Pergamon

*Tetrahedron Letters*, Vol. 36, No. 44, pp. 8011-8014, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01675-9

# A Convenient Preparation of Allylic Amines

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***Abstract:*** *Addition of aldehydes to the bis-lithio derivative of aminosulfone 1, followed by treatment of the resulting mixture with N,N'-carbonyl diimidazole gave phenylsulfonyloxazinones. Reduction by Na/Hg then afforded almost pure (E)- allylamines.*

In the course of an ongoing synthetic programme, we needed to prepare some unsaturated amines by the transformation shown.

$$RCHO \Longleftarrow (E)\text{-}R\text{-}CH{=}CH\text{-}CHNH_2$$

The literature data displayed by the General Subject Index of *Chemical Abstracts* under the "allylic-amine-preparation" sub-heading reveals a strong activity in this area,[1] a result of the occurrence of the 3-aminopropene moiety in a wide range of biologically-active natural compounds.[2] Methods aimed at achieving the above transformation are not so varied however and are mostly confined to the use of β-acylamino phosphorylated ylids,[3] with the consequence of both a partial stereoselectivity in the olefination process and usual difficulties associated with the removal of the N-protecting group, especially when a phtalimido residue is concerned. Improved protection of the nitrogen atom has been designed however.[3b, 4]

Among the methodologies which have been devised to supplement the Wittig process, the Julia-Paris-Kocienski (*i.e.* JPK) coupling-reaction has gained in popularity.[5] The JPK reaction of a N-BOC-β-aminoethylsulfone with an aldehyde has been shown to give the N-BOC derivative of the corresponding allylamine.[5c] However, pre-treatment of the aldehyde by diisobutylaluminium methoxide proved necessary to force the condensation to take place and the reaction is not general. Some improvements were desirable.

Toward this end, N-(4-methoxybenzyl)-aminoethyl phenylsulfone, **1**, was selected as a possible reagent for executing, as shown, the intended conversion.


**1** **2** **3**

*(**Σ**= phenylsulfonyl; **PMB**=* para-*methoxybenzyl)*

The choice of the 4-methoxybenzyl (*i.e.* PMB) residue as protecting group was motivated by the ease with which it could be removed under neutral conditions.[6] Furthermore, supposing that condensation of the lithio derivative of sulfone **1** with aldehydes would take place as expected, an extra driving force should eventually result from complexation of the incipient alkoxide by the amino group.

We are pleased to report herein that the use of sulfone **1** in the JPK olefination process allowed us to prepare stereoselectively *trans* allyl amines.

Sulfone **1** was conveniently prepared by $CF_3CO_2H$-catalysed addition of 4-methoxybenzylamine to vinyl phenylsulfone.[7a] A first attempt to prepare a lithio derivative of this aminosulfone by adding a solution of *n*-BuLi in hexane (1 eq.) to a cooled (-78°C) solution of **1** in THF proved much disappointing, resulting only in decomposition, with departure of the amino group. This unexpected elimination was suppressed by adding slowly a solution of the sulfone **1** in THF to *n*-BuLi in excess (2 eq.) at low temperature (-78°C); apparently, formation of the amide ion prevents the elimination to take place. Evidence of the desired anionisation was provided by adding $D_2O$ to the resulting yellow solution, which resulted in the incorporation of deuterium next to the sulfonyl group (NMR). Treatment of the bis-lithiated species by benzaldehyde, followed by hydrolysis, resulted in the isolation of the anticipated hydroxysulfone **2a**, as an approximately 1:1 mixture of two diastereomers in good yield (81%). Several aldehydes were subsequently experimented (Table 1). In each cases studied, the yield was pretty good.

Table 1: $\Sigma\text{-CH}_2\text{-CH}_2\text{-NHPMB}$ (**1**) $\xrightarrow[\text{2- RCHO}]{\text{1- } n\text{-BuLi (2 éq.)}}$ $\text{R-CH(OH)-CH}(\Sigma)\text{-CH}_2\text{-NHPMB}$ (**2**)

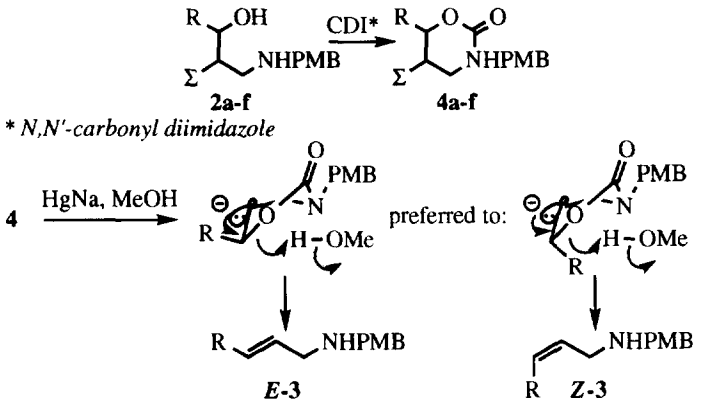
| RCHO | Product, Yield, % |
|---|---|
| Ph-CHO | **2a**, 81 |
| $CH_3CHO$ | **2b**, 61 |
| (*E*)-$CH_3$-CH=CH-CHO | **2c**, 92 |
| $CH_3$-C($CH_3$)=CH-CHO | **2d**, 91 |
| (*E*)-$CH_3$-CH=C($CH_3$)-CHO | **2e**, 81 |
| Ph-CH=CH-CHO | **2f**, 90 |

Attempts to reduce directly the crude hydroxysulfone **2a** by sodium amalgam proved not to be really useful, the allylic amine **3a** being then formed in an acceptable 58% yield but with a moderate selectivity (*E*/*Z*=85/15).

