Synthesis of Secondary Amines by Reduction of α-Amidoalkylphenyl Sulfones with Sodium Acetoxyborohydride

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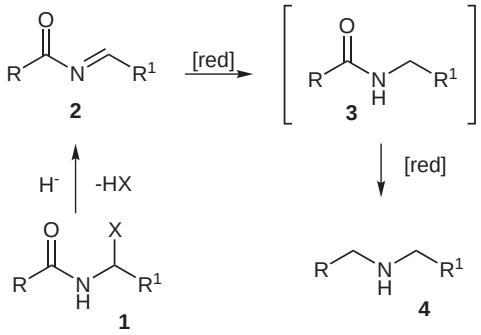
Abstract: α-Amidoalkylphenyl sulfones are stable precursors of reactive *N*-acylimines and can be fully reduced to the corresponding secondary amines using sodium acetoxyborohydride in dioxane at reflux.

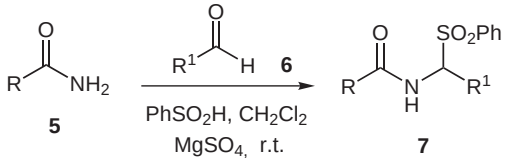
Key words: amides, amines, imines, reductions, sulfones

Secondary amines, occupy a foreground position among nitrogenous derivatives featured by a relevant biological activity.[1] N-Alkylation of primary amines would represent a direct method for the preparation of secondary amines, but overalkylation constitutes a severe drawback which practically restricts the utilization of this synthetic procedure.[2] Nucleophilic addition to imino derivatives provides an alternative and efficient entry to secondary amines.[3] This process, when a hydride ion is used as nucleophile, is often referred as a reductive amination and requires a preliminary condensation of a primary amine with an aldehyde followed by a reduction of the intermediate imine.[4] Similarly, nitrones which can be considered as imine *N*-oxides, are reduced to secondary amines using alkaline metals in various solvents.[5] Reduction of N-monosubstituted amides and peptides with hydride reagents represents a viable procedure to functionalized secondary amines. A common feature to all these synthetic approaches is the utilization of primary amines as nitrogenous derivatives for the preparation of reducible substrates. The search for alternative preparations of secondary amines, avoiding manipulation of primary amines, would be highly desirable since these derivatives are quite toxic and volatile compounds. An ideal substrate for this purpose would be readily accessible from simple precursors but also highly reactive towards reducing agents. In this context, *N*-acylimines **2** conveniently join some important properties of the amido and imino groups (Scheme 1).[6] Indeed, compounds **2** are imino derivatives endowed with an outstanding electrophilicity at the carbon-nitrogen double bond, but they also include another reducible function as the amido group. A tandem reduction of these two functions by the same reducing agent would directly afford secondary amines **4** from compound **2** probably through an amide **3** as intermediate. Although *N*-acylimines **2** are too unstable to be prepared and conveniently stored, they can be suitably formed in situ by reaction of α-amidoalkyl derivatives **1** with a basic reagent.[7] Among these derivatives, α-amidoalkylphenyl sulfones **7** have recently emerged as stable precursors of *N*-acylimines in many synthetic processes.[8]



Scheme 1

Sulfones **7** are conveniently prepared by reaction of an amide **5** with an appropriate aldehyde **6** in the presence of benzenesulfinic acid (Scheme 2, Table 1).[8a]



Scheme 2

Compounds **7** are usually obtained in good yield and can be easily purified either by crystallization or column chromatography. Conversion of sulfones **7** to secondary amines has been initially attempted using common reducing agents as $LiAlH_4$ or boranes under different conditions, but none of them gave satisfactory results. On the other hand, $NaBH_4$ is able to reduce *N*-carbamoylalkyl sulfones to the corresonding *N*-Boc amines but this hydride does not affect the amido function.[9] However, the reactivity of borohydride reagents can be suitably tuned by addition of some additives.[10] Carboxylic acids react with $NaBH_4$ giving $NaBH_n(O_2CR)_{4-n}$ species which show different reducing aptitudes, depending on the amount of acid employed.[11]

