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Conjugate addition of amines to vinyl sulfoximides: a general method for the synthesis of β-amino sulfoximides

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Abstract—The synthesis of a range of β-amino sulfoximide derivatives is described. The conjugate addition of simple amines or amino acids to *N*-tosyl phenyl vinyl sulfoximide was achieved in moderate to good yield (41–95%). Electron poor nucleophiles such as tosyl amide or benzyl carbamate were found to be unreactive under analogous conditions. © 2002 Published by Elsevier Science Ltd.

1. Introduction

As part of ongoing research projects into the use of sulfoximide derivatives as ligands in asymmetric synthesis and as building blocks in the synthesis of peptidomimetics we required a simple, yet potentially diverse, method for the preparation of β-amino sulfoximide derivatives (Fig. 1).

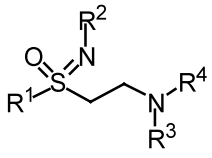
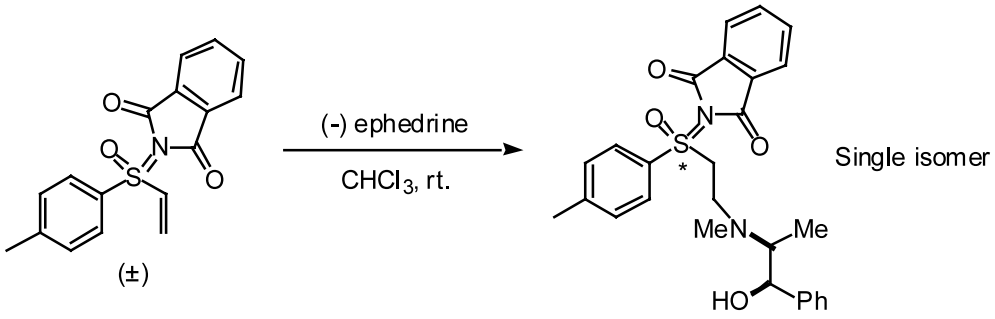


Figure 1.

There are surprisingly few examples of β-amino sulfoximides in the literature. Pyne and Reggelin have independently described the intramolecular addition of nitrogen nucleophiles to α,β-unsaturated sulfoximides in order to generate nitrogen heterocycles.[1,2] An example of the intermolecular addition of amine nucleophiles into vinyl sulfoximides has been reported by Annunziata et al.,[3] who described the kinetic resolution of *N*-phthaloyl vinyl sulfoximides using ephedrine (Scheme 1). Taking this precedent as a starting point we decided to investigate the generality of the conjugate addition of nitrogen nucleophiles into vinyl sulfoximides.

2. Results and discussion

Previous work in our group[4] has shown that *N*-sulfonyl protected vinyl sulfoximides can be readily prepared



Scheme 1.

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from the corresponding vinyl sulfoxide using iminoiodane reagents as described by Muller et al.[5] In this case we chose to prepare the *N*-tosyl derivative **1** in racemic form from commercially available racemic phenyl vinyl sulfoxide (Scheme 2). The enantiomerically pure sulfoxide can be prepared by addition of vinyl magnesium bromide into a chiral sulfinamide using methodology developed by Evans,[6] however we chose to pursue our studies using the racemic derivative in the first instance.

The addition of a number of amine nucleophiles to vinyl sulfoximide **1** using the conditions described by Annunziata et al. [3] was carried out (Scheme 3) and the results are shown in Table 1.

Primary and secondary amines proved to be good nucleophiles resulting in the formation of the desired β-amino sulfoximides in excellent yields (78–95%) however, the electron deficient nucleophiles, tosyl amide and benzyl carbamate, gave no reaction under these conditions. The efficient addition of benzylamine was very encouraging since the benzyl group can potentially be removed to allow further manipulation of the β-amino group allowing for the preparation of a wide range of β-amino sulfoximide derivatives.

Our interest in the use of β-amino sulfoximides as peptidomimetics prompted us to explore the scope of the amine addition reaction using amino acids as nucleophiles. The addition of a number of amino acid methyl esters to vinyl sulfoximide **1** was carried out in a parallel reactor† using the corresponding hydrochloride salts in the presence of triethylamine with dichloromethane as solvent (Scheme 4). The results are presented in Table 2.

The products were isolated in moderate to good yields (41–78%) as a 1:1 mixture of diastereoisomers except in the case of the glycine derivative, which lacks a second stereocentre. In all cases the reactions proceeded cleanly with no evidence of side reactions and the mass balance could be accounted for by recovery of unreacted **1**.

Table 1.

Entry	R^1	R^2	Time (h)	Yield (%)
1	H	Bn	24	79
2	Et	Et	8	78
3	$-(CH_2)_5-$	–	4	95
4	H	Ts	24	0[a]
5	H	Cbz	24	0[a]

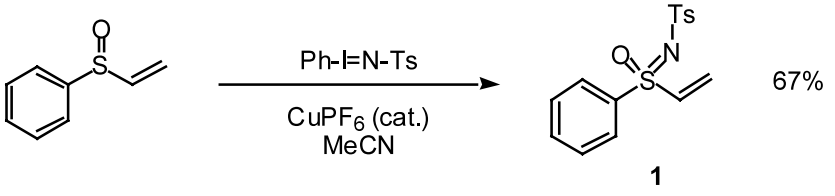
[a] No reaction was observed.

