# Lithiation and Substitution of *N*′-(ω-Phenylalkyl)-*N*,*N*-dimethylureas

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**Abstract:** Lithiation of *N*′-phenethyl-*N*,*N*-dimethylurea with three equivalents of *tert*-butyllithium in anhydrous tetrahydrofuran at –78 °C takes place on the nitrogen and on the side-chain of the $CH_2$ next to the phenyl ring (α-lithiation). The 2-lithio isomer can be obtained via bromine–lithium exchange of *N*′-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea using methyllithium followed by *tert*-butyllithium in tetrahydrofuran at –78 °C. The lithium reagents thus obtained react with various electrophiles to give the corresponding substituted derivatives in excellent yields. Lithiation of *N*′-(3-phenylpropyl)-*N*,*N*-dimethylurea takes place on the α-$CH_2$ with *tert*-butyllithium at 0 °C. On the other hand, lithiation of *N*′-(4-phenylbutyl)-*N*,*N*-dimethylurea with *tert*-butyllithium at 0 °C takes place on one of the methyl groups of the urea unit.

**Key words:** *N*′-phenethyl-*N*,*N*-dimethylurea, side-chain lithiation, bromine–lithium exchange, electrophile, synthesis

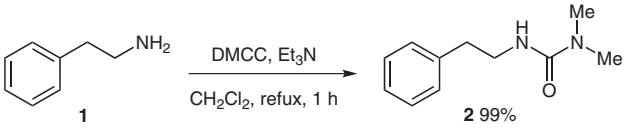
Many aromatic compounds undergo lithiation *ortho* to a functional group,[2–4] and the organolithium reagents in such reactions are useful intermediates for the synthesis of *ortho*-disubstituted aromatics.[5] Moreover, *ortho*-lithiation has been applied to various heterocycles to produce the corresponding substituted derivatives.[6]

For example, we have developed several efficient lithiation procedures for preparation of various substituted aromatics and heteroaromatics that might be difficult to prepare by other means.[7] As part of such studies we have successfully lithiated and substituted various *N*-(substituted benzyl)pivalamides and *N*′-(substituted benzyl)-*N*,*N*-dimethylureas selectively using *n*-butyllithium or *tert*-butyllithium in tetrahydrofuran.[8–10] Such processes have been applied for the production of substituted isoindoline and isoquinoline derivatives.[11–13]

As part of such studies we became interested in directed lithiation of *N*′-phenethyl-*N*,*N*-dimethylureas. Lithiation of *N*-phenethylpivalamide derivatives have been reported by Schlosser.[14,15] For example, lithiation of *N*-phenethylpivalamide itself took place on the side chain (α-lithiation) with three equivalents of *tert*-butyllithium in tetrahydrofuran at –75 °C. Reaction of the dilithium reagent thus obtained with carbon dioxide, the only electrophile tried, gave the corresponding acid in 72% yield.[14] However, there are no reports of lithiation and substitution of *N*′-phenethyl-*N*,*N*-dimethylureas, and pivalamide and dimethylurea derivatives do not always behave in an identical manner towards lithiation[9] and the urea derivatives are more generally useful for synthesis.

We now report the successful lithiation and substitution of *N*′-phenethyl-*N*,*N*-dimethylureas using a simple, general and efficient α-lithiation procedure using *tert*-butyllithium. We also report a procedure for ring-substitution by Br–Li exchange with methyllithium followed by *tert*-butyllithium in tetrahydrofuran at –78 °C.

The first tasks were to synthesise *N*′-phenethyl-*N*,*N*-dimethylurea (**2**)[16] and to try to find conditions under which its lithiation could be effected. Reaction of phenethylamine (**1**) with dimethylcarbamoyl chloride (DMCC) in dichloromethane and in the presence of triethylamine under reflux for one hour gave **2** in 99% yield (Scheme 1) after crystallisation.




**Scheme 1** Synthesis of *N*′-phenethyl-*N*,*N*-dimethylurea (**2**)

Initially the reaction of **2** with *n*-butyllithium (2.2 equiv) was carried out in anhydrous tetrahydrofuran under a nitrogen atmosphere at –78 °C. Initial addition of *n*-butyllithium provided a pale yellow solution, presumably because of formation of the monolithium reagent **3**, until approximately one equivalent had been added, then gave a deep yellow solution as the remaining *n*-butyllithium was added, presumably because of formation of the dilithium reagent **4**. The mixture was stirred for two hours at –78 °C. Benzaldehyde (1.1 equiv) was added and the mixture was stirred for another two hours (Scheme 2) at –78 °C and then quenched by the addition of aqueous ammonium chloride solution. The starting material **2** was recovered in 95% yield, but a new compound, shown by its $^1$H NMR spectrum to be **5**, was produced in very low yield (Table 1, entry 1).

Several experiments were conducted to try to improve the yield of **5** or to find conditions under which *ortho*-lithiation could be achieved instead. Double lithiations of **2** with various lithiating agents (*n*-BuLi, *t*-BuLi, LDA) at various reaction temperatures (–78 and 0 °C) followed by reaction with benzaldehyde were attempted. The crude products were analysed by $^1$H NMR spectroscopy and the approximate yields of **5** obtained are summarised in Table 1.

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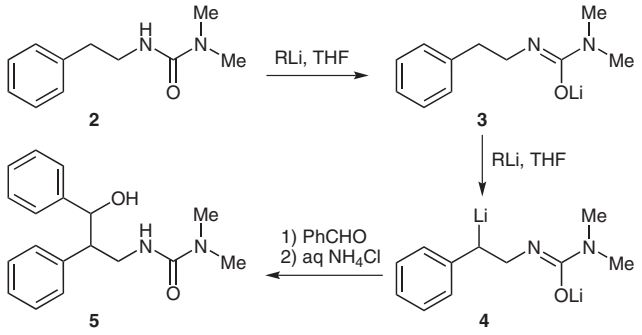



**Scheme 2** Lithiation of **2** followed by reaction with benzaldehyde

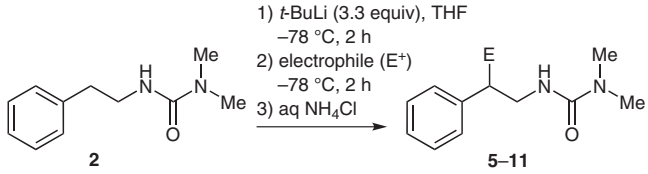
**Table 1** Synthesis of **5** under Various Reaction Conditions

| Entry | Lithium reagent (equiv) | Temp (°C) | Yield (%) |
|---|---|---|---|
| 1 | *n*-BuLi (2.2) | –78 | 2[a,b] |
| 2 | *n*-BuLi (2.2) | 0 | –[c] |
| 3 | *t*-BuLi (2.2) | 0 | –[c] |
| 4 | *t*-BuLi (3.3) | 0 | –[c] |
| 5 | *t*-BuLi (4.4) | 0 | –[c] |
| 6 | *t*-BuLi (2.2) | –78 | 62[d] |
| 7 | *t*-BuLi (3.3) | –78 | 97[d] |
| 8 | LDA (2.2) | 0 | –[c] |

[a] Yield by $^1$H NMR analysis.
[b] Starting material **2** was recovered in significant quantities.
[c] A complex mixture of unidentified products was formed.
[d] Yield of **5** after purification.

The results clearly indicated that the optimum conditions involved use of three equivalents of *tert*-butyllithium as the lithium reagent at –78 °C (Table 1, entry 7) to give **5** in 97% yield after purification by column chromatography. The $^1$H NMR spectrum of **5** showed diastereotopicity for the $CH_2$ protons in both diastereoisomers.

It was of interest to see if the reaction of the lithium intermediate **4** with other electrophiles would be useful and general. Consequently, reactions of **4**, prepared in situ from **2** under the conditions described above, with various electrophiles were carried out. Each reaction was conducted under identical conditions. The crude products were purified by column chromatography (silica gel; $Et_2O$–hexane, 1:3), to give the corresponding substituted derivatives **6**–**11** (Scheme 3) in high yields (Table 2).




