Rapid Synthesis of 4-Benzyl-4-aminopiperidines by Addition of Grignard Reagents to *N*-(1-Boc-Piperidin-4-ylidene)-*tert*-butanesulfinyl Imine

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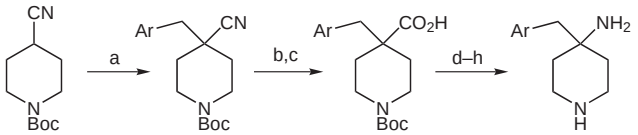
Abstract: Two concise methods for the synthesis of aryl-substituted 4-benzyl-4-aminopiperidines by the addition of benzyl Grignard reagents to sulfinyl imines were developed. The hydration-prone *tert*-butanesulfinyl imine derived from *N*-Boc-piperidin-4-one was trapped as a stable α-(*N*-sulfinyl)aminonitrile, which underwent displacement of the nitrile on treatment with Grignard reagents. Alternatively, benzyl and allyl Grignards added to the sulfinyl imine in situ in a one-pot procedure. Acid deprotection provided various substituted 4-benzyl-4-aminopiperidines.

Key words: heterocycles, piperidines, imines, Grignard reactions, tandem reactions

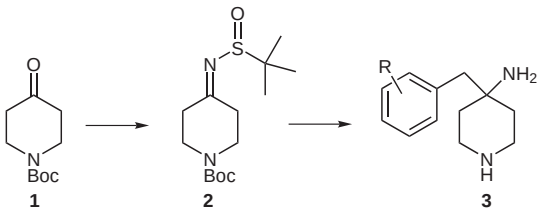
The utility of 4-aminopiperidines as scaffolds in biologically active synthetic compounds has long been apparent.[1] Our particular need for 4-benzyl-4-aminopiperidines with various aryl substitution patterns prompted a search for suitable synthetic approaches, and showed that relatively few literature methods currently exist for the synthesis of such species. Of these, the most versatile employs a Curtius rearrangement as the key transformation.[1c] Other procedures involve the Ritter reaction of 4-substituted piperidin-4-ols[2] or the addition of organometallic reagents to the imines formed from the condensation of piperidin-4-ones with anilines[3] or benzylamines.[4]



Scheme 1 *Reagents and conditions*: (a) LDA, $ArCH_2Br$; (b) 6 M HCl, reflux; (c) Boc_2O, Et_3N, CH_2Cl_2, r.t.; (d) *i*-BuOCOCl, Et_3N, THF, –15 °C; (e) NaN_3, THF–H_2O, r.t.; (f) 90 °C, toluene, then HCl (g) Boc_2O, 2 M NaOH, r.t.; (h) 4 M HCl in dioxane, MeOH, r.t.

Initially we found that a synthesis based on the Curtius rearrangement, related to a recently published procedure,[1c] was an effective route to 4-benzyl-4-aminopiperidines (Scheme 1). Typical yields for the sequence were 28–39%, with the Curtius rearrangement itself being the least efficient step (50–53%). Although amenable to multigram scale up, the introduction of the substituted aryl group at an early stage in this multi-step synthesis made it less suitable for the rapid preparation[5,6b,d] of a wide range of substituted 4-benzyl-4-aminopiperidines, and we therefore sought a more direct route.

The development of organometallic additions to *N*-(*tert*-butanesulfinyl)imines by the groups of Ellman and others is well known,[6] with the examples based on *N*-cyclohexylidene sulfinamides of particular relevance to this work.[6c] Here, we describe the application of the sulfinyl imine addition methodology to the synthesis of 4-benzyl-4-aminopiperidines **3** from *N*-Boc-piperidin-4-one **1** (Scheme 2). This starting material was chosen since both the *N*-Boc and *N*-sulfinamide protecting groups were anticipated to be easily removed by treatment with acid in a single final synthetic step.



Scheme 2

Our initial strategy was to follow the procedure reported by Ellman, whereby *N*-cyclohexylidene sulfinamide intermediates were first prepared.[6c] Although observed to be susceptible to hydrolysis on silica gel, these sulfinyl imines could nonetheless be isolated and purified in good yield. In the case of sulfinyl imine **2**, immediate use of a crude sample of the worked-up reaction did lead to reaction with benzyl Grignard reagents. However, attempts to isolate **2** gave predominantly the hydrate **4**[7] as a white solid following aqueous workup and trituration with hexane (Scheme 3). The identity of **4** was assigned by mass spectrometry and NMR, in particular the presence of a characteristic quaternary carbon resonance at ca. δ = 80 ppm (piperidine C-4) and the presence of a readily exchangeable proton (δ = 5.52 ppm; OH) in the ^1H spectrum determined in DMSO-d_6. The facile hydration of **2** parallels the known propensity of piperidin-4-ones to form hydrates.[8]

