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Diastereoselective synthesis of β-aminosulfones from the 1,2-addition to *N*-(*para*-methoxyphenyl) imines

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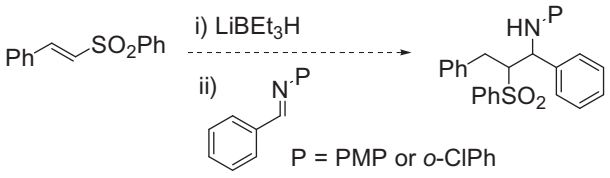
ABSTRACT

The base-promoted 1,2-addition of alkyl phenylsulfones to *N*-(*para*-methoxyphenyl) imines was investigated as a direct route to stereochemically defined β-aminosulfones. Using ^{n}BuLi as base, 2-(phenylsulfonyl)ethylbenzene was added to a range of *N*-(*para*-methoxyphenyl) imines to give β-aminosulfone products in high yields as single *anti*-diastereoisomers. Other less substituted alkyl phenylsulfones were not as successful.

Stereochemically pure β-aminosulfones are a predominant substructure of biologically active compounds[1] and have been identified as HIV protease inhibitors,[2] MMP-13 inhibitors for the treatment of rheumatoid arthritis[3] and DNA alkylating agents for cancer treatment.[4] They are also valuable synthetic intermediates in the preparation of cyclic and acyclic nonproteinogenic α-amino acids,[5] amines[6] and alkaloids,[7] taking advantage of the fact that sulfones can be involved in versatile synthetic transformations.[8] Enantioselective syntheses of acyclic β-aminosulfones often rely on chiral *N*-sulfinyl imines or other activated imines for their preparation,[5a,7,9] but the use of more substituted precursors to give vicinal stereocentres has been limited.[5,6,9a–c] Although methods for the racemic synthesis of β-aminosulfones have been reported,[10] to the best of our knowledge, there is no study of the inherent diastereoselectivity of a direct 1,2-addition approach to β-aminosulfones using less reactive imine precursors. In this Letter we describe the diastereoselective 1,2-addition of alkyl phenylsulfones to *N*-(*para*-methoxyphenyl) imines to give diastereomerically pure β-aminosulfones.

We have developed a new methodology for the syntheses of β-nitroamines with excellent diastereo- and enantioselectivity using a reductive nitro-Mannich reaction.[11] The nitro-Mannich reaction is particularly efficient for the formation of β-nitroamines with two contiguous stereocentres, often with high levels of enantio- and diastereoselectivities.[12] We wanted to investigate whether the sulfone group would act as a similar activating group to the nitro function for the addition of sulfone-stabilised carbanions to imines, to obtain similarly complex stereochemically pure building blocks. Initial attempts at applying this methodology directly to α,β-unsaturated sulfones for the synthesis of β-aminosulfones were unsuccessful (Scheme 1). The reduction procedure, using Superhydride, proceeded cleanly, but disappointingly, no 1,2-addition to the imine was observed with or without Brønsted or Lewis acids.



Scheme 1.

To confirm whether the 1,2-addition could occur we generated the α-sulfone carbanion from 2-(phenylsulfonyl)ethylbenzene (**1**) with a range of bases and then added imine **2**. With ^{n}BuLi we observed 90% conversion with a crude dr of 90:10 and the major compound **3** could be isolated in 78% yield as a single diastereoisomer (Scheme 2). The base LiHMDS gave a slightly lower 70% conversion and dr of 85:15, with the pure product being isolated

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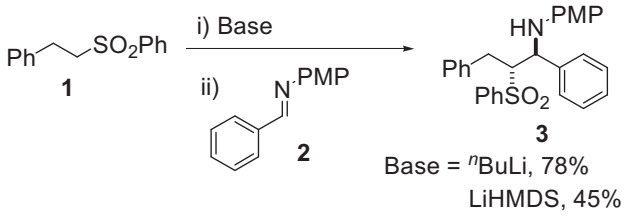
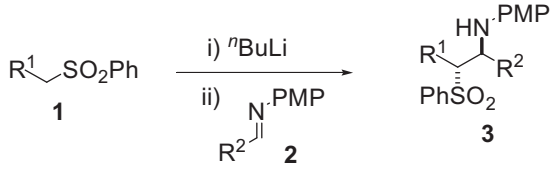


Scheme 2.

in 45% yield. The major diastereoisomer was assigned *anti*- based on a comparison of distinctive coupling constants with similar compounds from the nitro-Mannich series (vide infra). Conversion was minimal when the *N*-(*ortho*-chlorophenyl) protected imine was used.