**Scheme 3** Lithiation and substitution of *N*′-phenethyl-*N*,*N*-dimethylurea (**2**)

Clearly, lithiation and substitution of **2** took place on the side chain. In the $^{13}$C NMR spectrum of compound **7** the carbons of the two phenyl groups appeared as separated signals, verifying that they are diastereotopic. Similarly, the carbons of the two methyl groups originating from acetone in compound **8** and the two sides of the cyclohexane ring in compound **9** appeared as separated signals in their $^{13}$C NMR spectra. Also, the NMR spectra of all compounds showed that the signals of the two hydrogens of the $CH_2$ group are diastereotopic.

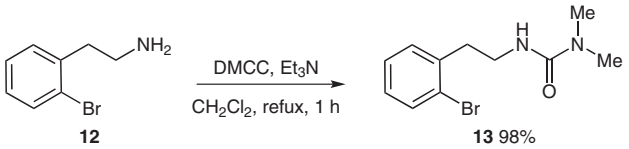
**Table 2** Synthesis of Substituted *N*′-Phenethyl-*N*,*N*-dimethylureas **5**–**11**

| Product | Electrophile | E | Yield (%)[a] |
|---|---|---|---|
| **5** | PhCHO | PhCH(OH) | 97[b] |
| **6** | PhCOMe | PhC(OH)Me | 96[b] |
| **7** | $Ph_2CO$ | $Ph_2C(OH)$ | 98 |
| **8** | $Me_2CO$ | $Me_2C(OH)$ | 98 |
| **9** | $(CH_2)_5CO$ | $(CH_2)_5C(OH)$ | 98 |
| **10** | EtI | Et | 86 |
| **11** | $D_2O$ | D | 99 |

[a] Yield of pure product after isolation.
[b] The $^1$H NMR showed the presence of two diastereoisomers in approximately equal proportions.

Clearly, directed lithiation of *N*′-phenethyl-*N*,*N*-dimethylurea (**2**) did not take place on the ring. However, ring substitution could in principle be achieved via bromine–lithium exchange of the corresponding bromo substrate. Therefore, we decided to synthesise *N*′-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea (**13**) and attempt its bromine–lithium exchange and substitution.

*N*′-2-(2-Bromophenyl)ethyl-*N*,*N*-dimethylurea (**13**) was synthesised in 98% yield as described in Scheme 4, based on a literature procedure for analogous compounds.[16]



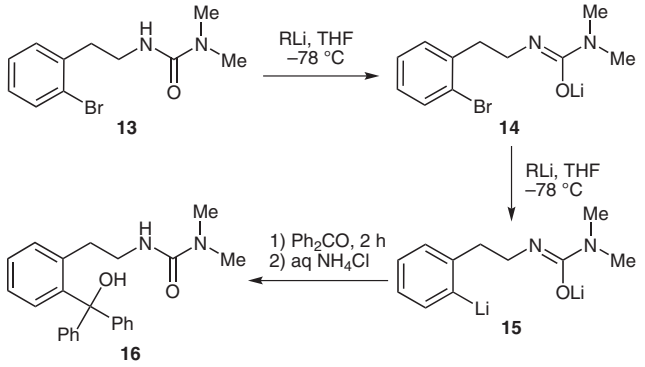

**Scheme 4** Synthesis of *N*′-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea (**13**)

Successful bromine–lithium exchange of **13**, which possesses a proton-donating group (PDG), followed by trapping of the organolithium reagent with an electrophile, relies on clean initial deprotonation of the urea group (Scheme 5). If bromine–lithium exchange should precede deprotonation, then the incipient organolithium reagent could self-quench to give species **3** (Scheme 2). However, there are also other potential complications. For example, the initially formed intermediate **14** could complex further



organolithium reagent RLi and provide intramolecular assistance for bromine–lithium exchange. If this process becomes faster than the initial deprotonation, the new organolithium intermediate can then compete with the added organolithium for deprotonation of further **13**, which would ultimately lead to recovery of **2**.




**Scheme 5** Bromine–lithium exchange of **13** followed by reaction with benzophenone

Some of these issues were investigated by Beak et al. for 2-bromo-*N*-ethylbenzamide and other substrates possessing PDGs, but primarily from a mechanistic rather than synthetic perspective.[17] For other PDG-containing substrates a Japanese group has used the less reactive dibutylmagnesium to effect the initial deprotonation, prior to bromine–lithium exchange,[18] but this suffers from the complication that the waste products of the reaction will contain two different metals, making recovery of the metals more difficult. The same group has also used mesityllithium for initial deprotonation of substrates containing active methylene groups,[19] but mesityllithium is more expensive and less widely available than common organolithium reagents, is more wasteful of organic material, and produces a by-product that is less volatile and more difficult to remove. We have previously found that methyllithium can be used for selective deprotonation of *N*-(2-bromobenzyl)pivalamide, followed by two equivalents of *tert*-butyllithium to effect bromine–lithium exchange.[9] This method is more attractive to us and therefore we proposed to investigate this method in the first instance if simple use of *tert*-butyllithium alone should prove unsatisfactory for Br–Li exchange of **13**.

Against this background, Br–Li exchange of **13** was attempted under various reaction conditions, followed by reaction with benzophenone as an electrophile. The results obtained are recorded in Table 3.

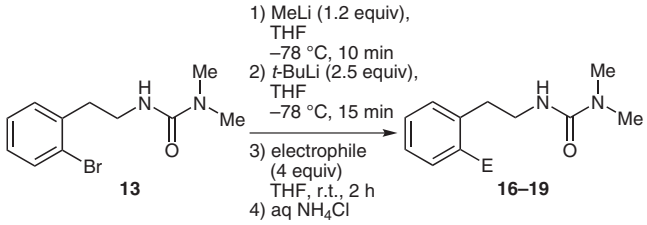
The results reported in Table 3 showed that treatment of **13** with *tert*-butyllithium alone (2.2 or 3.3 equiv, at –78 °C or 0 °C, for short or long periods) did not provide more than traces of the desired product **16**. However, use of 1.2 equivalents of methyllithium (to deprotonate the nitrogen) to give the monolithium reagent **14** and then 2.5 equivalents of *tert*-butyllithium to bring about bromine–lithium exchange led smoothly at –78 °C in tetrahydrofuran for 15 minutes to the dilithium reagent **15** (Scheme 5), which could be trapped with excess benzophenone at room temperature in tetrahydrofuran. After workup, the crude product was purified by column chromatography (silica gel; $Et_2O$–hexane, 1:3) to give **16** in 95% yield (Table 3, entry 9). Other conditions were successful to produce **16** but in lower yields.

Reactions of **15**, prepared in situ from **13** under the optimum conditions, with representative electrophiles (4 equiv) were carried out at room temperature for two hours. Purification of the crude products by column chromatography (silica gel; $Et_2O$–hexane, 1:3) gave the corresponding substituted derivatives **17**–**19** (Scheme 6) in high yields (Table 4).

**Table 3** Synthesis of **16** under Various Reaction Conditions

| Entry | Lithiation step (–78 °C), RLi (equiv) | | | Reaction with $Ph_2CO$ | | Yield (%)[a] |
|---|---|---|---|---|---|---|
| | MeLi | *t*-BuLi | Time (min) | Temp (°C) | Equiv | |
| 1 | 0 | 2.5 | 5 | –78 | 1.2 | 19 (8)[b] |
| 2 | 0 | 2.5 | 120 | –78 | 1.2 | 23 |
| 3 | 0 | 3.3 | 120 | –78 | 1.2 | 30 |
| 4 | 0 | 2.5 | 60 | 0 | 1.2 | 9 |
| 5 | 1.2 | 2.5 | 15 | –78 | 2.0 | 46 |
| 6 | 1.2 | 2.5 | 15 | 20 | 1.2 | 72 |
| 7 | 1.2 | 2.5 | 15 | 20 | 2.0 | 82 |
| 8 | 1.2 | 2.5 | 15 | 20 | 3.0 | 86 |
| 9 | 1.2 | 2.5 | 15 | 20 | 4.0 | 95 |
| 10 | 1.2 | 2.5 | 60 | 20 | 2.0 | 90 |

[a] Yield of pure **16**.
[b] The figure in parentheses is for a similar reaction in anhyd $Et_2O$.