To avoid this unproductive transformation we attempted to trap the sulfinyl imine **2** through a Strecker reaction with trimethylsilylcyanide before workup.[9] A stable

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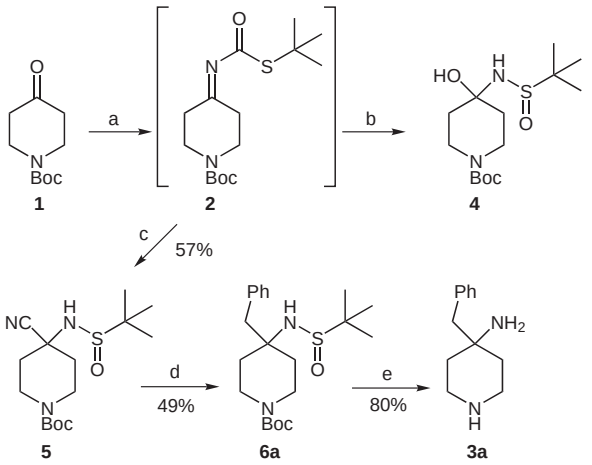


Scheme 3 *Reagents and conditions*: (a) *tert*-butanesulfinamide, $Ti(OEt)_4$, THF, reflux; (b) aqueous workup; c) TMSCN, THF, reflux; (d) BnMgCl, THF, reflux; (e) 4 M HCl in dioxane, MeOH, r.t.

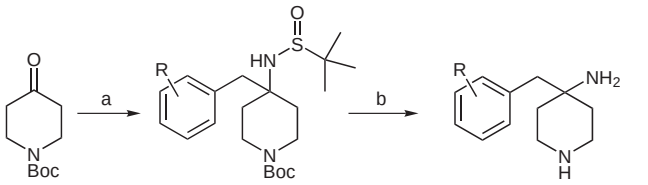
α-(*N*-sulfinyl)aminonitrile **5** was formed in 57% yield (Scheme 3),[13] which could be stored indefinitely at room temperature.

The reactions of N-aryl and N-alkyl α-aminonitriles with organomagnesium or organolithium species leading to displacement of the nitrile group through in situ formation of reactive imines have been described.[10] By analogy, reaction of α-(*N*-sulfinyl)aminonitrile **5** with Grignard reagents was expected to give the required 4-substituted-4-(*tert*-butanesulfinamido)piperidines. Indeed, treatment of **5** with two equivalents of benzylmagnesium chloride in refluxing tetrahydrofuran afforded the adduct **6a** in 49% yield. To our knowledge, this is the first time this transformation has been demonstrated for α-(*N*-sulfinyl)aminonitriles. The sulfinamide **6a** was deprotected by treatment with acid to give 4-benzyl-4-aminopiperidine (**3a**; 80%).

Although an effective means of overcoming the unwanted hydration, an extra step had been added to the process. Therefore an attempt was made to react the sulfinyl imine **2** directly in situ with benzylmagnesium chloride. Although alkyl Grignard reagents containing β-hydrogen atoms react with titanium alkoxides to form low-valent titanium reagents,[11] this was not anticipated to be a problem for benzylic systems. The compatibility of Grignard reagents with titanium alkoxides in the context of intramolecular chelate-controlled additions has been previously demonstrated.[12] Gratifyingly, addition of five equivalents of benzylmagnesium chloride to the reaction mixture after formation of the sulfinylimine yielded the sulfinamide **6a**[13] in 39% yield after chromatography. This one-pot procedure compared favourably with the yield for the two-step procedure via the nitrile **5** (28%). The use of only 2.5 equivalents of Grignard reagent reduced the yield (23%), while an improvement was seen when ten equivalents were added (50%).

The protocol was successfully extended to a range of substituted benzylic Grignard reagents bearing both electron-donating and electron-withdrawing substituents (Table 1).[13]

Table 1 In situ Reaction of Sulfinimine **2** with Benzyl Grignards



Entry[a]	R	Yield of **6** (%)[b]	Yield of **3** (%)[b]
a	H	39	80
b	2-Cl	42	88
c	3-OMe	48	88
d	3-OCF_3	35	89
e	2,4-Cl	57	77
f	2-Cl-4-F	32	86
g	2,6-Cl	66	76
h	2-OCF_3	39	80
i	2,5-Cl	59	84
j	2,3-Cl	55	88
k	4-Ph	57	60

