b**) (1.0 g, 0.0035 mol) were dissolved in acetonitrile (50 ml) and the mixture was stirred at room temperature for 1 h, after which NMR analysis indicated that the reaction was complete. A solution of *N*-benzylmethylamine (0.423 g, 0.0035 mol) and DBU (0.532 g, 0.0035 mol) in acetonitrile (10 ml) was then added and the resulting mixture was heated at reflux for 3.5 h, after which NMR analysis indicated that the reaction was complete. The solvent was removed by evaporation *in vacuo*, the residue was dissolved in dichloromethane (100 ml), and the solution was washed with 10% w/v sodium hydroxide solution (3x50 ml) and brine (50 ml). The organic solution was dried (Na_2SO_4), filtered, and the solvent was removed by evaporation *in vacuo* to leave an oil (1.3 g). This was chromatographed on neutral alumina (eluant:- dichloromethane grading to dichloromethane : methanol 95:5) to give 1.16 g (97%) of (**7a**) as an off-white solid, mp 102-103 °C, υ_{max} (KBr)/cm^{-1} 1616 (C=O); δ_H (400 MHz; $CDCl_3$) 1.36 (2H, dq, *J* 4, 15), 1.92 (2H, br d, *J* 13), 2.11 (2H, br t, *J* 13), 2.74 (2H, bd, *J* 12), 2.88 (3H, s), 3.46 (2H, s), 3.71 (1H, m), 4.22 (1H, d, *J* 8) 4.46 (2H, s), 7.28 (10H, m); δ_C (400 MHz; $CDCl_3$) 33.00 (CH_2), 34.51 (CH_3), 47.77 (CH), 52.25 (CH_2), 52.41 (CH_2), 63.11 (CH_2), 126.97 (CH), 127.18 (CH), 127.34 (CH), 128.18 (CH), 128.71 (CH), 129.09 (CH), 137.99 (C), 138.55 (C) 157.70 (C); *m/z* = 337. Anal calcd for $C_{21}H_{27}N_3O$: C, 74.74; H, 8.06; N, 12.45. Found: C, 74.63; H, 7.95; N, 12.43.

***N*-*endo*-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-*N*'-benzyl-*N*-methylurea (7b).** *endo*-3-Amino-8-methyl-8-azabicyclo[3.2.1]octane (**3**) (0.49 g 0.0035 mol) and 4-methoxyphenyl 4-nitrophenyl carbonate (**9b**) (1.0 g, 0.0035 mol) were dissolved in acetonitrile (50 ml) and the solution was stirred at room

temperature for 1 h, after which NMR analysis indicated that the reaction was complete. A solution of *N*-benzylmethylamine (0.423 g, 0.0035 mol) in acetonitrile (10 ml) was added and the resulting mixture was heated at reflux for 15 h, after which NMR analysis indicated that the reaction was complete. The solvent was removed by evaporation *in vacuo*, the residue was dissolved in dichloromethane (100 ml) and the resulting solution was washed with 10% w/v sodium hydroxide solution (3x50 ml) and water (50 ml). The organic solution was dried (Na_2SO_4) and filtered, and the solvent was removed by evaporation *in vacuo* to yield a dark coloured oil (1.0 g). The crude product was purified by column chromatography on neutral alumina (eluant:- dichloromethane : methanol 95:5 v/v) to give 0.993 g (97%) of a dark oil. This was recrystallised from ethyl acetate to give 0.92 g (92%) of (**7b**) as off-white crystals, mp 82-85 °C, υ_{max} (KBr)/cm^{-1} 1614 (C=O); δ_H (400 MHz; $CDCl_3$) 1.49 (2H, q, *J* 2, 5), 1.57 (2H, bd, *J* 14), 1.98 (2H, m), 2.11 (2H, m), 2.25 (3H, s), 2.95 (3H, s), 3.08 (2H, bs), 3.97 (1H, q *J* 2, 10), 4.47 (2H, s), 4.70 (1H, bd, *J* 6), 7.30 (5H, m); δ_C (400 MHz; $CDCl_3$) 25.67 (CH_2); 34.96 (CH_3), 36.73 (CH_2); 39.90 (CH_3); 42.16 (CH), 52.45 (CH_2); 60.01 (CH); 126.93 (CH); 127.52 (CH); 128.89 (CH); 137.97 (C); 157.84 (C); *m/z* = 287. Anal calcd for $C_{17}H_{25}N_3O$: C, 71.05; H, 8.77; N, 14.62. Found: C, 66.92; H, 8.75; N, 13.73.