**Scheme 6** Lithiation and substitution of *N*′-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea (**13**)

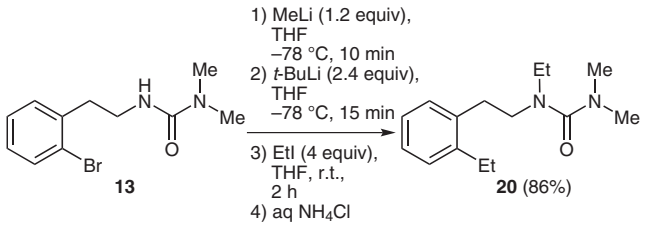
**Table 4** Synthesis of *N*′-2-(2-Substituted phenyl)ethyl-*N*,*N*-dimethylureas **16**–**19**

| Product | Electrophile | E | Yield (%)[a] |
|---|---|---|---|
| **16** | $Ph_2CO$ | $Ph_2C(OH)$ | 95 |
| **17** | PhCHO | PhCH(OH) | 90 |
| **18** | 4-$MeOC_6H_4CHO$ | 4-$MeOC_6H_4CH(OH)$ | 87 |
| **19** | $D_2O$ | D | 98 |

[a] Yield of pure product after isolation.

The $^1$H NMR spectra of compounds **17** and **18** showed that the signals for the two hydrogens of the two $CH_2$ groups are diastereotopic.

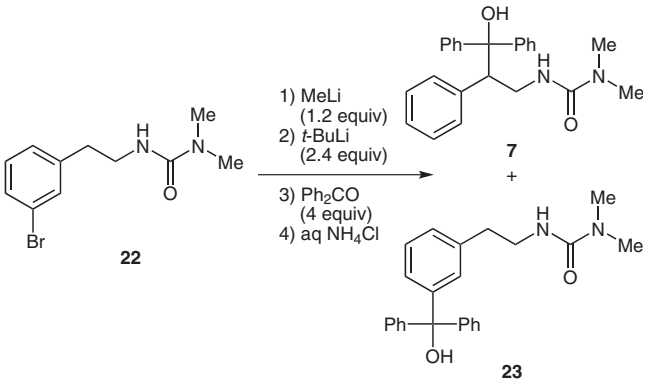
Reaction of the dilithium reagent **15**, obtained from **13**, with excess of iodoethane (4.0 equiv) gave rise to the diethyl derivative **20** in 86% isolated yield (Scheme 7). Although we did not attempt to prepare the monoethyl derivative in this case, there is ample precedent to show that C-ethylation occurs much more readily than N-ethylation (see formation of **10**, Table 2, for example), so that simple C-ethylated products are easily obtained when the amount of iodoethane is restricted to one equivalent.




**Scheme 7** Lithiation of **13** followed by reaction with iodoethane

It was of interest to see whether the conditions that were successful for Br–Li exchange of **13** would also apply for Br–Li exchange of a compound with the Br at a different location on the ring. Therefore, *N*′-2-(3-bromophenyl)ethyl-*N*,*N*-dimethylurea (**22**; Figure 1) was synthesised from **21** in 98% yield by the method[16] shown in Scheme 4 for synthesis of **13**.

The Br–Li exchange of **22** under conditions identical to those used in Scheme 6, followed by reaction with benzophenone (4 equiv), gave a mixture of **7** and **23** (Scheme 8) in 85 and 13% yield, respectively. Product **23** would be produced as a result of Br–Li exchange followed by reaction with benzophenone at the 3-position. We assume that product **7** arose as a result of isomerisation of the 3-lithio derivative formed by the initial Br–Li exchange reaction into the α-lithio derivative, probably because the 3-lithio reagent acted as a base to remove a proton from the side chain of another molecule. In an attempt to improve the yield of **23** we shortened the reaction time with *tert*-butyllithium so as to reduce the opportunity for such isomerisation. Indeed, the yield of **23** was improved to 58% when the reaction time with *tert*-butyllithium was only 5 minutes, while the yield of **7** decreased to 13%. A significant quantity (22%) of unbrominated starting material **2** was also recovered, which supports the assumption that the initial Br–Li exchange product acts as a base.




**Scheme 8** Bromine–lithium exchange of **21** followed by reaction with benzophenone

It was also of interest to know whether lithiation of other *N*′-(ω-phenylalkyl)-*N*,*N*-dimethylureas would behave in the same way towards lithiation as the phenethyl derivative. Therefore, *N*′-(3-phenylpropyl)-*N*,*N*-dimethylurea (**26**) and *N*′-(4-phenylbutyl)-*N*,*N*-dimethylurea (**27**) were synthesised (in 94 and 90% yields, respectively) from the corresponding amino derivatives **24** and **25**. Lithiation of **26** under the standard conditions that were used for **2** (Scheme 2) followed by reaction with benzophenone as a representative electrophile at –78 °C gave the corresponding α-substituted product **28** in 44% yield. The yield of **28**

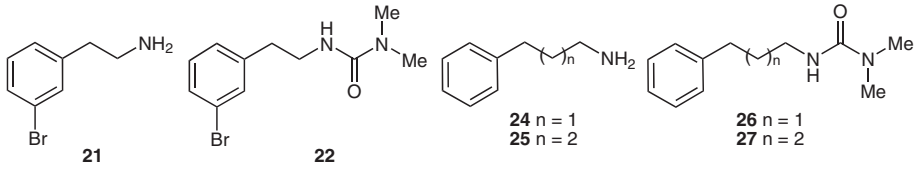
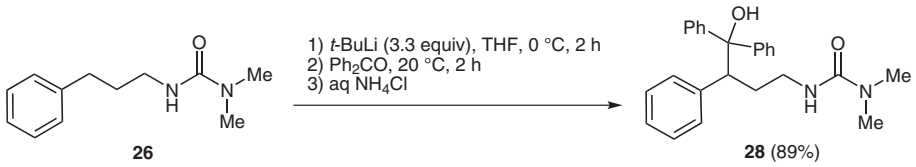
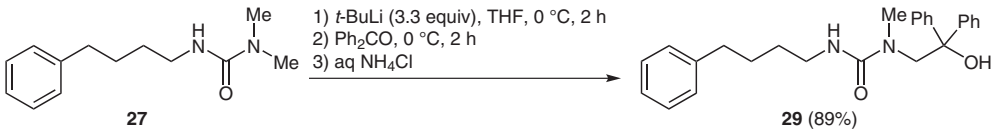



**Figure 1** Structures of compounds **21**, **22**, and **24**–**27**




**Scheme 9** Lithiation of **26** followed by reaction with benzophenone




**Scheme 10** Lithiation of **27** followed by reaction with benzophenone

was improved to 85% when the whole reaction was carried out at 0 °C and to 89% when the lithiation was conducted at 0 °C and reaction with benzophenone was carried at room temperature (Scheme 9).

By contrast, lithiation of **27** followed by reaction with benzophenone at 0 °C gave product **29**, in which lithiation and substitution had taken place on a methyl group of the urea (Scheme 10), in 89% yield. No product was obtained when the reaction was carried out at –78 °C.

These results illustrate how sensitive reactions of this nature are to subtle variations in structure, method of generation of lithium compound and reaction conditions. For the series of compounds $Ph(CH_2)_nNHCONMe_2$, with n = 0–4, direct lithiation at –20 °C gives side-chain substitution on a methyl group of the urea unit for n = 0,[7e] *ortho*-substitution at –78 °C for n = 1,[9] and α-substitution for n = 2 (this work) at –78 °C. Although α-substitution also prevails for n = 3, a higher temperature during the lithiation step is needed for a good yield, while no lithiation occurs at –78 °C for n = 4 and at 0 °C lithiation occurs on an *N*-methyl group. Similarly, conditions optimised for Br–Li exchange of 2-bromophenethyl derivative **13** produced only a low yield of the corresponding product from 3-bromophenethyl derivative **21**, although the yield could be improved substantially by varying the reaction conditions. Optimisation of each of these cases is beyond the scope of this work, but it is clear that it is important for researchers to be aware of the need for such optimisation for any specific case of interest.