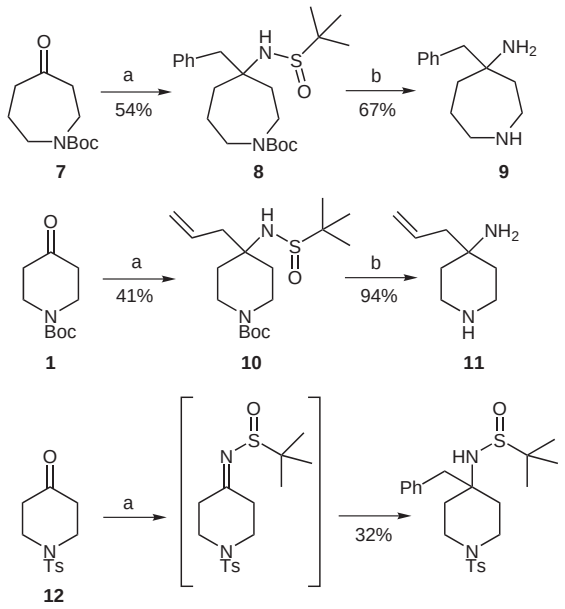
[a] Reagents and conditions: (a) *tert*-butylsulfinamide, $Ti(OEt)_4$ (2 equiv), THF, reflux; then Grignard reagent (5 equiv), THF, r.t.; (b) 4 M HCl in dioxane, MeOH, r.t.

[b] Yields are unoptimised and refer to isolated materials, homogeneous by NMR analysis, TLC and/or HPLC, and characterised by NMR and MS.

The 4-benzyl-4-(*tert*-butanesulfinamido)piperidines **6a**–**k** thus prepared were deprotected under acidic conditions as anticipated to provide the required diamines **3a**–**k** in a simple two-pot procedure from readily available *N*-Boc-piperidin-4-one. The overall yields of the diamines were moderate (28–50%) but compared well with typical yields (29–39%) from the Curtius route (Scheme 1). Additionally, the considerable reduction in the number of synthetic transformations made this route preferable for the construction of a diverse range of 4-benzyl-4-aminopiperidine scaffolds.

Having developed successful methodology for the concise synthesis of 4-benzyl-4-aminopiperidines, the scope of the reaction with other substrates and organometallics was tested. The ring-expanded *tert*-butyl 4-oxoazepane-1-carboxylate **7** gave protected amine **8** in 54% yield under the standard reaction conditions and was deprotected to the 4-benzyl-4-aminoazepane (**9**; Scheme 4). No desired product could be detected when the sulfinyl imine **2** was treated in situ with a range of other Grignard reagents. This contrasts with the results of Ellman and colleagues,[6c] where many organometallics were found to be effective nucleophiles in reactions with the sulfinyl imines derived from cyclohexanones. However, the procedure was successful when allylmagnesium chloride was used, giving

10 with similar efficiency (41%) to the benzylic examples (Scheme 4). Variation of the N-protecting group was tested using *N*-tosylpiperidin-4-one (**12**). A similar reactivity profile was observed to that of **1** in that only benzyl Grignards were found to be effective nucleophiles (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) *tert*-butylsulfinamide, $Ti(OEt)_4$, THF; then Grignard reagent, THF; (b) 4 M HCl in dioxane, MeOH, r.t.

In summary, concise procedures for the synthesis of aryl substituted 4-benzyl-4-aminopiperidines by the addition of benzyl Grignard reagents to sulfinyl imines have been developed, which show advantages over the more traditional Curtius approach in terms of the reduced number of synthetic manipulations and are competitive in overall yield. The hydration-prone *tert*-butanesulfinyl imine derived from *N*-Boc-piperidin-4-one can be trapped as a stable α-(*N*-sulfinyl)aminonitrile, which undergoes displacement of the nitrile on treatment with Grignard reagents. Alternatively, benzyl and allyl Grignards will add to the sulfinyl imine in situ in a one-pot procedure. Simple acid deprotection provides various substituted 4-benzyl-4-aminopiperidines which should prove useful scaffolds for the synthesis of biologically active compounds.

Acknowledgment

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(7) Compound **4**: ^{1}H NMR (500 MHz, DMSO): δ = 1.11 (s, 9 H), 1.39 (s, 9 H), 1.66–1.69 (m, 4 H), 3.11–3.14 (m, 2 H), 3.45–3.50 (m, 2 H), 5.30 (s, 1 H), 5.52 (s, 1 H, signal removed on addition of D_2O). ^{13}C NMR (125 MHz, DMSO): δ = 22.6, 28.1, 37.2, 38.0, 54.5, 78.5, 81.4, 153.8. MS (ES+): *m*/*z* = 343 [M + Na^+], 303 [M + H^+ – H_2O].

