One-pot synthesis of substituted isoindolin-1-ones *via* lithiation and substitution of *N*′-benzyl-*N*,*N*-dimethylureas†

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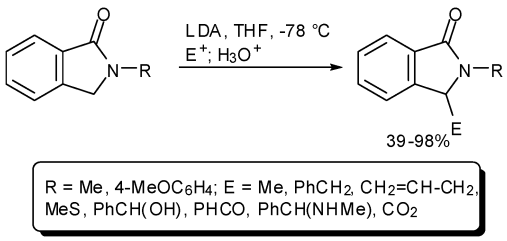
Lithiation of various *N*′-benzyl-*N*,*N*-dimethylureas with *t*-BuLi (3.3 mole equivalents) in anhydrous THF at 0 °C followed by reactions with various electrophiles afforded the corresponding 3-substituted isoindolin-1-ones in high yields.

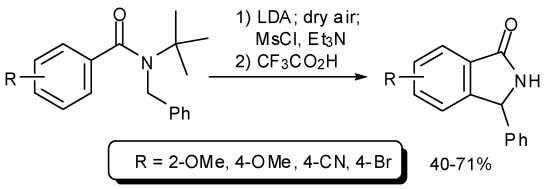
Although the isoindolinone skeleton was not commonly encountered in the past, in recent years there has been a great deal of interest in such compounds since they represent the core unit of numerous naturally occurring substances.[1] Also, several members belonging to this family have shown interesting biological properties.[2]

Several methods are available for the synthesis of isoindolinones,[3,4] based on the use of Grignard reagents,[5] Diels–Alder reactions,[6] Wittig reagents,[7] reduction processes,[8] rearrangement processes[9] and photochemical reactions.[10] However, such methods generally require multiple reaction steps, and are often unsatisfactory, in yield and/or generality. In recent years a number of new approaches have been developed for the synthesis of substituted isoindolines, of which the most generally useful involve palladium-catalysed reactions[11] or lithiation procedures.[12–15]

In particular, among the methods involving lithiation two useful approaches to the synthesis of 2,3-dihydroisoindolin-1-ones have been reported (Schemes 1 and 2).[12a,13a] One method simply involves lithiation of a preformed 2,3-dihydroisoindol-l-one ring system at the 3-position followed by treatment with an electrophile (Scheme 1).[12a] Clearly, the general utility of this approach depends on the availability of appropriately substituted analogues of the dihydroisoindolin-1-one ring system.



Scheme 1 Lithiation and substitution of 2,3-dihydroisoindol-1-ones.



Scheme 2 Lithiation and cyclization of *N*-*tert*-butyl-*N*-benzylbenzamides.

The other, potentially more useful, approach involves generation of the isoindolin-1-one ring system during the lithiation step. For example, lithiation of *N*-*tert*-butyl-*N*-benzylbenzamides gives intermediates that cyclise to form a dearomatised species. Oxidation to re-aromatise the system and treatment with trifluoroacetic acid to remove the *tert*-butyl group gives the corresponding 2,3-dihydroisoindolin-1-ones (Scheme 2).[13a] However, this approach gives more modest yields, requires the additional step to remove the *t*-Bu group, and also involves incorporating the eventual C-3 substituent into the starting material, which limits the generality.

Clayden and Menet have improved the yield of 2,3-dihydroisoindolin-1-ones using 2-methoxy amides as the starting materials; in this case the methoxy group acts as a leaving group, avoiding the need for an oxidation step.[13a] However, this approach still requires an additional step to remove the *t*-Bu group.

Based on our own experience in the use of lithium reagents in organic synthesis and in directed lithiation reactions,[16] we felt that it ought to be possible to develop a general, simple and efficient procedure for the synthesis of 2,3-dihydroisoindolin-1-ones. We now report a new method that involves both cyclization to give the ring system and incorporation of a C-3 substituent in a single synthetic step *via* lithiation and substitution of *N*′-benzyl-*N*,*N*-dimethylureas.