In conclusion, simple and efficient procedures that allow side-chain lithiation of *N*′-(phenylalkyl)-*N*,*N*-dimethylureas have been developed. Lithiation of *N*′-phenethyl-*N*,*N*-dimethylurea took place at the $CH_2$ group next to the phenyl ring (α-lithiation) with three equivalents of *tert*-butyllithium in tetrahydrofuran at –78 °C. Ring substitution could be achieved via bromine–lithium exchange of *N*′-2-(2-bromophenyl)ethyl-*N*,*N*-dimethylurea using methyllithium followed by *tert*-butyllithium in tetrahydrofuran at –78 °C. Reactions of the dilithium reagents obtained with a variety of electrophiles gave the corresponding α- or 2-substituted derivatives in high yields. Similarly, lithiation of *N*′-(3-phenylpropyl)-*N*,*N*-dimethylurea took place on the α-$CH_2$, although a higher temperature was required for a good yield. By contrast, lithiation of *N*′-(4-phenyl)butyl-*N*,*N*-dimethylurea took place on one of the methyl groups of the urea unit.

Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AV500 spectrometer operating at 500 MHz for $^1$H and 125 MHz for $^{13}$C measurements. Chemical shifts δ are reported in parts per million (ppm) relative to TMS and coupling constants *J* are in Hz and have been rounded to the nearest whole number. $^{13}$C multiplicities were revealed by DEPT signals. Assignments of signals are based on integration values, coupling patterns, and expected chemical shift values, and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Low-resolution mass spectra were recorded on a Waters GCT Premier spectrometer and high-resolution mass spectra were recorded on a Waters LCT Premier XE instrument. IR spectra were recorded on a Jasco FT/IR-660 plus instrument by dissolving the product in $CHCl_3$, applying droplets on a NaCl plate and allowing evaporation of the solvent. Column chromatography was carried out using Fischer Scientific silica 60A (35–70 micron). Alkyllithiums were obtained from Aldrich Chemical Company and were estimated prior to use by the method of Watson and Eastham.[20] Other chemicals were obtained from Aldrich Chemical Company and used without further purification. Solvents were purified by standard procedures.[21,22]

***N*′-Phenethyl-*N*,*N*-dimethylurea (2)**

A stirred mixture of **1** (10.39 g, 85.8 mmol), dimethylcarbamoyl chloride (DMCC, 10.37 g, 96.5 mmol) and $Et_3N$ (11.97 g, 118.3 mmol) in $CH_2Cl_2$ (100 mL) was heated under reflux for 1 h. The mixture was allowed to cool and the solid formed was collected by filtration and then washed with $H_2O$ (2 × 25 mL). The solid was purified by crystallisation from a mixture of EtOAc and $Et_2O$ (1:3 by volume) to give pure **2**; yield: 16.30 g (99%); colourless crystalline solid; mp 88–90 °C (Lit.[16a] mp 81–82 °C, Lit.[16b] mp 98 °C).

IR (FT): 3341, 2933, 1634, 1539, 1332, 1203 cm$^{-1}$.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.19 (m, 5 H, $C_6H_5$), 4.38 (br s, 1 H, NH, exch.), 3.48 (app q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.85 [s, 6 H, N(CH$_3$)$_2$], 2.82 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ph).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C=O), 139.5 (s, C-1 of $C_6H_5$), 128.8 (d, C-3/C-5 of $C_6H_5$), 128.5 (d, C-2/C-6 of $C_6H_5$), 126.3 (d, C-4 of $C_6H_5$), 42.1 (t, $CH_2NH$), 36.5 (t, *C*H$_2$Ph), 36.1 [q, N(CH$_3$)$_2$].

MS (EI): *m/z* (%) = 192 (29, [M]$^+$), 147 (8), 101 (42), 72 (100).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{11}H_{16}N_2O$: 192.1263; found: 192.1260.

**Substituted *N′*-Phenethyl-*N*,*N*-dimethylureas 5–11; General Procedure**

A solution of *t*-BuLi in pentane (4.51 mL, 1.9 M, 8.60 mmol) was added to a stirred solution of **2** (0.50 g, 2.60 mmol) at –78 °C in anhyd THF (20 mL) under a $N_2$ atmosphere. The mixture was stirred at –78 °C for 2 h and a solution of the electrophile (2.60 mmol), in anhyd THF (8 mL) if solid, neat otherwise, was added. The reaction mixture was stirred for 2 h at –78 °C, and then allowed to warm to r.t. The mixture was quenched with a sat. aq $NH_4Cl$ (20 mL) and diluted with $Et_2O$ (20 mL). The organic layer was separated, washed with $H_2O$ (2 × 20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel; $Et_2O$–hexane, 1:3) to give the pure products **5**–**11**. The yields obtained were in the range of 86–99% (Table 2).

***N′*-(3-Hydroxy-2,3-diphenylpropyl)-*N*,*N*-dimethylurea (5)**

Product **5** was a mixture of two racemic diastereoisomers in approximately equal proportions; yield: 0.75 g (97%); white solid; mp 180–184 °C.

IR (FT): 3352, 2929, 1633, 1537, 1332, 1230 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.23–7.11 (m, 20 H, 4 $C_6H_5$), 6.25 (t, *J* = 7 Hz, 1 H, NH, exch.), 6.00 (t, *J* = 7 Hz, 1 H, NH, exch.), 5.72 (d, *J* = 4 Hz, 1 H, OH, exch.), 5.53 (d, *J* = 4 Hz, 1 H, OH, exch.), 4.94 (app t, *J* = 4 Hz, 1 H, C*H*OH), 4.81 (dd, *J* = 4, 7 Hz, 1 H, C*H*OH), 3.58–3.49 (m, 2 H, 2 C*H*Ph), 3.44 (dd, *J* = 7, 14 Hz, 1 H, C$H_aH_b$), 3.28 (m, 1 H, $CH_aH_b$), 3.18 (dd, *J* = 7, 14 Hz, 1 H, C$H_aH_b$), 3.13–3.09 (m, 1 H, $CH_aH_b$), 2.77 [s, 6 H, $N(CH_3)_2$], 2.71 [s, 6 H, $N(CH_3)_2$].

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 159.1, 158.8 (2 s, 2 C=O), 144.7, 144.6, 142.0, 140.7 (4 s, C-1 of 4 $C_6H_5$), 129.8, 129.3, 128.1, 127.9 (4 d, C-3/C-5 of 4 $C_6H_5$), 127.9, 127.8, 127.1, 126.7 (4 d, C-2/C-6 of 4 $C_6H_5$), 126.9, 126.6 (2 d, C-4 of 4 $C_6H_5$), 75.8, 73.0 (2 d, 2 CHOH), 53.34, 53.32 (2 d, 2 *C*HPh), 43.5, 42.7 (2 t, 2 $CH_2$), 36.3, 36.2 [2 q, 2 $N(CH_3)_2$].

MS (EI): *m/z* (%) = 298 (2, $[M]^+$), 280 (20), 208 (32), 180 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{22}N_2O_2$: 298.1681; found: 298.1677.

***N′*-(3-Hydroxy-2,3-diphenylbutyl)-*N*,*N*-dimethylurea (6)**

Product **6** was a mixture of two racemic diastereoisomers in approximately equal proportions; yield: 0.78 g (96%); white solid; mp 131–135 °C.