With this result in hand we surveyed the scope of the reaction (Scheme 3, Table 1).[13] The addition reaction of 2-(phenylsulfonyl)ethylbenzene (**1**) gave good yields and diastereoselectivities with a range of imines (entries 1–6). The cyclohexyl alkyl group (entry 6) gave similar diastereoselectivity to the aromatic substituents (entries 1–5). The addition reaction with ethyl phenylsulfone (entry 7) gave poor diastereoselectivity (60:40), which suggests the distal phenyl group of 2-(phenylsulfonyl)ethylbenzene is in part responsible for the good diastereoselectivity. Low conversions and low dr were found with benzyl phenyl sulfone (entry 8) under a variety of conditions. Attempts with methyl phenyl sulfone (entry 9) gave only traces of addition product.

The sense of diastereoselectivity was assigned based on the magnitude of the $PhSO_2CH$–CHNH coupling constant. The $PhSO_2CH$ proton was in most cases poorly defined as a multiplet in the ^{1}H NMR spectra, but the CHNH proton was either a broad singlet or a small doublet J = 2.3–2.5 Hz. This is in good agreement with the coupling constants across the NO_2CH–CHN group in β-nitro amines, which are normally below 5.5 Hz and are smaller than the *syn* coupling constant.[12,14] The *syn*-diastereoisomer is much rarer, but is characterised by a larger coupling constant across the NO_2CH–CHN group, typically around 8.0 Hz.[15] This tentative



Scheme 3.

Table 1
Preparation of β-aminosulfones from PMP imines[13]

Entry	R^1	R^2	Conversion[a] (%)	dr[a]	Yield[b] of **3** (%)
1	CH_2Ph	Ph	90	90:10	78
2	CH_2Ph	*p*-MeC_6H_4	75	85:15	60
3	CH_2Ph	*p*-ClC_6H_4	90	90:10	71
4	CH_2Ph	3-Furyl	99	90:10	87
5	CH_2Ph	3-Thienyl	90	90:10	78
6	CH_2Ph	Cyclohexyl	85	90:10	73
7	CH_3	Ph	99	60:40	55[c]
8	Ph	Ph	10–20[d]	—	—
9	H	Ph	<5[d]	—	—

[a] Determined by ^{1}H NMR spectroscopy.
[b] Isolated yield.
[c] 30% of the *syn*-diastereoisomer was also isolated.
[d] Conditions attempted: Et_2O, TBME, PhMe, −78 °C, 20 °C, 0 °C.

assignment is further supported by analysis of the two diastereoisomers in entry 7. The major compound that we have assigned as the *anti*-diastereoisomer has J($PhSO_2CH$–CHNH) = 2.3 Hz, whereas the minor compound that we assigned as the *syn*-diastereoisomer has J($PhSO_2CH$–CHNH) = 8.8 Hz.

In conclusion we have found that simple PMP-imines react with 2-(phenylsulfonyl)ethylbenzene (**1**) to give β-aminosulfones in high yield as single diastereoisomers. The reaction was found to be sensitive to the sulfone substituents which affects both the diastereoselectivity and in the cases of methyl phenylsulfone and benzyl phenylsulfone, conversion. These results suggest that the addition of sulfone-stabilised carbanions to imines that do not possess an electron-withdrawing protecting group,[5a,7,9,10] such as sulfonyl, sulfoximine or carbonyl, is much more difficult. This niche reactive window may be useful to prepare these or similar products with simple aryl groups on nitrogen as useful chiral building blocks for further functionalisation towards biologically active targets.

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Supplementary data

Supplementary data (experimental procedures and characterisation data for all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.017.