Simple lithiation and substitution of *N*′-benzyl-*N*,*N*-dimethylureas have been reported previously.[17,18] For example, we have shown that lithiation of *N*′-(2-methoxybenzyl)-*N*,*N*-dimethylurea (**1**) with two equivalents of *t*-BuLi (Scheme 3) at −20 °C followed by reaction with 4-anisaldehyde gave **2** (49% yield) and **3** (40%).[18b]

Recently, we found that when the reaction was carried out at 0 °C rather than at −20 °C it produced lower yields of **2** and **3**, along with some residual **1** and a small amount of a new product, **4**, the structure of which was confirmed by X-ray crystallography (Fig. 1).[19] Compound **4** would be expected to be formed as a pair of racemic diastereoisomers; however, its NMR spectra showed what appeared to be a single set of signals, indicating that the isolated product was a single racemic diastereoisomer.[20] It is possible that a small amount

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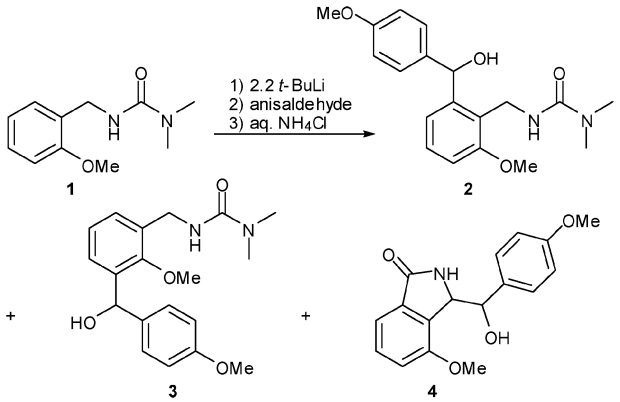
† Electronic supplementary information (ESI) available: Experimental procedure; characterization data; NMR spectra and X-ray information for representative compounds. CCDC 737415. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b926983e



Scheme 3 Lithiation and substitution of **1**.

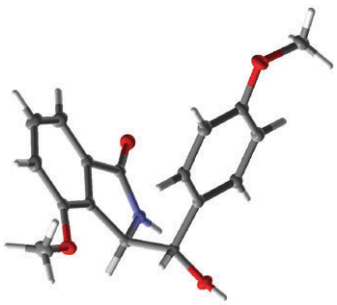


Fig. 1 X-Ray crystal structure of **4**.

of the other diastereoisomer was formed but washed out during the purification process. Indeed, the ^{1}H NMR spectrum of the crude product showed the presence of an additional minor diastereoisomer. The X-ray crystallography of compound **4** confirmed the crystal structure as (*R**)-3-((*S**)-hydroxy(4-methoxyphenyl)methyl)-4-methoxyisoindolin-1-one (Fig. 1).[19]

Formation of **2** and **3** presumably involves lithium intermediates **5** and **6**, respectively (Fig. 2), while **4** would arise by cyclization of **5** to give **7**, followed by further lithiation to give **8** (Fig. 2), which on reaction with 4-anisaldehyde gives **4**. Therefore, it appeared likely that the yield of **4** could be increased by the use of a larger quantity of *t*-BuLi.

Indeed, lithiation of **1** with *t*-BuLi (3.3 mole equivalents) in anhydrous THF at 0 °C for 6 h, followed by treatment with 4-anisaldehyde (1.1 mole equivalents), gave **4** in high yield. While an increased yield of **4** was expected, the disappearance of **3** was a surprise. It would appear that at 0 °C, not only does

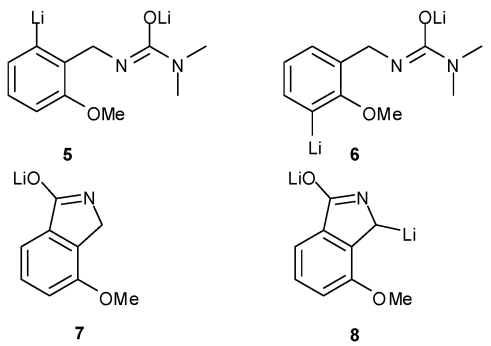
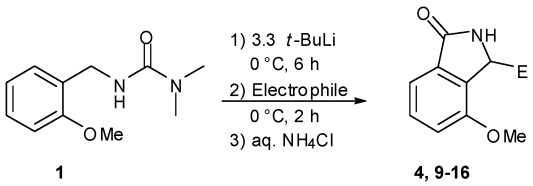


Fig. 2 Structures of **5**–**8**.



Scheme 4 Lithiation, substitution and cyclization of **1**.

5 cyclise to give **7**, but **6** is also in equilibrium with **5**, allowing its eventual conversion into **7** and then **8**.

This fortuitous finding appeared to offer potential as a general synthesis and the same lithiation procedure was therefore used with a range of different electrophiles. Following work-up of the reaction mixtures the crude products were triturated and/or washed with diethyl ether to give pure products **4** and **9–16** (Scheme 4) in high yields (Table 1).