IR (FT): 3365, 2928, 1615, 1537, 1367, 1222 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.44–7.13 (m, 20 H, 4 $C_6H_5$), 3.94 (br s, 1 H, NH, exch.), 4.82 (br s, 1 H, NH, exch.), 4.77 (dd, *J* = 4, 7 Hz, 1 H, CH), 3.78 (m, 1 H, CH), 3.52 (m, 1 H, C$H_aH_b$), 3.40 (m, 1 H, $CH_aH_b$), 3.31 (dd, *J* = 7, 14 Hz, 1 H, C$H_aH_b$), 3.18 (dd, *J* = 7, 14 Hz, 1 H, $CH_aH_b$), 2.83 [s, 6 H, $N(CH_3)_2$], 2.42 [s, 6 H, $N(CH_3)_2$], 1.10 (s, 3 H, $CH_3$), 0.85 (s, 3 H, $CH_3$).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 159.9, 158.3 (2 s, 2 C=O), 149.0, 148.9, 140.5, 140.4 (4 s, C-1 of 4 $C_6H_5$), 129.7, 128.4, 128.35, 128.31 (4 d, C-3/C-5 of 4 $C_6H_5$), 127.89, 127.86, 127.5, 127.0 (4 d, C-2/C-6 of 4 $C_6H_5$), 126.2, 125.9, 124.67, 124.62 (4 d, C-4 of 4 $C_6H_5$), 75.3, 75.0 (2 s, 2 COH), 56.3, 49.2 (2 d, 2 CH), 42.1, 42.0 (2 t, 2 $CH_2$), 35.7, 36.3 [2 q, 2 $N(CH_3)_2$], 31.3, 31.1 (2 q, 2 $CH_3$).

MS (EI): *m/z* (%) = 294 (40, $[M – H_2O]^+$), 279 (3), 208 (32), 192 (100).

HRMS (EI): *m/z* $[M – H_2O]^+$ calcd for $C_{19}H_{22}N_2O$: 294.1732; found: 294.1737.

***N′*-(3-Hydroxy-2,3,3-triphenylpropyl)-*N*,*N*-dimethylurea (7)**

Yield: 0.95 g (98%); white solid; mp 202–205 °C.

IR (FT): 3239, 2920, 1609, 1531, 1360, 1211 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.77–6.80 (m, 15 H, 3 $C_6H_5$), 6.38 (br s, 1 H, OH, exch.), 5.96 (t, *J* = 6 Hz, 1 H, NH, exch.), 4.28 (app t, *J* = 7 Hz, 1 H, CH), 3.62 (m, 1 H, C$H_aH_b$), 3.26 (m, 1 H, $CH_aH_b$), 2.43 [s, 6 H, $N(CH_3)_2$].

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 148.2, 149.0, 141.6 (3 s, C-1 of 3 $C_6H_5$), 127.6, 127.9, 127.5 (3 d, C-3/C-5 of 3 $C_6H_5$), 126.2, 126.3, 126.0 (3 d, C-2/C-6 of 3 $C_6H_5$), 125.95, 125.92, 125.3 (3 d, C-4 of 3 $C_6H_5$), 79.0 (s, COH), 52.6 (d, CH), 43.6 (t, $CH_2$), 35.9 [q, $N(CH_3)_2$].

MS (EI): *m/z* (%) = 356 (40, $[M – H_2O]^+$), 311 (15), 256 (100), 192 (97).

HRMS (EI): *m/z* $[M – H_2O]^+$ calcd for $C_{19}H_{22}N_2O$: 356.1889; found: 356.1883.

***N′*-(3-Hydroxy-3-methyl-2-phenylbutyl)-*N*,*N*-dimethylurea (8)**

Yield: 0.74 g (98%); white solid; mp 148–151 °C.

IR (FT): 3321, 2968, 1617, 1547, 1351, 1221 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 5 H, $C_6H_5$), 4.41 (br s, 1 H, NH, exch.), 3.85 (dd, *J* = 6, 14 Hz, 1 H, C$H_aH_b$), 3.37 (dd, *J* = 9, 14 Hz, 1 H, $CH_aH_b$), 2.73 (dd, *J* = 6, 9 Hz, 1 H, CH), 2.72 [s, 6 H, $N(CH_3)_2$], 1.23 (s, 3 H, $CH_3$), 1.16 (s, 3 H, $CH_3$).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 140.4 (s, C-1 of $C_6H_5$), 129.4 (d, C-3/C-5 of $C_6H_5$), 128.3 (d, C-2/C-6 of $C_6H_5$), 126.9 (d, C-4 of $C_6H_5$), 72.5 (s, COH), 56.5 (d, CH), 41.7 (t, $CH_2$), 35.9 [q, $N(CH_3)_2$], 29.1, 27.6 (2 q, 2 $CH_3$).

MS (EI): *m/z* (%) = 232 (25, $[M – H_2O]^+$), 217 (10), 192 (100).

HRMS (EI): *m/z* $[M – H_2O]^+$ calcd for $C_{14}H_{20}N_2O$: 232.1576; found: 232.1570.

***N′*-[2-(1-Hydroxycyclohexyl)-2-phenylethyl]-*N*,*N*-dimethylurea (9)**

Yield: 0.74 g (98%); white solid; mp 149–151 °C

IR (FT): 3358, 2931, 1634, 1538, 1380, 1228 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.33–7.18 (m, 5 H, $C_6H_5$), 3.88 (dd, *J* = 5, 14 Hz, 1 H, C$H_aH_b$), 3.42 (dd, *J* = 9, 14 Hz, 1 H, $CH_aH_b$), 2.78 (dd, *J* = 5, 9 Hz, 1 H, CH), 2.64 [s, 6 H, $N(CH_3)_2$], 1.07–1.57 (m, 10 H, *c*-Hex).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 140.1 (s, C-1 of $C_6H_5$), 129.7 (d, C-3/C-5 of $C_6H_5$), 128.3 (d, C-2/C-6 of $C_6H_5$), 126.8 (d, C-4 of $C_6H_5$), 72.9 (s, C-1 of *c*-Hex), 55.5 (d, CH), 40.9 (t, $CH_2$), 36.2, 36.0 (2 t, C-3/C-5 of *c*-Hex), 35.9 [q, $N(CH_3)_2$], 25.6 (t, C-4 of *c*-Hex), 21.9, 21.7 (2 t, C-2/C-6 of *c*-Hex).

MS ($ES^+$): *m/z* (%) = 581 (48, $[M + MH]^+$), 354 (55, $[M + MeCNNa]^+$), 313 (47, $[M + Na]^+$), 291 (100, $[MH]^+$), 272 (30).

HRMS ($ES^+$): *m/z* $[MH]^+$ calcd for $C_{17}H_{27}N_2O_2$: 291.2073; found: 291.2080.

***N′*-(2-Phenylbutyl)-*N*,*N*-dimethylurea (10)**

Yield: 0.50 g (88%); yellow oil.

IR (FT): 3346, 2928, 1635, 1540, 1377, 1230 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.25–7.08 (m, 5 H, $C_6H_5$), 4.11 (br s, 1 H, NH, exch.), 3.62 (m, 1 H, C$H_aH_b$NH), 3.06 (m, 1 H, $CH_aH_b$NH), 2.67 [s, 6 H, $N(CH_3)_2$], 2.60 (m, 1 H, CH), 1.65 (m, 1 H, C$H_aH_b$CH$_3$), 1.50 (m, 1 H, $CH_aH_b$CH$_3$), 0.74 (t, *J* = 7 Hz, 3 H, $CH_3$).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 159.3 (s, C=O), 143.1 (s, C-1 of $C_6H_5$), 128.6 (d, C-3/C-5 of $C_6H_5$), 127.8 (d, C-2/C-6 of $C_6H_5$), 126.5 (d, C-4 of $C_6H_5$), 48.0 (t, $CH_2$), 46.3 (d, CH), 35.9 [q, $N(CH_3)_2$], 26.5 (t, *C*H$_2$CH$_3$), 11.9 (q, $CH_3$).

MS ($ES^+$): *m/z* (%) = 463 (20, $[2 M + Na]^+$), 243 (100, $[M + Na]^+$), 221 (30, $[MH]^+$).

HRMS ($ES^+$): *m/z* $[MH]^+$ calcd for $C_{13}H_{21}N_2O$: 221.1646; found: 221.1654.