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(13) ***tert*-Butyl 4-Cyano-4-(*tert*-butanesulfinamido)piperidine-1-carboxylate (5)**: A solution of *N*-Boc-piperidin-4-one (**1**; 0.90 g, 4.52 mmol), *tert*-butanesulfinamide (0.58 g, 4.8 mmol) and $Ti(OEt)_4$ (1.9 mL, 9 mmol) in anhyd THF (20 mL) was refluxed under N_2 for 20 h. The red solution was cooled, TMSCN (0.66 mL, 5 mmol) was added and the solution was refluxed for 3 h. The cooled solution was diluted with brine (20 mL) and EtOAc (20 mL). The suspension was filtered through Celite, washing with further EtOAc. The filtrate was separated and the organic layer was dried (Na_2SO_4) and concentrated. Flash column chromatography, eluting with EtOAc, gave **5** as a white powder (0.851 g, 2.58 mmol, 57%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 1.46 (s, 9 H), 1.70–1.78 (m, 1 H), 1.81–1.90 (m, 1 H), 2.20–2.30 (m, 2 H), 3.15–3.25 (m, 2 H), 3.65 (br s, 1 H), 3.95–4.15 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 28.4, 36.2, 37.5, 40.0, 56.9, 80.5, 119.6, 154.2. MS (ES+): *m*/*z* = 352 [M + Na^+], 329 [M + H^+]. ***tert*-Butyl 4-Benzyl-4-(*tert*-butanesulfinamido)piperidine-1-carboxylate(6a)**; **Via Nitrile 5**: A solution of **5** (0.206 g, 0.625 mmol) and benzylmagnesium chloride (2 M

in THF, 0.70 mL, 1.4 mmol) in anhyd THF (3 mL) was refluxed under N_2 for 3 h. The cooled reaction mixture was diluted with sat. aq NH_4Cl (10 mL) and extracted with EtOAc (2 × 10 mL). The extracts were dried (Na_2SO_4) and concentrated. Flash column chromatography, eluting with EtOAc, gave **6a** as a straw-coloured oil (0.122 g, 0.309 mmol, 49%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (s, 9 H), 1.25–1.32 (m, 1 H), 1.46 (s, 9 H), 1.52–1.60 (m, 1 H), 1.72–1.80 (m, 1 H), 2.37–2.42 (m, 1 H), 2.71 (d, *J* = 13.0 Hz, 1 H), 2.94–3.15 (m, 2 H), 3.21 (d, *J* = 13.0 Hz, 1 H), 3.32 (s, 1 H), 3.72–3.95 (m, 2 H), 7.25–7.39 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.0, 24.2, 28.4, 33.7, 36.5, 39.0, 49.0, 55.6, 56.5, 79.6, 126.7, 128.2, 131.8, 135.6, 154.8. MS (ES+): *m*/*z* = 416 [M + Na^+], 395 [M + H^+].

Direct Synthesis: A solution of **1** (0.615 g, 3.09 mmol), *tert*-butylsulfinamide (0.390 g, 3.21 mmol) and $Ti(OEt)_4$ (1.26 mL, 6.00 mmol) in anhyd THF (15 mL) was refluxed under N_2 for 14 h. The solution was cooled to 0 °C and a solution of benzylmagnesium chloride (2 M in THF, 0.77 mL, 15.45 mmol) was added. After stirring for 20 h at r.t., the crude reaction mixture was absorbed onto silica gel. Flash column chromatography, eluting with EtOAc–hexane (2:1), gave **6a** (0.473 g, 1.20 mmol, 39%).

4-Benzylpiperidin-4-amine (3a): A solution of **6a** (0.094 g, 0.238 mmol) in MeOH (5 mL) and 4 M HCl–dioxane (5 mL) was stirred for 24 h. Concentration and purification by ion-exchange on an SCX-2 Isolute column, eluting with MeOH then 2 M NH_3–MeOH, gave **3a** as a yellow oil (0.036 g, 0.189 mmol, 80%). ^{1}H NMR (500 MHz, MeOD): δ = 1.38–1.43 (m, 2 H), 1.60–1.66 (m, 2 H), 2.74 (s, 2 H), 2.84–2.92 (m, 4 H), 7.21–7.32 (m, 5 H). ^{13}C NMR (125 MHz, MeOD): δ = 32.2, 38.5, 49.2, 50.8, 127.6, 129.2, 131.8, 138.2. MS (ES+): *m*/*z* (ES+) = 191 [M + H^+], 174 [M + H^+ – NH_3].