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Preparation of α-amino ketones, β-amino hydroxylamines using asymmetric aza-Henry reactions of *N*-*p*-tolylsulfinylimines with nitroethane

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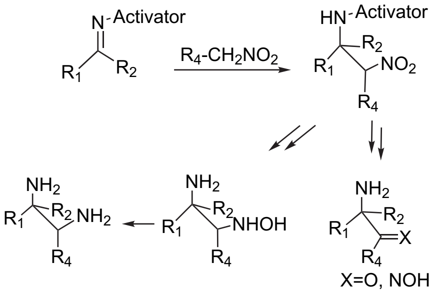
Abstract—*N*-Sulfinylimines derived from aromatic and aliphatic aldehydes react with nitroethane and NaOH, yielding mainly two diastereoisomeric β-nitroamines as the result of a highly diastereoselective reaction and further epimerization of the carbon linked to the nitro group. The resulting β-nitroamines are used as precursors of *N*-sulfonyl α-amino methyl ketones and β-amino hydroxylamines.

1. Introduction

Diastereoselective and enantioselective versions of the aza-Henry (or nitro-Mannich) reaction are recently attracting a great deal of attention.[1–3] This interest is due to the formation of optically pure β-nitroamines, which are attractive targets in asymmetric synthesis mainly due to their possible but not always easy conversion to diamines.[4] Additionally, the nitro moiety can be transformed into other interesting functional groups like carbonyl groups,[5] hydroxylamines,[6] and oximes or nitriles[7] (Scheme 1).



Scheme 1. Aza-Henry reaction and some interesting transformations.

We have recently reported the asymmetric diastereoselective aza-Henry reaction of nitromethane with a wide variety of *N*-*p*-tolylsulfinylimines from aliphatic and aromatic aldehydes as well as from ketones, even when they have enolizable protons.[8] Depending on the reaction conditions employed (NaOH or TBAF) we were able to obtain as the major product one of the two possible diastereoisomers.

As a part of our ongoing investigations on the asymmetric aza-Henry reaction, we present herein the results obtained when these *N*-*p*-tolylsulfinylimines are treated with nitroethane under the conditions previously optimized with nitromethane, and the transformation of the resulting β-nitro sulfinylamines into other compounds of interest such as α-amino methyl ketones and β-amino hydroxylamines.

2. Results and discussion

N-Sulfinylimines **1a–i** have been obtained by condensation of the corresponding aldehydes and ketones with (*S*)-*N*-*p*-tolylsulfinylamide following the $Ti(OEt)_4$ Davis' protocol[9] with slight modifications in the work-up.[10]

Aza-Henry reactions of *N*-sulfinylimines **1** with $EtNO_2$, under the same reaction conditions optimized when $MeNO_2$ was used as nucleophile,[8] led to a mixture of diastereoisomers (Table 1). The four possible ones were obtained with very low diastereoselectivity with the aromatic *N*-sulfinylaldimine **1a** using TBAF as the base (entry 1) with no improvement by lowering the reaction temperature. Nevertheless, when this reaction was carried out in the presence of NaOH, diastereoisomers **2a** and **3a** were clearly predominant and can be easily separated from **4a** and **5a** by simple crystallization in ether (entry 2). A similar result was

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Keywords: Asymmetric synthesis; Diastereoselectivity; Imines; Amines; Sulfoxides.

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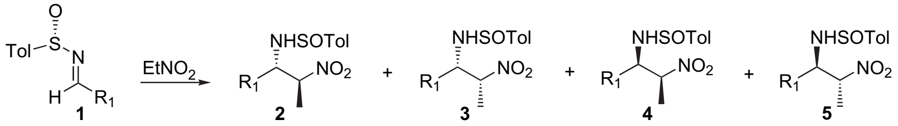
Table 1. Aza-Henry reaction of nitroethane with *N*-sulfinylaldimines (*S*s)-**1a**–**g**



