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A facile synthesis of *N*-sulfinylaldimines

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Abstract—A simple and efficient procedure for the synthesis of *N*-sulfinylaldimines (sulfinimines) from sulfinamides and aldehydes is described. The reaction was carried out in the presence of *t*-BuOK or NaOH. The method is applicable for the synthesis of optically active sulfinimines.
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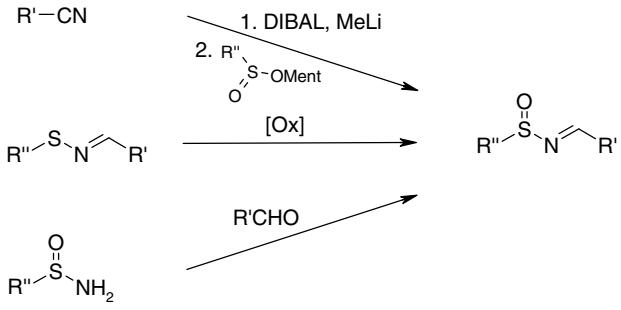
1. Introduction

N-Sulfinylimines are widely recognized as versatile substrates for the synthesis of enantiomerically enriched amines and derivatives. Davis et al. introduced *p*-tolylsulfinimines, which were obtained from diastereoisomerically pure menthyl sulfinate.[1] Ellman et al. developed the synthesis of enantiomerically pure *t*-butylsulfinamide, which appeared to be an excellent substrate for sulfinimine preparation.[2] Both derivatives, that is, *p*-tolyl and *t*-butylsulfinyl were used in a number of syntheses of natural products.[3] Some other sulfinyl derivatives of imines have also been developed.[3]

The main methods for the preparation of optically active sulfinimines include: (a) reaction of nitriles with an organometallic reagent (DIBAL, MeLi) and menthyl sulfinate;[4] (b) asymmetric oxidation of sulfenimines;[5] and (c) condensation of sulfinamides with aldehydes and ketones (Scheme 1). The last method seems to be the most useful because enantiomerically pure *p*-tolyl and *t*-butylsulfinamides are now commercially available.

The very first procedures of condensation used *N*,*N*-bistrimethylsilylsulfinamide, which in the presence of CsF, reacted with aldehydes.[4] Later studies showed that the addition of CsF was not necessary.[6] Davis and Ellman reported, independently, the use of mild Lewis acids as activating agents for aldehydes and water scavengers



Scheme 1. Methods for the preparation of sulfinimines.

[$CuSO_4$, $Ti(OEt)_4$, MS].[7] Nakata and co-workers described the use of Cs_2CO_3 as a Lewis acid and dehydrating agent.[8] In another method, $Yb(OTf)_3$ was used in stoichiometric amounts.[9] Also $KHSO_4$ may be used as a good catalyst for condensation of sulfinamide with aldehydes.[10]

2. Results and discussion

Our approach to the synthesis of sulfinimines is based on the activation of the sulfinamide instead of the aldehyde. Herein we report that sulfinimines can be easily obtained by condensation of primary sulfinamides with aldehydes using simple bases. Sulfinamides are known as very weak nucleophiles. However, in the presence of bases, they form aza-anions which react more readily with electrophiles such as aldehydes or alkyl halides.

Our first experiments were carried out using racemic benzenesulfinamide and anisaldehyde (Scheme 2). We

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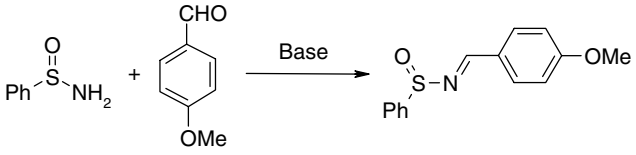
attempted to find the best conditions to obtain sulfinimines in good yields and the results are presented in Table 1. For the bases, we have used potassium *t*-butanolate and sodium hydroxide, which are inexpensive and easy to handle. Equimolar amounts of base gave slightly better results than catalytic amounts (entries 6 and 8). The majority of solvents may be used, however the solvent of choice appeared to be the reagent grade methanol. To obtain the best yields of the product, we extended the reaction time to 24 h (usually overnight). The formation of a sulfinimine is so strongly preferred that the reaction took place in water (entry 9). Usually excess of the aldehyde (1.5 equiv) was used; there was no need to use anhydrous solvents or protection from air.