Compounds **9** and **10** would be expected to be formed as pairs of racemic diastereoisomers; however, their NMR spectra each showed what appeared to be just one set of signals, indicating that the isolated product in each case was a single racemic diastereoisomer, and the X-ray crystallography of both compounds confirmed the crystal structures as the (*R**)-3-(*S**)- isomers. However, although these compounds were isolated in high yields, again it seems likely that small amounts of the other diastereoisomers were formed but washed out during purification of the crude products by washing with diethyl ether.

From the results recorded in Table 1 it was clear that the reaction with a variety of electrophiles is a general process, producing 3-substituted 4-methoxyisoindolin-1-ones **4** and **9–16** in high yields.

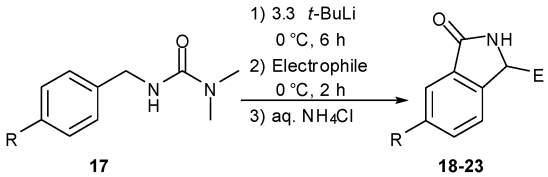
The generality of the process was tested further using other ring-substituted *N*′-benzyl-*N*,*N*-dimethylureas **17** (Scheme 5). Each substrate was lithiated according to the standard procedure, and then treated with various electrophiles. Following work-up as described above pure products **18–23** were obtained in high yields (Table 2).

In conclusion, we have developed a novel, simple, efficient and high yielding procedure for the synthesis of isoindolin-1-ones in a one-step reaction. It allows easy incorporation of a range of substituents on the initial benzene ring and incorporation of a range of substituents derived from the electrophiles used. Isolation of the pure products is also extremely easy, involving simple trituration and/or washing of the crude product after work-up. Therefore, this promises to be a very useful new

Table 1 Synthesis of various 3-substituted 4-methoxyisoindolin-1-ones **4** and **9–16**

Product	Electrophile	E	Yield[a] (%)
4[b]	4-MeOC_6H_4CHO	4-MeOC_6H_4CH(OH)	81
9[b]	PhCHO	PhCH(OH)	80
10[b]	BuCOMe	BuC(OH)Me	78
11	Ph_2CO	Ph_2C(OH)	81
12	$(CH_2)_5CO$	$(CH_2)_5C$(OH)	78
13	H_2O	H	82
14	MeI	Me	79
15	EtI	Et	84
16	BuBr	Bu	72

[a] Yield of pure product. [b] The X-ray crystallography confirmed the crystal structure as (*R**)-3-(*S**)- isomer.



Scheme 5 Synthesis of isoindolin-1-ones **18–23**.

Table 2 Synthesis of various 3-substituted isoindolin-1-ones **18–23**

Product	R	Electrophile	E	Yield[a] (%)
18[21]	H	EtI	Et	77
19	H	Ph_2CO	$Ph_2C(OH)$	74
20	Me	Ph_2CO	$Ph_2C(OH)$	85
21	Me	$(CH_2)_5C{=}O$	$(CH_2)_5C(OH)$	72
22	OMe	MeI	Me	76
23	OMe	BuBr	Bu	77

[a] Yield of pure product.

approach for the synthesis of such compounds. We are currently conducting further work in order to understand the stereochemical consequences of the reactions.

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19 Crystal data for **4**: colourless, $C_{17}H_{17}NO_4$, T = 293(2) K, centrosymmetric, space group *P-1*, a = 7.5240(3) Å, b = 9.4100(3) Å, c = 11.9960(5) Å, α = 83.877(2)°, β = 77.311(2)°, γ = 68.559(2)°, 5071 reflections collected, 3513 independent reflections, R = 0.0570, wR = 0.1277, R_{int} = 0.0334. CCDC 737415.

20 Analytical data for **4**: mp: 199–201 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.77 (s, exch., 1H), 7.31 (app. t, J = 8 Hz, 1H), 7.16 (d, J = 8 Hz, 1H), 6.93 (d, J = 8 Hz, 1H), 6.89 (d, J = 9 Hz, 2H), 6.58 (d, J = 9 Hz, 2H), 5.73 (d, J = 3 Hz, exch., 1H), 5.39 (app. t, J = 3 Hz, 1H), 4.89 (d, J = 3 Hz, 1H), 3.97 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7, 158.4, 155.0, 134.9, 131.6, 131.5, 130.1, 128.3, 114.9, 113.6, 112.5, 71.6, 61.5, 56.0, 55.1; HRMS (CI): calcd for $C_{17}H_{18}NO_4$ [MH$^+$] 300.1230; found 300.1231; FT (FT): ν_{max} 3304, 2872, 1677, 1604, 1512, 1273, 1048 cm^{-1}.

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