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Table 1 Synthesis and Reduction of α-Amidoalkylphenyl Sulfones with Sodium Acetoxyborohydride

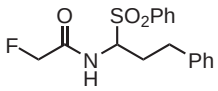
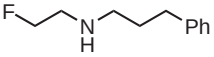
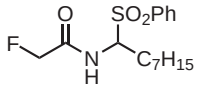
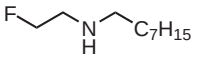
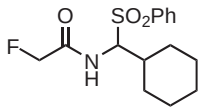
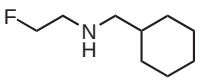
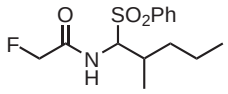
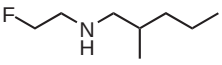
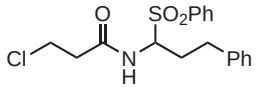
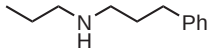
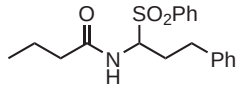
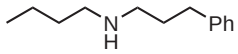
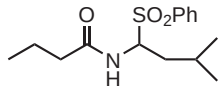
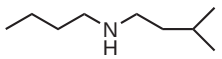
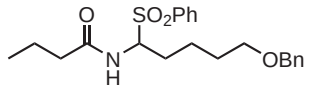
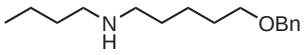
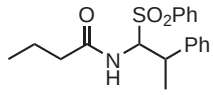
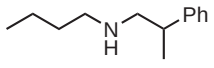
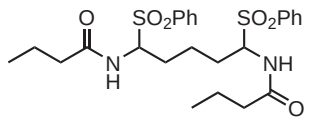
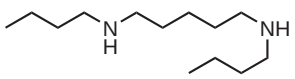
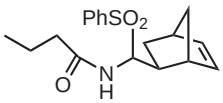
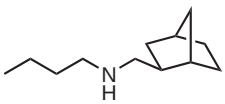
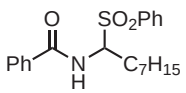
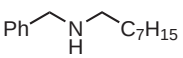
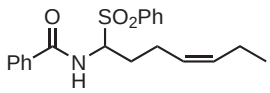
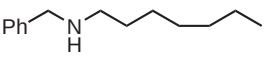
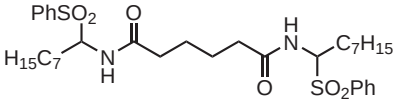
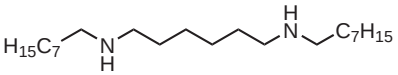
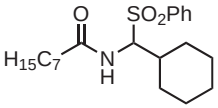
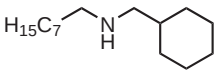
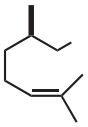
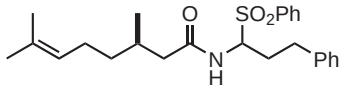
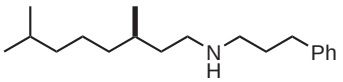
Entry	Amide R	Aldehyde R^1	Sulfone	Yield %[a]	Amine	Yield %[a]
1	FCH_2 **5a**	$PhCH_2CH_2$ **6a**	 **7a**	73	 **4a**	85[b]
2	**5a**	n-C_7H_{15} **6b**	 **7b**	82	 **4b**	86[b]
3	**5a**	c-C_6H_{11} **6c**	 **7c**	70	 **4c**	88[b]
4	**5a**	$CH_3CH_2CH_2CHCH_3$ **6d**	 **7d**	69	 **4d**	78[b]
5	$ClCH_2CH_2$ **5b**	**6a**	 **7e**	80	 **4e**	73
6	n-C_3H_7 **5c**	**6a**	 **7f**	81	 **4f**	84
7	**5c**	$(CH_3)_2CHCH_2$ **6e**	 **7g**	85	 **4g**	68
8	**5c**	$BnO(CH_2)_4$ **6f**	 **7h**	65	 **4h**	81
9	**5c**	$PhCHCH_3$ **6g**	 **7i**	78	 **4i**	75
10	**5c**	-(CH_3)- **6h**	 **7j**	96	 **4j**	87
11	**5c**	 **6i**	 **7k**	75	 **4k**	96
12	Ph **5d**	**6b**	 **7l**	97	 **4l**	91
13	**5d**	(*Z*)-EtCH=CH$(CH_2)_2$ **6j**	 **7m**	76	 **4m**	94