Scheme 2. Base catalyzed reaction of benzenesulfinamide with anisaldehyde.

Table 1. Various conditions for condensation of benzenesulfinamide with anisaldehyde

Entry	Base	Solvent	Temp (°C)/time (h)	Yield[a] (%)
1	*t*-BuOK	THF	45/3.5 then rt/18	90
2	*t*-BuOK	*t*-BuOH	rt/24	91
3	*t*-BuOK	CH_2Cl_2	rt/24	92
4	*t*-BuOK	MeOH	rt/3	20
5	*t*-BuOK	MeOH	rt/6	87
6	*t*-BuOK	MeOH	rt/24	99
7	*t*-BuOK[b]	MeOH	rt/24	35
8	*t*-BuOK[c]	MeOH	rt/24	94
9	*t*-BuOK	H_2O	rt/24	24
10	NaOH	MeOH	rt/24	90

[a] The yield was calculated from ^{1}H NMR spectra of crude reaction mixture.
[b] Stoichiometric amount of aldehyde.
[c] Catalytic amount of base (10 mol %).

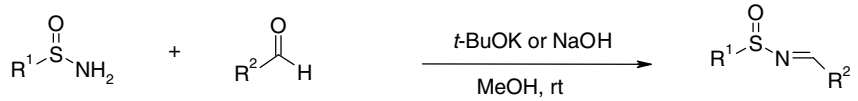
Using the above conditions,[11] we have synthesized a number of racemic *N*-*p*-tolyl- and *N*-*t*-butylsulfinyl imines (Scheme 3 and Table 2). Good yields were obtained for aromatic derivatives. Due to the strong basic conditions aliphatic aldehydes tend to enolize and the yields of aliphatic derivatives of sulfinimines are much lower, even though, they are higher than in the procedure of Nakata[8] using Cs_2CO_3 (15% vs 40%). The ketones seemed to be unreactive and acetophenone did not give the expected product. However the presented procedure may be easily applied for multigram scale synthesis.

The most important question was whether relatively strong bases such as NaOH or *t*-BuOK may cause epimerization at the sulfur atom. First, we determined that (*S*)-(+) *p*-toluenesulfinamide did not racemize in the presence of *t*-BuOK for 24 h in methanol.[12] Next, we used enantiomerically pure *p*-tolyl- and *t*-butylsulfinamides for the synthesis of *N*-benzylidene and *N*-*p*-methoxybenzylidene derivatives of sulfinimines. Specific rotations of the products were very close to that published in the literature (Table 3). Independently we checked the enantiomeric purity by ^{1}H NMR

Table 2. Synthesis of *N*-sulfinylimines **3**[a]

Entry	R^1	R^2	Product	Yield[b] (%)	
				NaOH	*t*-BuOK
1	*p*-Tol	Ph	**3aa**	80	93
2		*m*-ClC_6H_4	**3ab**	64	79
3		*p*-$MeOC_6H_4$	**3ac**	90	89
4		*p*-$NO_2C_6H_4$	**3ad**	88	82
5		2-Furyl	**3ae**	57	86
6		(*E*)-MeCH=CH[c]	**3af**	—	76
7		*i*-Pr	**3ag**	59	40
8	*t*-Bu	Ph	**3ba**	91	60
9		*p*-$MeOC_6H_4$	**3bc**	92	64
10		*p*-$NO_2C_6H_4$	**3bd**	88	58
11		2-Furyl	**3be**	87	—
12		(*E*)-MeCH=CH[c]	**3bf**	—	72

[a] Conditions: rt, MeOH, sulfinamide 1 equiv, base 1 equiv, aldehyde 1.5 equiv, 16 h.
[b] Isolated yields.
[c] THF was used as a solvent.



1a R^1 = *p*-Tol
b R^1 = *t*-Bu

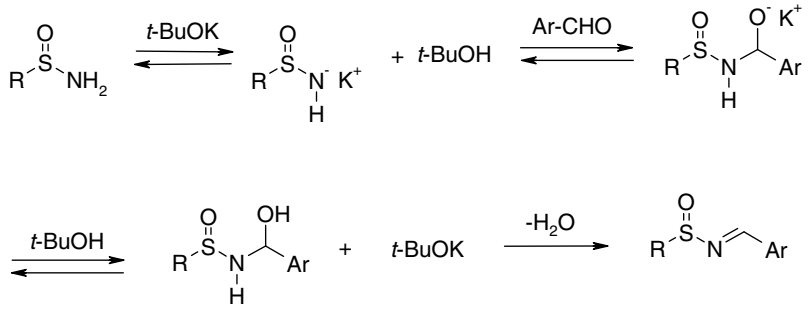
2a R^2 = Ph
b R^2 = *m*-ClC_6H_4
c R^2 = *p*-$MeOC_6H_4$
d R^2 = *p*-$NO_2C_6H_4$
e R^2 = 2-Furyl
f R^2 = (*E*)-Me-CH=CH
g R^2 = *i*-Pr