3. Conclusion

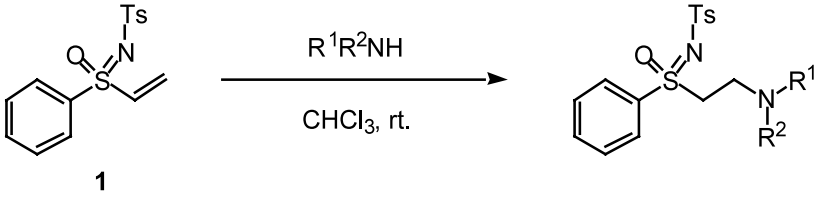
We have demonstrated that a wide range of amine nucleophiles can be added to a vinyl sulfoximide to give the corresponding β-amino sulfoximides in good yield under mild reaction conditions. The scope of the reaction is likely to be extended by manipulation of the amine protecting group in the case of the benzylamine derivative. Reaction at the nitrogen of the sulfoximide group may also be possible if a removable protecting group is utilized at this position (e.g. N-SES[4]). Further investigations into these synthetic aspects are currently under way along with enantioselective variants employing a single enantiomer of vinyl sulfoximide **1**.

4. Experimental

Example procedure for the reaction of an amino acid methyl ester with vinyl sulfoximide **1**: Vinyl sulfoximide **1** (200 mg) was dissolved in dry DCM (5 ml) under an inert atmosphere of N_2. To this was added glycine methyl ester hydrochloride salt (55 mg) and triethylamine (86 μl). The resulting solution was agitated at room temperature for a period of 24 h. After this time

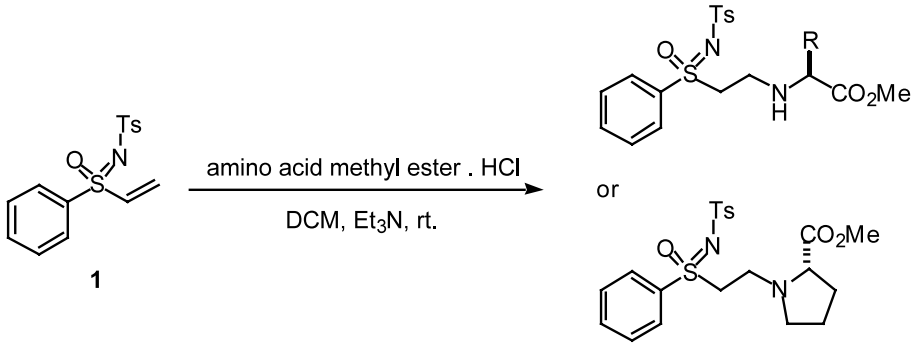


Scheme 2.



Scheme 3.

† Reactions were carried out using a FirstMate™ parallel synthesizer supplied by Argonaut Technologies.



Scheme 4.

Table 2.

Entry	Amino acid	Yield (%)
1	Glycine	41
2	Alanine	60[a]
3	Valine	64[a]
4	Leucine	78[a]
5	Phenylalanine	77[a]
6	Proline	60[a]

[a] Isolated as a 1:1 mixture of diastereoisomers.

the reaction was washed with saturated aqueous sodium bicarbonate (5 ml) and the organic phase dried using sodium sulfate. The solvent was evaporated to give a clear glass, which was purified by flash column chromatography on silica eluting with ethyl acetate. The desired product was isolated as a waxy white solid (105 mg, 41%). IR: ($CHCl_3$, cm^{-1}) 3330 (w), 3024 (s), 1741 (s), 1317 (s), 1226 (s), 1206 (s), 1154 (s), 1095 (s), 1066 (s); ^1H NMR: (300 MHz, $CDCl_3$) 7.95 (2H, d, 7.7), 7.79 (2H, d, 8.1), 7.70–7.60 (1H, m), 7.59-7.50 (2H, m), 7.20 (2H, d, 8.1), 3.79–3.51 (2H, m), 3.66 (3H, s), 3.32–3.22 (2H, m), 3.06–2.89 (2H, m), 2.33 (3H, s), 1.73 (1H, s, NH); ^{13}C NMR: (75.5 MHz, $CDCl_3$) 174.9 (C=O), 145.3 (C), 143.5 (C), 139.0 (C), 136.9 (CH), 132.1 (CH), 131.7 (CH), 130.7 (CH), 129.1 (CH), 60.5 (CH_2), 54.4 (CH_3), 52.6 (CH_2), 45.2 (CH_2), 24.0 (CH_3); MS: (Electrospray) 433.0 (100%) $[M+Na]^+$; HRMS: (Electrospray) Found: 433.0882, calcd for $C_{18}H_{22}N_2O_5NaS_2$ 433.0868.

Acknowledgements

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