***N*-(4-Pyridylmethyl)-*N'*-benzyl-*N'*-methylurea (7c).** 4-(Aminomethyl)-pyridine (**4**) (0.378 g, 0.0035 mol) and 4-methoxyphenyl 4-nitrophenyl carbonate (**9b**) (1.0 g, 0.0035 mol) were dissolved in acetonitrile (50 ml) and the solution was stirred at room temperature for 2 h, after which NMR analysis indicated that the reaction was complete. A solution of *N*-benzylmethylamine (0.423 g, 0.0035 mol) and DBU (0.532 g, 0.0035 mol) in acetonitrile (10 ml) was then added and the resulting mixture was heated at reflux for 3 h, after which NMR analysis indicated that the reaction was complete. The solvent was removed by evaporation

in vacuo, the residue was dissolved in dichloromethane (100 ml), and the resulting solution was washed with 10% w/v sodium hydroxide solution (3x50 ml) and brine (50 ml). The organic solution was dried (Na_2SO_4) and filtered, and the solvent was removed by evaporation *in vacuo* to leave an oil (1.2 g). This was chromatographed on neutral alumina (eluant:- dichloromethane : methanol 95:5 v/v) to give 0.87 g (97%) of (**7c**) as an oil which solidified on standing to an off-white solid, mp 109-111 °C, υ_{max} (KBr)/cm^{-1} 1629 (C=O); δ_H (400 MHz; $CDCl_3$) 2.93 (3H, s), 4.40 (2H, d, *J* 6), 4.51 (2H, s), 5.13 (1H, bt, *J* 6), 7.12 and 8.46 (4H, AA'BB'), 7.28 (5H, m); δ_C (400 MHz; $CDCl_3$) 34.59 (CH_3), 43.70 (CH_2), 52.32 (CH_2), 122.05 (CH), 127.14 (CH), 127.47 (CH), 128.78 (CH), 137.65 (C), 149.06 (C), 149.80 (CH), 158.22 (C); *m/z* = 255. Anal calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 69.40; H, 6.45; N, 15.97.

***N,N'*-Bis(1-benzylpiperidin-4-yl)urea (8a).**

(i) *From the carbamates (**10a, b, d, f, g**).* The following procedure using carbamate (**10g**) is representative of the general procedure used (see also Table 2). 4-Amino-1-benzylpiperidine (**2**) (0.028 g, 0.00015 mol) and 1-benzyl-*N*-4-methylsulfonylphenoxycarbonylpiperidine-4-amine (**10g**) (0.058 g, 0.00015 mol) were dissolved in acetonitrile (7 ml) and the solution was stirred at room temperature for 15 h. The solvent was removed by evaporation *in vacuo*, the residue was dissolved in chloroform (50 ml), and the resulting solution was washed with 10% w/v sodium hydroxide solution (3x10 ml), water (3x10 ml) and brine (10 ml). The organic solution was dried (Na_2SO_4) and filtered, and the solvent was removed by evaporation *in vacuo* to leave an oil. This was purified by column chromatography on neutral alumina (eluent:- chloroform) to give 0.045 g (74%) of (**8a**) as a colourless solid, mp 168-170 °C. This product was identical in all respects to the material prepared using phosgene, as follows.

(ii) *From phosgene and 4-amino-1-benzylpiperidine (2).* 4-Amino-1-benzylpiperidine (**2**) (1 g, 0.0053 mol) and triethylamine (0.7 ml, 0.5 g, 0.005 mol) were dissolved in dichloromethane (30 ml) and the mixture was cooled to 0 °C in an ice bath. Phosgene in toluene solution (2M, 1.3 ml, 0.0026 mol) was dissolved in dichloromethane (20 ml) and the resulting solution was added dropwise to the reaction mixture over 0.5 h. The mixture was maintained at this temperature for a further 1 h and then allowed to warm to room temperature overnight. It was then transferred to a separating funnel, with rinsings of dichloromethane (10 ml). Water (100 ml) and 40% w/v sodium hydroxide solution (5 ml) were added, the organic layer was separated, and the aqueous layer was further extracted with dichloromethane (30 ml). The dichloromethane extracts were combined, washed with water (50 ml) and saturated brine (50 ml) and then dried (Na_2SO_4). Filtration and removal of the solvent by evaporation *in vacuo* yielded an oil (1.5 g). This was dissolved in ethyl acetate (50 ml), which immediately promoted crystallisation. The crystalline solid was isolated by filtration to give, after drying, 0.45 g (43%) of pure product (**8a**) as a colourless solid, mp 169-171 °C, υ_{max} (KBr)/cm^{-1} 1626 (C=O); δ_H (400 MHz; $CDCl_3$) 1.40 (2H, dq, *J* 2, 11), 1.90 (2H, br d, *J* 13), 2.10 (2H, br t, *J* 13), 2.79 (2H, bd, *J* 12), 3.48 (2H, s), 3.54 (1H, m), 4.18 (1H, d, *J* 8), 7.30 (5H, m); δ_C (400 MHz; $CDCl_3$) 32.85 (CH_2); 47.27 (CH), 52.32 (CH_2), 63.01 (CH_2), 127.17 (CH), 128.26 (CH), 129.24 (CH), 137.88 (C), 156.65 (C); *m/z* = 406. Anal calcd for $C_{25}H_{34}N_4O$: C, 73.85; H, 8.43; N, 13.78. Found: C, 73.67; H, 8.42; N, 13.82.