3aa R^1 = *p*-Tol, R^2 = Ph
ab R^1 = *p*-Tol, R^2 = *m*-ClC_6H_4
ac R^1 = *p*-Tol, R^2 = *p*-$MeOC_6H_4$
ad R^1 = *p*-Tol, R^2 = *p*-$NO_2C_6H_4$
ae R^1 = *p*-Tol, R^2 = 2-Furyl
af R^1 = *p*-Tol, R^2 = (*E*)-Me-CH=CH
ag R^1 = *p*-Tol, R^2 = *i*-Pr
ba R^1 = *t*-Bu, R^2 = Ph
bc R^1 = *t*-Bu, R^2 = *p*-$MeOC_6H_4$
bd R^1 = *t*-Bu, R^2 = *p*-$NO_2C_6H_4$
be R^1 = *t*-Bu, R^2 = 2-Furyl
bf R^1 = *t*-Bu, R^2 = (*E*)-Me-CH=CH

Scheme 3. Synthesis of *N*-*p*-tolyl- and *N*-*t*-butylsulfinylimines.

Table 3. Synthesis of optically active *N*-sulfinylimines

Entry	Sulfinimine	Method	Yield (%)	Observed $[\alpha]_D^{20}$	Lit. $[\alpha]_D^{20}$
1	(*S*)-**3aa**	*t*-BuOK	90	+111.7 (1.1, $CHCl_3$)	+114 (1.0, $CHCl_3$)[8]
2	(*S*)-**3ac**	*t*-BuOK	88	+38.1 (1.0, $CHCl_3$)	+37.9 (1.49, $CHCl_3$)[4b]
3	(*R*)-**3ba**	*t*-BuOK	58	−104.7 (1.0, $CHCl_3$)	−101 (1.0, $CHCl_3$)[14]



Scheme 4. Possible mechanism of the formation of sulfinimines.

using (*S*)-(−)-BINOL as the chiral solvating agent[13] and a sample of **3ba** by chiral HPLC. Racemization was negligible in all cases.

A possible mechanism for the formation of the sulfinimines is shown in Scheme 4. The first steps include formation of the aza-anion of sulfinamide and its addition to the aldehyde. Elimination of water gives *N*-sulfinimines. Usually 5–10 min after addition of the aldehyde, a precipitate is formed, which dissolves gradually within a few hours.

3. Conclusion

In conclusion we have developed a simple and efficient procedure for the synthesis of *N*-sulfinyl aldimines from sulfinamides and aldehydes. The reaction can be carried out without any special protection from air or moisture. The yields for aromatic sulfinimines are very good. As a result of the strongly basic conditions the yields of the aliphatic sulfinimines are lower. The procedure is applicable for the synthesis of optically active sulfinimines. It may also be useful for the preparation of large libraries of aromatic amines.

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11. *General experimental procedure for the synthesis of sulfinimines*: The reaction was carried out in a round bottom flask not protected from either air or moisture. To a solution of sulfinamide (0.71 mmol) in methanol (3.5 mL) was added potassium *t*-butoxide or sodium hydroxide (0.71 mmol). The mixture was stirred for 15 min and aldehyde (1.065 mmol) then added. The reaction mixture was stirred at rt for 16 h. Methanol was evaporated and the residue dissolved in methylene chloride (2 mL) and aqueous NH_4Cl solution (2 mL). The organic layer was separated and the water phase extracted twice with CH_2Cl_2 (2 mL). The organic extracts were dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by chromatography on silica gel using a mixture of ethyl acetate–hexane as an eluent. All compounds have spectral data identical to those published in the literature.
12. Observed specific rotation: $[\alpha]_D^{20} = +80.5$ (*c* 1.1, $CHCl_3$), lit.[7b] $[\alpha]_D^{20} = +80.2$ (*c* 1.2, $CHCl_3$).
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