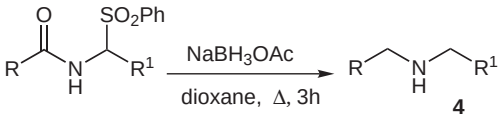
Table 1 Synthesis and Reduction of α-Amidoalkylphenyl Sulfones with Sodium Acetoxyborohydride (continued)

Entry	Amide R	Aldehyde R^1	Sulfone	Yield %[a]	Amine	Yield %[a]
14	-$(CH_2)_4$- **5e**	**6b**	 **7n**	73[c]	 **4n**	93
15	*n*-$C_{17}H_{35}$ **5f**	**6c**	 **7°**	74	 **4o**	77
16	 **5g**	**6a**	 **7p**	68	 **4p**	75

[a] Yields of pure, isolated products.
[b] Reaction mixture is heated at reflux for 1.5 h.
[c] Prepared using sodium benzenesulfinate-formic acid in THF–H_2O (3:7) and heating at 60 °C for 18 h.[8a]

The more reactive form of these reagents is $NaBH_3(O_2CR)$ obtained adding one equivalent of acid to $NaBH_4$. In particular, $NaBH_3(O_2CCH_3)$ and $NaBH_3(O_2CCF_3)$ are able to reduce nitriles and amides to the corresponding amino derivatives.[12] In addition, these reagents are expected to be basic enough to promote elimination of $PhSO_2H$ from sulfones **7** to give the corresponding *N*-acylimine **2**.

Reduction of sulfones **7** with $NaBH_3(O_2CCH_3)$ in dioxane at reflux directly affords secondary amines **4** in good yield (Scheme 3, Table 1).



7 **4**

Scheme 3

Crude amines **4** can be purified by usual column chromatography or through their conversion into hydrochloride salts.[13] Sulfones **7a**–**d** obtained from fluoroacetamide **5a** are efficiently reduced to fluoroamines **4a**–**d** in good yield[14] while chlorine atom in sulfone **7e** is removed under our conditions giving amine **4e**. This procedure can also be extended to the synthesis of diamino derivatives (Table 1, entries 10, 14). Indeed, bissulfonylamido compounds **7j**,**n** obtained from difunctional substrates such as glutaraldehyde and adipamide respectively, are reduced to the corresponding diamines **4j**,**n**. Although the reducing ability of $NaBH_3(O_2CCF_3)$ is far better than $NaBH_3(O_2CCH_3)$, the utilization of the former reagent does not significantly improve the yields of the produced amines **4**. Sulfones **7k**,**m**,**p** which include unsaturations in the molecular framework, are converted into secondary amines **4k**,**m**,**p** with concomitant reduction at the double bond (Table 1, entries 11, 13, 16). This behavior was somewhat expected since $NaBH_3(O_2CCH_3)$ is also known as a chemoselective hydroborating reagent,[15] even though in some instances double bonds are retained when nitriles and amides are reduced with $NaBH_3(O_2CCF_3)$.[16]

In conclusion, α-amidoalkylphenyl sulfones **7** can be considered stable precursors of *N*-acylimines, which are generated from them by treatment with basic reagents. Therefore, a tandem reduction of the imino and amido functions using $NaBH_3(O_2CCH_3)$ in dioxane at reflux can lead to the synthesis of secondary amines in good yields.