***N*′-(2-Deuterio-2-phenylethyl)-*N*,*N*-dimethylurea (11)**
Yield: 0.50 g (99%); white solid; mp 89–90 °C (Lit.[16a], undeuterated analogue mp 81–82 °C; Lit.[16b] mp 98 °C).

IR (FT): 3342, 2932, 1634, 1538, 1382, 1231 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.24–7.11 (m, 5 H, $C_6H_5$), 4.38 (br s, 1 H, NH, exch.), 3.40–3.38 (m, 2 H, $CH_2$), 2.76 [s, 6 H, $N(CH_3)_2$], 2.72 (m, 1 H, CH).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.4 (s, C=O), 139.4 (s, C-1 of $C_6H_5$), 128.8 (d, C-3/C-5 of $C_6H_5$), 128.5 (d, C-2/C-6 of $C_6H_5$), 126.3 (d, C-4 of $C_6H_5$), 42.1 (t, $CH_2$), 36.1 [q, $N(CH_3)_2$], 36.2 (seen as three lines, 1:1:1, because of coupling to D, CH).

MS (EI): *m/z* (%) = 193 (48, $[M]^+$), 180 (8), 101 (55), 83 (89), 72 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{15}DN_2O$: 193.1325; found: 193.1328.

***N*′-(2-Bromophenethyl)-*N*,*N*-dimethylurea (13)**
The procedure was identical with that described for the synthesis of **2** in which a stirred mixture of **12** (8.00 g, 40.0 mmol), DMCC (5.37 g, 49.9 mmol), and $Et_3N$ (5.57 g, 55.0 mmol) in $CH_2Cl_2$ (60 mL) was heated under reflux for 1 h. Following workup, the crude product was purified by column chromatography (silica gel; $Et_2O$) to give pure **13**; yield: 10.73 g (99%); yellow oil.

IR (FT): 3333, 2931, 1633, 1537, 1356, 1230 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8 Hz, 1 H, H-3), 7.16–7.19 (m 2 H, H-4, H-6), 7.01 (m, 1 H, H-5), 4.43 (br s, 1 H, NH, exch.), 3.41 (app q, *J* = 7 Hz, 2 H, C*H*$_2$ NH), 2.90 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar), 2.80 [s, 6 H, $N(CH_3)_2$].

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.4 (s, C=O), 138.9 (s, C-1), 132.7 (d, C-3), 131.0 (d, C-6), 128.0 (d, C-4), 127.5 (d, C-5), 124.5 (s, C-2), 40.7 (t, $CH_2NH_2$), 36.5 (t, *C*$H_2$Ar), 36.1 [q, $N(CH_3)_2$].

MS (EI): *m/z* (%) = 273 (4, $[M^{81}Br + H]^+$), 271 (4, $[M^{79}Br + H]^+$), 192 (100, $[M - {}^{79}Br]^+$), 171 (98), 146 (10), 101 (97).

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{16}{}^{79}BrN_2O$: 271.0446; found: 271.0441.

***N*′-2-(2-Substituted Phenyl)ethyl-*N*,*N*-dimethylureas 16–20; General Procedure**
A solution of MeLi in $Et_2O$ (1.38 mL, 1.6 M, 2.2 mmol) was added to a stirred solution of **13** (0.50 g, 1.84 mmol) at –78 °C in anhyd THF (20 mL) under a $N_2$ atmosphere. The mixture was stirred for 10 min after which a solution of *t*-BuLi in pentane (2.42 mL, 1.9 M, 4.6 mmol) was added. The mixture was stirred at –78 °C for 15 min and a solution of the electrophile (7.36 mmol), in anhyd THF (8 mL) if solid, neat otherwise, was added. The cooling bath was removed and the reaction mixture was stirred for 2 h at r.t. The mixture was quenched with a sat. aq $NH_4Cl$ (20 mL) and diluted with $Et_2O$ (20 mL). The organic layer was separated, washed with $H_2O$ (2 × 20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel; $Et_2O$–hexane, 1:3) to give the pure products **16**–**20**. The yields obtained were in the range of 86–98% (Table 4).

***N*′-[2-(Hydroxydiphenylmethyl)-2-phenyl]ethyl-*N*,*N*-dimethylurea (16)**
Yield: 0.65 g (95%); white solid; mp 186–188 °C.

IR (FT): 3348, 2925, 1624, 1541, 1334, 1191 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 13 H, 2 $C_6H_5$, H-4, H-5, and OH), 7.02 (m, 1 H, H-6), 6.63 (d, *J* = 8 Hz, 1 H, H-3), 4.93 (br s, 1 H, NH, exch.), 3.37 (app q, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.81 [s, 6 H, $N(CH_3)_2$], 2.68 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.7 (s, C=O), 147.6 (s, C-1 of 2 $C_6H_5$), 145.4 (s, C-2), 139.2 (s, C-1), 131.8 (d, C-6), 130.0 (d, C-4), 127.81 (d, C-2/C-6 of 2 $C_6H_5$), 127.83 (d, C-3/C-5 of 2 $C_6H_5$), 127.6 (d, C-5), 127.0 (d, C-4 of 2 $C_6H_5$), 125.2 (d, C-3), 82.9 (s, COH), 42.5 (t, $CH_2NH_2$), 36.0 [q, $N(CH_3)_2$], 34.3 (t, *C*$H_2$Ar).

MS (EI): *m/z* (%) = 356 (90, $[M - H_2O]^+$), 312 (20), 279 (97), 255 (65), 191 (40), 178 (100), 165 (68), 105 (90).

HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{24}H_{24}N_2O$: 356.1889; found: 356.1892.

***N*′-2-{2-[Hydroxy(phenyl)methyl]phenyl}ethyl-*N*,*N*-dimethylurea (17)**
Yield: 0.49 g (90%); white solid; mp 145–148 °C.

IR (FT): 3325, 2932, 1626, 1537, 1358, 1218 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.40–7.17 (m, 10 H, H-3, H-4, H-5, H-6, $C_6H_5$, and OH), 6.17 (s, 1 H, C*H*OH), 4.66 (br s, 1 H, NH, exch.), 3.52–3.39 (m, 2 H, C*H*$_2$NH), 3.04 (m, 1 H, C$H_aH_b$Ar), 2.83 [s, 6 H, $N(CH_3)_2$], 2.79 (m, 1 H, $CH_aH_b$Ar).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 143.7 (s, C-1 of $C_6H_5$), 142.2 (s, C-1), 137.1 (s, C-2), 130.2 (d, C-6), 128.3 (d, C-3), 128.2 (d, C-3/C-5 of $C_6H_5$), 127.6 (d, C-4), 127.2 (d, C-4 of $C_6H_5$), 126.74 (d, C-5), 126.73 (d, C-2/C-6 of $C_6H_5$), 72.6 (d, CHOH), 42.0 (t, $CH_2NH_2$), 36.1 [q, $N(CH_3)_2$], 33.5 (t, *C*$H_2$Ar).

MS ($ES^-$): *m/z* (%) = 335 (40), 333 (100, $[M + Cl]^-$), 319 (1).

HRMS ($ES^-$): *m/z* $[M + Cl]^-$ calcd for $C_{18}H_{22}{}^{35}ClN_2O_2$: 333.1370; found: 333.1384.

***N*′-2-{2-[Hydroxy(4-methoxyphenyl)methyl]phenyl}ethyl-*N*,*N*-dimethylurea (18)**
Yield: 0.52 g (87%); white solid; mp 149–151 °C.

IR (FT): 3437, 2930, 1640, 1509, 1390, 1173 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 7 H, H-3, H-4, H-5, H-6, H-2/H-6 of 4-$MeOC_6H_4$, and OH), 6.87 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-$MeOC_6H_4$), 6.11 (s, 1 H, C*H*OH), 4.63 (br s, 1 H, NH, exch.), 3.81 (s, 3 H, $OCH_3$), 3.48–3.40 (m, 2 H, C*H*$_2$NH), 3.01 (m, 1 H, C$H_aH_b$Ar), 2.83 [s, 6 H, $N(CH_3)_2$], 2.79 (m, 1 H, $CH_aH_b$Ar).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.8 (s, C-4 of 4-$MeOC_6H_4$), 158.6 (s, C=O), 142.3 (s, C-1), 137.0 (s, C-1 of 4-$MeOC_6H_4$), 135.9 (s, C-2), 130.2 (d, C-6), 128.0 (d, C-2/C-6 of 4-$MeOC_6H_4$), 127.9 (d, C-3), 127.5 (d, C-4), 126.6 (d, C-5), 113.7 (d, C-3/C-5 of 4-$MeOC_6H_4$), 72.3 (d, CHOH), 55.2 (q, $OCH_3$), 41.9 (t, $CH_2NH_2$), 36.1 [q, $N(CH_3)_2$], 33.3 (t, *C*$H_2$Ar).