N-(1-Benzylpiperidin-4-yl)-N'-methyl-N'-phenylurea (11).

(i) *From the carbamates (10a, d, f, g).* The following procedure using carbamate (**10g**) is representative of the general procedure used (see also Table 2). *N*-Methylaniline (0.016 g, 0.00015 mol) and 1-benzyl-*N*-4-methylsulfonyl-

phenoxycarbonylpiperidine-4-amine (**10g**) (0.058 g, 0.00015 mol) were dissolved in acetonitrile (7 ml) and the solution was heated at reflux for 9 h. The solvent was removed by evaporation *in vacuo*, the residue was dissolved in chloroform (25 ml) and the resulting solution was washed with 10% w/v sodium hydroxide solution (3x10 ml), water (3x10 ml) and brine (10 ml). The organic solution was dried (Na_2SO_4) and filtered, and the solvent was removed by evaporation *in vacuo* to leave a pale yellow solid. This was purified by column chromatography on neutral alumina (eluent:- petroleum ether bp 60-80 °C : chloroform 1:1 v/v grading to chloroform). This gave 0.043 g (88%) of (**11**) as a colourless oil, the NMR spectrum of which was identical to that of the material prepared from 4-amino-1-benzylpiperidine and *N*-methyl-*N*-phenylcarbamoyl chloride, as follows.

(ii) *From 4-amino-1-benzylpiperidine and N-methyl-N-phenylcarbamoyl chloride.*

(a) *N-Methyl-N-phenylcarbamoyl chloride.* *N*-Methylaniline (10.7 g, 0.10 mol) was dissolved in toluene (100 ml) the solution was added to a toluene solution of phosgene (2.0 M, 55 ml, 0.11 mol), and the resulting mixture was stirred at room temperature for 1 h. Hplc analysis indicated 60% conversion, and hence the mixture was heated to reflux for 1.5 h, after which hplc analysis showed 99% conversion. The reaction mixture was then heated for a further 1 h with nitrogen purging (negative test for phosgene vapour with Draeger tube), after which the solvent was removed by evaporation *in vacuo* to leave a grey/white solid (16.3 g, 96%), mp 85-87 °C (Lit mp[9] 88-89 °C), υ_{max} ($CHCl_3$)/cm^{-1} 1730 (C=O); δ_H (400 MHz; $CDCl_3$) 3.37 (3H, s), 7.35 (5H, m); δ_C (400 MHz; $CDCl_3$) 40.65 (CH_3), 127.66 (CH), 128.49 (CH), 129.66 (CH), 143.52 (C), 149.52 (C); *m/z* 169. Anal calcd for C_8H_8ClNO: C, 56.65; H, 4.75; N, 8.26. Found: C, 57.12; H, 4.81, N, 8.29.

(b) *N-(1-Benzylpiperidin-4-yl)-N'-methyl-N'-phenylurea* (**11**). 4-Amino-1-benzylpiperidine (**2**) (1.12 g, 0.0059 mol) was dissolved in toluene (25 ml) and

the solution was added dropwise to a stirred solution of *N*-methyl-*N*-phenylcarbamoyl chloride (1.0 g, 0.0059 mol) in toluene (25 ml) at room temperature. The reaction mixture was stirred for 15 h at room temperature, then at reflux for 2 h. The solvent was removed by evaporation *in vacuo* and the residue dissolved in dichloromethane (50 ml). The mixture was transferred to a separating funnel, the solution was washed with water (25 ml), and the aqueous layer was further extracted with dichloromethane (50 ml). The dichloromethane extracts were combined, washed with water (2x25 ml) and saturated brine (25 ml), dried (Na_2SO_4), filtered and the solvent removed by evaporation *in vacuo* to leave a red oil (2 g). This crude product was chromatographed on basic alumina (Brockmann Type II pH 9.3; eluant:- petroleum ether bp 60-80 °C : dichloromethane 1:1 v/v, grading to petroleum ether bp 60-80 °C : dichloromethane 25:75 v/v) to give 1.0 g (52%) of (**11**) as a colourless solid, mp 71-73 °C, υ_{max} (KBr)/cm^{-1} 1626 (C=O); δ_H (400 MHz; $CDCl_3$) 1.35 (2H, dq, *J* 2, 11), 1.94 (2H, br d, *J* 13), 2.15 (2H, br t, *J* 11), 2.76 (2H, bd, *J* 11), 3.33 (3H, s), 3.51 (2H, s), 3.75 (1H, m), 4.24 (1H, d, *J* 8), 7.39 (10H, m); δ_C (400 MHz; $CDCl_3$) 33.01 (CH_2), 37.24 (CH_3), 47.62 (CH), 52.56 (CH_2), 63.32 (CH_2), 127.19 (CH), 127.42 (CH), 127.47 (CH), 128.41 (CH), 129.29 (CH), 130.21 (CH), 138.81 (C), 143.78 (C), 156.62 (C); *m/z* = 323. Anal calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.36; H, 7.85; N, 13.06.

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