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(13) **Typical Reduction Procedure:** To a stirred suspension of $NaBH_4$ (10 mmol) in dry dioxane (10 mL), HOAc (10 mmol) was added dropwise in 10 min. After stirring for further 15 min, sulfone **7** (2 mmol) dissolved in dioxane (3 mL) was added and the white suspension was refluxed for 3 h. After cooling at r.t. the mixture was treated with H_2O (4 mL), extracted with $CHCl_3$ (4 × 10 mL) and the organic phase was dried over Na_2SO_4. After evaporation of the solvent the crude amine was purified by column chromatography. Alternatively the crude amine was dissolved in HCl sat. in MeOH to obtain the corresponding hydrochloride salt. MeOH was evaporated and the residue was taken up in dry Et_2O to precipitate the salt. After filtration, the salt was dissolved in 2 N NaOH (10 mL) and the free amine was extracted with $CHCl_3$ (4 × 10 mL). The organic phase was dried over Na_2SO_4 and the pure amine was recovered after evaporation of the solvent. Spectroscopic data for some representative compounds follows. Compound **4b**: oil. IR (neat): 3255 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, 3 H, *J* = 6.6 Hz), 1.10–1.57 (m, 12 H), 2.51–2.66 (m, 5 H), 2.85 (dt, 2 H, *J* = 47.6, 4.7 Hz), 4.90 (dt, 2 H, *J* = 28.2, 4.7 Hz). Compound **4h**: oil. IR (neat): 3255 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, *J* = 7.0 Hz), 1.21–1.78 (m, 10 H), 2.54–2.66 (m, 5 H), 3.47 (t, 2 H, *J* = 6.2 Hz), 4.50 (s, 2 H), 7.18–7.38 (m, 5 H). Compound **4n**: mp 52 °C. IR(nujol): 3300 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 6 H, *J* = 6.6 Hz), 1.11–1.61 (m, 32 H), 2.58 (t, 8 H, *J* = 6.6 Hz). Compound **7b**: mp 58 °C. IR (nujol): 3300, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 6.7 Hz), 1.21–1.52 (m, 10 H), 1.75–1.91 (m, 1 H), 2.22–2.38 (m, 1 H), 4.46 (dd, 1 H, *J* = 47.3, 14.6 Hz), 4.68 (dd, 1 H, *J* = 47.2, 14.6 Hz), 5.17 (dt, 1 H, *J* = 10.7, 3.1 Hz), 6.65 (d, 1 H, *J* = 8.5 Hz), 7.73–7.58 (m, 2 H), 7.63–7.69 (m, 1 H), 7.88–7.91 (m, 2 H). Compound **7n**: mp 106 °C. IR (nujol): 3300, 1665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, 6 H, *J* = 6.6 Hz), 1.10–1.55 (m, 20 H), 1.60–1.91 (m, 4 H), 1.95–2.25 (m, 8 H), 5.26 (dt, 1 H, *J* = 10.6, 3.6 Hz), 4.68 (dd, 1 H, *J* = 47.2, 14.6 Hz), 5.17 (dt, 1 H, *J* = 10.7, 3.1 Hz), 6.50 (dd, 1 H, *J* = 10.6, 7.7 Hz), 7.50–7.71 (m, 3 H), 7.82–7.93 (m, 2H).

(14) Sulfones **7a**–**d** obtained from fluoroacetamide are reduced faster (1–1.5 h) than other sulfones. Prolonged refluxing times (3–4 h) causes partial removal of the fluorine atom. *N*-Substituted fluoroacetamides have been previously reduced using BH_3–THF system: Aoki, K.; Tomioka, K.; Noguchi, H.; Koga, K. *Tetrahedron* **1997**, *53*, 13641.

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