MS ($ES^-$): *m/z* (%) = 365 (38), 363 (100, $[M + Cl]^-$), 349 (1).

HRMS ($ES^-$): *m/z* $[M + Cl]^-$ calcd for $C_{19}H_{24}{}^{35}ClN_2O_3$: 363.1475; found: 363.1480.

***N*′-2-(2-Deuteriophenyl)ethyl-*N*,*N*-dimethylurea (19)**
Yield: 0.34 g (98%); white solid; mp 89–91 °C (Lit.[16a], undeuterated analogue mp 81–82 °C; Lit.[16b] mp 98 °C).

IR (FT): 3337, 2929, 1634, 1539, 1357, 1231 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 4 H, H-3, H-4, H-5, H-6), 4.46 (br s, 1 H, NH, exch.), 3.49 (t, *J* = 7 Hz, 2 H, C*H*$_2$NH), 2.85 [s, 6 H, $N(CH_3)_2$], 2.83 (t, *J* = 7 Hz, 2 H, C*H*$_2$Ar).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C=O), 139.4 (s, C-1), 128.8 (d, C-5), 128.54 (d, C-3), 128.52 (seen as three lines, 1:1:1, because of coupling to D, C-2), 128.4 (d, C-6), 126.3 (d, C-4), 42.1 (t, $CH_2NH$), 36.4 (t, *C*$H_2$Ar), 36.0 [q, $N(CH_3)_2$].

MS (EI): *m/z* (%) = 193 (90, $[M]^+$), 148 (28), 101 (93), 72 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{15}DN_2O$: 193.1325; found: 193.1329.

***N*′-Ethyl-*N*′-2-(2-ethylphenyl)ethyl-*N*,*N*-dimethylurea (20)**
Yield: 0.39 g (86%); yellow oil.

IR (FT): 2965, 1646, 1489, 1354, 1230 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.12–7.02 (m, 4 H, H-3, H-4, H-5, H-6), 3.20 (t, *J* = 7 Hz, 2 H, $ArCH_2CH_2N$), 3.13 (q, *J* = 7 Hz, 2 H,

$CH_3CH_2N$), 2.77 (t, $J$ = 8 Hz, 2 H, $ArCH_2CH_2N$), 2.73 [s, 6 H, $N(CH_3)_2$], 2.62 (q, $J$ = 7 Hz, 2 H, $ArCH_2CH_3$), 1.16 (t, $J$ = 7 Hz, 3 H, $CH_3CH_2N$), 1.04 (t, $J$ = 7 Hz, 3 H, $ArCH_2CH_3$).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 165.2 (s, C=O), 142.2 (s, C-1), 137.1 (s, C-2), 129.7 (d, C-6), 128.4 (d, C-3), 126.5 (d, C-4), 125.8 (d, C-5), 48.9 (t, $ArCH_2CH_2N$), 43.5 (t, $CH_3CH_2N$), 38.6 [q, $N(CH_3)_2$], 31.2 (t, $ArCH_2CH_2N$), 25.4 (t, $ArCH_2CH_3$), 15.5 (q, $ArCH_2CH_3$), 13.3 (q, $CH_3CH_2N$).

MS (ES): *m/z* (%) = 519 (100, $[2 M + Na]^+$), 312 (50, $[M + MeCNNa]^+$), 287 (5, $[M + K]^+$), 271 (23, $[M + Na]^+$), 249 (15, $[MH]^+$).

HRMS (ES): *m/z* $[MH]^+$ calcd for $C_{15}H_{25}N_2O$: 249.1967; found: 249.1959.

### *N*′-2-(3-Bromophenyl)ethyl-*N*,*N*-dimethylurea (22)

The procedure was identical to that described for the synthesis of **2** except that it involved stirring a mixture of **21** (5.00 g, 25.1 mmol), DMCC (3.44 g, 32.1 mmol), and $Et_3N$ (3.56 g, 35.3 mmol) in $CH_2Cl_2$ (30 mL) under reflux for 1 h. Following workup, the crude product was purified by crystallisation from a mixture of hexane and $Et_2O$ (3:1 by volume) to give pure **22**; yield: 6.65 g (98%); white crystalline solid; mp 62–64 °C.

IR (FT): 3337 2928, 1635, 1538, 1356, 1230, 1071 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 2 H, H-2, H-4), 7.20–7.13 (m, 2 H, H-5, H-6), 4.42 (br s, 1 H, NH, exch.), 3.47 (app q, $J$ = 7.0 Hz, 2 H, $CH_2NH$), 2.88 [s, 6 H, $N(CH_3)_2$], 2.80 (t, $J$ = 7.0 Hz, 2 H, $CH_2Ar$).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.2 (s, C=O), 141.9 (s, C-1), 131.9 (d, C-2), 130.1 (d, C-4), 129.4 (d, C-6), 127.5 (d, C-5), 122.5 (s, C-3), 41.9 (t, $CH_2NH$), 36.2 [q, $N(CH_3)_2$], 36.1 (t, $CH_2Ar$).

MS ($ES^+$): *m/z* (%) = 272 ($[M^{81}Br]^+$, 100), 270 ($[M^{79}Br]^+$, 98), 227 (12), 225 (14).

HRMS ($ES^+$): *m/z* $[M]^+$ calcd for $C_{11}H_{15}{}^{79}BrN_2O$: 270.0368; found: 270.0359.

### Lithiation and Substitution of *N*′-2-(3-Bromophenyl)ethyl-*N*,*N*-dimethylurea (22)

The procedure was identical with that described for the bromine–lithium exchange of **13** except that it involved **22** (0.36 g, 1.33 mmol) and the reaction time was varied. Following workup the crude product was purified by column chromatography (silica gel; $Et_2O$) to give the pure products **7** (13–85%) and **23** (13–58%). Product **7** was consistent in all respect with the one produced by direct lithiation of **2** followed by reaction with benzophenone.

### *N*′-2-[3-(Hydroxydiphenylmethyl)phenyl]ethyl-*N*,*N*-dimethylurea (23)

Yield: 0.065–0.29 g (13–58%); white solid; mp 174–176 °C.

IR (FT): 3348, 2930, 1634, 1532, 1357, 1219, 1032 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.25–7.13 (m, 12 H, 2 $C_6H_5$, H-5, and OH), 7.12 (s, 1 H, H-2), 7.01–6.99 (m, 2 H, H-4, H-6), 4.20 (br s, 1 H, NH, exch.), 3.35 (app q, $J$ = 7 Hz, 2 H, $CH_2NH$), 2.69 [s, 6 H, $N(CH_3)_2$], 2.68 (t, $J$ = 7 Hz, 2 H, $CH_2Ar$).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C=O), 147.2 (s, C-3), 146.9 (s, C-1 of 2 $C_6H_5$), 139.2 (s, C-1), 128.2 (d, C-5), 128.0 (d, C-2), 127.95 (d, C-3/C-5 of 2 $C_6H_5$), 127.90 (d, C-2/C-6 of 2 $C_6H_5$), 127.4 (d, C-4), 127.3 (d, C-4 of 2 $C_6H_5$), 126.2 (d, C-6), 81.9 (s, COH), 42.0 (t, $CH_2NH$), 36.5 (t, $CH_2Ar$), 36.0 [q, $N(CH_3)_2$].

MS ($ES^+$): *m/z* (%) = 375 ($[M + H]^+$, 4), 357 ($[M – OH]^+$, 80), 193 (100), 142 (10), 104 (18).