Entry	Substrate's R_1	s.m./prod	Conditions	Conv [%][a]	*t* [h]	Ratio of products **2/3/4/5**[a]	Yield[b] (**2/3**) [%]
1	C_6H_5	**a**	Method B	95	0.5	28:13:38:21	92 (**2**–**5**)
2	C_6H_5	**a**	Method A	81	36	50:44:3:3	75 [43 (**2a**)/32 (**3a**)] 70[d] (58:42)
3	*p*-CNC_6H_4	**b**	Method A	100	26	51:41:3:5	82 [45 (**2b**)/37 (**3b**)]
4	*p*-$MeOC_6H_4$	**c**	Method A	74	66	55:41:2:2	68 [40 (**2c**)/28 (**3c**)]
5	PhCH=CH	**d**	Method A	93	72	51:40:6:3[c]	70 [36 (**2d**)/34 (**3d**)]
6	Me	**e**	Method A	94	17	91 (**2**+**3**):5:4	80[e]
7	Me	**e**	Method A, $Yb(Oi\text{-}Pr)_3$ (1 equiv)	93	24	42:40:9:9	Not determined
8	*i*-Pr	**f**	Method A	62	138	83:17	48[f] (83:17) 42[d] (93:7)
9	*i*-Pr	**f**	NaOH (5 equiv), 40 °C	73	168	81:19	34[g]

Method A: $EtNO_2$ (solvent), NaOH (5 equiv), 4 Å MS, 40 °C. Method B: $EtNO_2$ (solvent), TBAF.

[a] Determined by ^1H NMR.

[b] After flash chromatography.

[c] Determined after isolation of products by flash chromatography.

[d] After crystallization in ether.

[e] After chromatography the ratio **2e**/**3e** was 55.2:44.8 (determined by HPLC).

[f] Recovered starting material: 17%.

[g] Recovered starting material: 15%.

obtained with other aromatic imines **1b**,**c**, α,β-unsaturated **1d**, and the aliphatic *N*-sulfinylimine **1e**, derived from acetaldehyde (entries 3–6). In the later case, the addition of $Yb(Oi\text{-}Pr)_3$ produced a deleterious effect on the stereoselectivity of the reaction (entry 7).[11] The bulkier aliphatic *i*-Pr substituent required longer reaction times to afford the β-nitroamines with higher stereoselectivity (entry 8). The results in entries 8 and 9 clearly illustrate that the isolated yields decreased when the reactions were carried out in the absence of molecular sieves, which could suggest that they have some role in preventing the hydrolysis of the *N*-sulfinylimine, by absorbing the water generated by the HO^-.

The bulky *tert*-butyl *N*-sulfinylimine reacts with nitroethane under both catalyzed ($Yb(Oi\text{-}Pr)_3$) and uncatalyzed conditions affording the corresponding β-nitroamines in very low yields.[12] Finally, *N*-sulfinylketimines failed to undergo aza-Henry reaction with nitroethane under the same reaction conditions.

The absolute configurations of compounds **2f** and **3a** were respectively established as (*S*s, 1*S*,2*S*) and (*S*s, 1*S*,2*R*) by X-ray crystallography (Fig. 1). The major diastereoisomers **2** obtained in the reactions carried out in the presence of NaOH have been assigned the same configurations as **2f** by assuming that all imines should evolve through the same stereochemical course.[13]

When compounds **2a** and **3a** were treated independently with nitromethane using NaOH as well as TBAF, a mixture

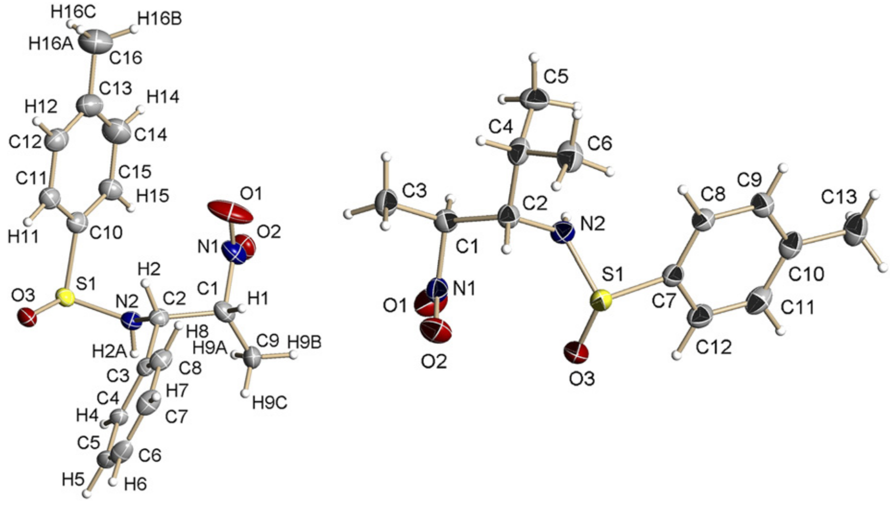


Figure 1. X-ray structure of **2f** and **3a**.