References and notes

1. (a) Paikt, S.; White, E. H. *Tetrahedron Lett.* **1996**, *37*, 4663; (b) Xue, C.-B.; Chen, X.-T.; He, X.; Roderick, J.; Corbett, R. L.; Ghavimi, B.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Ribadeneira, M. D.; Vaddi, K.; Trzaskos, J. M.; Newton, R. C.; Duan, J. J.-W.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4453; (c) Gauthier, J. Y.; Black, W. C.; Courchesne, I.; Cromlish, W.; Desmarais, S.; Houle, R.; Lamontagne, S.; Li, C.; Masse, F.; McKay, D. J.; Ouellet, M.; Robichaud, J.; Truchon, J.-F.; Truong, V.-L.; Wanga, Q.; Percival, M. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4929.
2. (a) Munroe, J. E.; Shepherd, T. A.; Jungheim, L. N.; Hornhadc, W. J.; Hatch, S. D.; Muesing, M. A.; Wiskerchen, M.; Su, K. S.; Campanale, K. M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2897; (b) Tamamura, H.; Koh, Y.; Ueda, S.; Sasaki, Y.; Yamasaki, T.; Aoki, M.; Maeda, K.; Watai, Y.; Arikuni, H.; Otaka, A.; Mitsuya, H.; Fujii, N. *J. Med. Chem.* **2003**, *46*, 1764; (c) Nakatani, S.; Hidaka, K.; Ami, E.; Nakahara, K.; Sato, A.; Nguyen, J.-T.; Hamada, Y.; Hori, Y.; Ohnishi, N.; Nagai, A.; Kimura, T.; Hayashi, Y.; Kiso, Y. *J. Med. Chem.* **2008**, *51*, 2992.
3. Becker, D. P.; Barta, T. E.; Bedell, L.; DeCrescenzo, G.; Freskos, J.; Getman, D. P.; Hockerman, S. L.; Li, M.; Mehta, P.; Mischke, B.; Munie, G. E.; Swearingen, C.; Villamil, C. I. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2719.
4. McIntyre, J. A.; Castaner, J. *Drugs Future* **2004**, *29*, 985.
5. (a) Pan, Y.; Zhao, Y.; Ma, T.; Yang, Y.; Liu, H.; Jiang, Z.; Tan, C.-H. *Chem. Eur. J.* **2010**, *16*, 779; (b) Díez, D.; García, P.; Marcos, I. S.; Basabe, P.; Garrido, N. M.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2005**, *61*, 11641.
6. Fustero, S.; Flores, S.; Cuñat, A. C.; Jiménez, D.; del Pozo, C.; Bueno, J.; Sanz-Cervera, J. F. *J. Fluorine Chem.* **2007**, *128*, 1248.
7. (a) Kumareswaran, R.; Hassner, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2269; (b) Hassner, A.; Usak, D.; Kumareswaran, K.; Friedman, O. *Eur. J. Org. Chem.* **2004**, 2421.
8. Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press, 1993.
9. (a) Velázquez, F.; Arasappan, A.; Chen, K.; Sannigrahi, M.; Venkatraman, S.; McPhail, A. T.; Chan, T.-M.; Shih, N.-Y.; Njoroge, F. G. *Org. Lett.* **2006**, *8*, 789; (b) Cadoni, E.; Arca, M.; De Montis, S.; Fattuoni, C.; Perra, E.; Cabiddu, M. G.; Usaia, M.; Cabiddu, S. *Tetrahedron* **2007**, *63*, 11122; (c) Zhang, H.; Li, Y.; Xu, W.; Zheng, W.; Zhou, P.; Sun, Z. *Org. Biomol. Chem.* **2011**, *9*, 6502.
10. (a) Naimi-Jamal, M. R.; Ipaktschi, J.; Saidi, M. R. *Eur. J. Org. Chem.* **2000**, 1735; (b) Mladenova, M. *Synth. Commun.* **1986**, *16*, 1089.
11. (a) Anderson, J. C.; Blake, A. J.; Koovits, P. J.; Stepney, G. J. *J. Org. Chem.* **2012**, *77*, 4711; (b) Anderson, J. C.; Noble, A.; Tocher, D. A. *J. Org. Chem.* **2012**, *77*, 6703; (c) Anderson, J. C.; Koovits, P. J. *Chem. Sci.* **2013**, *4*, 2897.
12. For a review specific to asymmetric methods, see: (a) Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401; For a comprehensive review of the nitro-Mannich reaction, see: (b) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887.
13. General procedure for the synthesis of β-aminosulfones **3**. To the sulfone (0.5 mmol, 1 equiv) in THF (4.0 mL) stirred under nitrogen at −78 °C was added a solution of ^{n}BuLi (1.0 M in hexane, 0.375 mL, 0.600 mmol). The reaction

mixture was stirred at −78 °C for 15 min to give a yellow solution. The imine (0.600 mmol, 1.2 equiv) in THF (1 mL) was then added slowly and stirred for 1 h at −78 °C. The reaction mixture was quenched with satd aq NH_4Cl (5 ml), and the aqueous layer extracted with Et_2O (2 × 20 mL). The organic phase was dried and evaporated in vacuo to give the crude product which was purified by flash chromatography to isolate the product.

14. (a) Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932; (b) Anderson, J. C.; Peace, S.; Pih, S. *Synlett* **2000**, 850; (c) Anderson, J. C.; Howell, G. P. *J. Org. Chem.* **2005**, *70*, 549; (d) Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 5665; (e) Anderson, J. C.; Chapman, H. A. *Org. Biomol. Chem.* **2007**, *5*, 2413; (f) Anderson, J. C.; Horsfall, L. R.; Kalogirou, A. S.; Mills, M. R.; Stepney, G. J.; Tizzard, G. J. *J. Org. Chem.* **2012**, *77*, 6186; (g) Anderson, J. C.; Kalogirou, A. S.; Porter, M. J.; Tizzard, G. J. *Beil. J. Org. Chem.* **2013**, *9*, 1737.

15. Anderson, J. C.; Stepney, G. J.; Mills, M. R.; Horsfall, L. R.; Blake, A. J.; Lewis, W. *J. Org. Chem.* **2011**, *76*, 1961.