HRMS ($ES^+$): *m/z* calcd for $C_{24}H_{25}N_2O$ ($[M – OH]^+$), 357.1967; found, 357.1978.

### *N*′-(Substituted Phenyl)-*N*,*N*-dimethylureas 26 and 27

The procedure was identical with that described for the synthesis of **2** except that a stirred mixture of **24** or **25** (63.75 mmol), DMCC (8.75 g, 81.36 mmol), $Et_3N$ (9.05 g, 89.44 mmol) in $CH_2Cl_2$ (50 mL) was heated under reflux for 1 h. Following workup the crude product was purified by column chromatography (silica gel; $Et_2O$) to give pure products.

### *N*′-(3-Phenylpropyl)-*N*,*N*-dimethylurea (26)

Yield: 12.36 g (94%); white crystals; mp 72–74 °C.

IR (FT): 3374, 2934, 1630, 1496, 1379, 1245 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.17–7.14 (m, 2 H, H-3, H-5), 7.0–7.05 (m, 3 H, H-2, H-4, H-6), 4.61 (br s, 1 H, NH, exch.), 3.15 (t, $J$ = 7.4 Hz, 2 H, $CH_2NH$), 2.71 [s, 6 H, $N(CH_3)_2$], 2.54 (t, $J$ = 7.4 Hz, 2 H, $CH_2Ph$), 1.74 (pent, $J$ = 7.4 Hz, 2 H, $CH_2CH_2CH_2$).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.5 (s, C=O), 141.9 (s, C-1), 128.38 (d, C-3/C-5), 128.36 (d, C-2/C-6), 125.8 (d, C-4), 40.7 (t, $CH_2NH_2$), 36.0 [q, $N(CH_3)_2$], 33.5 (t, $CH_2Ph$), 31.9 (t, $CH_2CH_2CH_2$).

MS (EI): *m/z* (%) = 206 ($[M]^+$, 47), 162 (49), 117 (49), 102 (47), 91 (69), 72 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{12}H_{18}N_2O$: 206.1419; found: 206.1418.

### *N*′-(4-Phenylbutyl)-*N*,*N*-dimethylurea (27)

Yield: 12.63 g (90%); yellow oil.

IR (FT): 3340, 2931, 1617, 1453, 1377, 1234 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.17–7.13 (m, 2 H, H-3, H-5), 7.06–7.03 (m, 3 H, H-2, H-4, H-6), 4.72 (br s, 1 H, NH, exch.), 3.10 (app q, $J$ = 7.6 Hz, 2 H, $CH_2NH$), 2.74 [s, 6 H, $N(CH_3)_2$], 2.51 (t, $J$ = 7.6 Hz, 2 H, $CH_2Ph$), 1.53 (m, 2 H, $CH_2CH_2Ph$), 1.42 (m, 2 H, $CH_2CH_2NH_2$).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.7 (s, C=O), 142.3 (s, C-1), 128.3 (d, C-3/C-5), 128.2 (d, C-2/C-6), 125.7 (d, C-4), 40.7 (t, $CH_2NH_2$), 36.1 [q, $N(CH_3)_2$], 35.6 (t, $CH_2Ph$), 33.0 (t, $CH_2CH_2NH_2$), 28.7 (t, $CH_2CH_2Ph$).

MS (EI): *m/z* (%) = 220 ($[M]^+$, 54), 175 (54), 146 (15), 130 (35), 116 (94), 104 (90), 91 (100), 72 (97).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_{20}N_2O$: 220.1576; found: 220.1580.

### Lithiation and Substitution of *N*′-(ω-Phenylalkyl)-*N*,*N*-dimethylureas 26 and 27

The procedure was identical with that described for lithiation and substitution of **2** except involving **26** or **27** (2.60 mmol), with benzophenone (0.47 g, 2.60 mmol) as the electrophile and carried out at 0 or 20 °C. Following workup, the crude product was purified by column chromatography (silica gel; $Et_2O$) to give the pure products **28** or **29**.

### *N*′-(4-Hydroxy-3,4,4-triphenylbutyl)-*N*,*N*-dimethylurea (28)

Yield: 0.86–0.89 g (85–89%); white solid; mp 229–231 °C.

IR (FT): 3349, 2928, 1636, 1492, 1360, 1221 $cm^{-1}$.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.53–6.91 (m, 16 H, 3 $C_6H_5$ and OH), 4.00 (br s, 1 H, NH, exch.), 3.73 (dd, $J$ = 2.7, 11 Hz, 1 H, CH), 3.14 (m, 1 H, $CH_aH_bNH$), 3.03 (m, 1 H, $CH_aH_bNH$), 2.61 [s, 6 H, $N(CH_3)_2$], 2.06–1.92 (m, 2 H, $CH_2CH$).

$^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 158.1 (s, C=O), 145.9, 145.8 (2 s, C-1 of 2 $C_6H_5$), 140.0 (s, C-1), 130.5, 128.4 (2 d, C-3/C-5 of 2 $C_6H_5$), 128.0, 127.7 (2 d, C-2/C-6 of 2 $C_6H_5$), 126.9 (d, C-3/C-5), 126.7 (d, C-2/C-6), 126.2 (d, C-4 and C-4 of one $C_6H_5$), 125.7 (d, C-4 of other $C_6H_5$), 81.0 (s, C–OH), 52.6 (d, CH), 40.2 (t, $CH_2NH$), 36.0 [q, $N(CH_3)_2$], 31.1 (t, $CH_2CH$).

MS (EI): *m/z* (%) = 370 (5, $[M – H_2O]^+$), 325 (28), 269 (30), 207 (53), 194 (90), 182 (93), 152 (46), 105 (100), 77 (97).

HRMS (EI): *m/z* [M – $H_2O$]$^+$ calcd for $C_{25}H_{26}N_2O$: 370.2045; found: 370.2034.

**_N_′-(2-Hydroxy-2,2-diphenylethyl)-_N_′-methyl-_N_-(4-phenylbutyl)urea (29)**
Yield: 0.93 g (89%); yellow oil.

IR (FT): 3348, 2934, 1601, 1543, 1318, 1217 cm$^{-1}$.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 1, 8 Hz, 4 H, H-2 and H-6 of 2 $C_6H_5$), 7.18–7.03 (m, 11 H, H-2, H-3, H-4, H-5, H-6, and H-3/H-4/H-5 of 2 $C_6H_5$), 6.05 (s, 1 H, OH, exch.), 4.34 (br s, 1 H, NH, exch.), 3.98 (s, 2 H, C$H_2$COH), 3.11 (app q, *J* = 7.6 Hz, 2 H, C$H_2$NH), 2.51 (t, *J* = 7.6 Hz, 2 H, C$H_2$Ph), 2.17 (s, 3 H, $NCH_3$), 1.51 (m, 2 H, C$H_2$$CH_2$Ph), 1.39 (m, 2 H, C$H_2$$CH_2$NH).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 160.7 (s, C=O), 145.8 (s, C-1 of 2 $C_6H_5$), 142.2 (s, C-1), 128.4 (d, C-3/C-5), 128.3 (d, C-2/C-6), 128.0 (d, C-3/C-5 of 2 $C_6H_5$), 126.9 (d, C-4 of 2 $C_6H_5$), 126.6 (d, C-2/C-6 of 2 $C_6H_5$), 125.8 (d, C-4), 78.6 (s, COH), 61.0 (t, *C*$H_2$COH), 40.9 (t, $CH_2$NH), 36.9 (t, *C*$H_2$Ph), 35.5 (q, $NCH_3$), 29.8 (t, *C*$H_2$$CH_2$$NH_2$), 28.5 (t, *C*$H_2$$CH_2$Ph).

MS (EI): *m/z* (%) = 403 ([M + H]$^+$, 100), 385 (98), 305 (25), 234 (25), 210 (59), 191 (68).

HRMS (EI): *m/z* [M]$^+$ calcd for $C_{26}H_{31}N_2O_2$: 403.2386; found: 403.2402.

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