It could be supposed that acylation of the hydroxy group, prior to the reduction step, would improve the yield. The usual acylating reagents could be predicted to be inefficient however: in the event, the more nucleophilic amino group should be acylated first, with the consequence of a possible departure of an acylamide anion. The stereoselectivity would stand to be low anyway. Besides, the acylating reagent had to be selected so as to permit later an easy deprotection of the nitrogen atom.

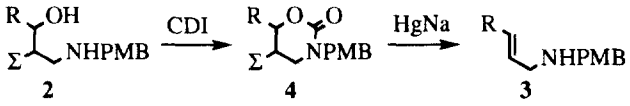
Accordingly, it was decided to convert the hydroxysulfones **2** into the corresponding oxazinones **4**: provided the reductive elimination process induced by NaHg would take place in the desired sense, the resulting carbamate ion should decarboxylate *in situ*, hence furnishing directly the target amine. Furthermore, high *E*-selectivity had to be surmised; in assuming that the reductive cleavage of the carbon sulphur bond would proceed through the

formation of a carbanion, followed by an $E_{1cb}$-type elimination process, it could be predicted that the anionic species leading to the *trans* product should be favoured, as indicated. This proved to be the case.




Treatment of sulfone **2a** by CDI in DMF resulted in the formation of the corresponding oxazinone **4a** in good yield (80 %). The $^1H$ NMR clearly shown the presence of two diastereomers in a 1/1 ratio, as observed for the starting hydroxysulfone. These oxazinones could be separated by flash-chromatography. Treatment of these two isomers, either separately or as a mixture, by 5% Na/Hg in methanol and in the presence of $NaH_2PO_4$ led, in each case, to the formation of N-PMB-cinnamylamine (*E*/*Z*=95/5). Similar treatment (*i.e.* CDI, then NaHg) of sulfones **2c-e** furnished the amines **3c-e** (Table 2) with a good stereoselectivity (*E*/*Z*=96/4).[7b, 8]

Table 2:




| R | 4, Yield,* % | 3, Yield,** % |
|---|---|---|
| Ph | **4a**, 62 | **3a**,62 |
| $CH_3$ | **4b**, 40 | — |
| (*E*)-$CH_3$-CH=CH | **4c**, 50 | **3c**, 43 |
| $CH_3$-C($CH_3$)=CH | **4d**, 52 | **3d**,54 |
| (*E*)-$CH_3$-CH=C($CH_3$) | **4e**, 65 | **3e**, 59 |
| Ph-CH=CH | **4f**, 81 | — |

* overall, from sulfone **1**.
** pure *E* isomer, after flash-chromatography.

Removal of the PMB protecting group was attempted on compound **3a**, which was treated first by $(BOC)_2O$ in a 1N NaOH-*t*-BuOH mixture in order to prevent oxidation of the free amine. Submitting the resulting N-BOC derivative to ceric ammonium nitrate in aqueous acetonitrile furnished the N-BOC derivative of cinnamyl amine, which was eventually converted into the corresponding free amine (73% yield, overall; identical with an authentic sample of the *trans* isomer) by treatment with trifluoroacetic acid.

*In conclusion*, conversion of the aminoalcools resulting from condensation of aminosulphone **1** with aldehydes into oxazinones, followed by reduction with sodium amalgam, constitutes a convenient procedure for preparing allylic amines with high *trans* stereoselectivity.

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7- a) **Preparation of sulfone 1**: 4-methoxybenzylamine (13 ml, 100 mmol) was mixed, under argon, with vinyl phenylsulfone (16.8 g, 100 mmol) in THF (130 ml). One drop of trifluoroacetic acid was added under cooling (iced water) and the resulting clear solution was stirred at room temperature. After a few hours, TLC (10% MeOH-$CH_2Cl_2$) indicated complete disappearance of the starting sulfone. The solvent was removed *in vacuo* and the oily residue was taken up in $CH_2Cl_2$. The resulting solution was washed with 1N KOH and brine, then dried ($K_2CO_3$). Evaporation of solvents left a pale yellow oil which was crystallised from diisopropyl ether. Recrystallisation (1/3 $CH_2Cl_2$/hexane) afforded white crystals (22.8 g, 79%; m.p. 65°C); b) **General protocol for JPK coupling reaction of sulfone 1:** *i) the condensation step*: A solution of sulfone **1** (10 mmol) in THF (20 ml) was added dropwise, in 10 mn, to a cooled (-78°C) 1.4N solution of n-BuLi in hexane (20 mmol), diluted with THF (20 ml). The resulting clear yellow solution was stirred 20 mn at the same temperature, after which the aldehyde was added via syringe. Stirring was pursued for 1 hour at -78°C. TLC (ether) indicated almost complete disappearance of the starting sulfone and the formation of a new, less polar product. The reaction mixture was poured into pH 7 phosphate buffer (50 ml; final pH: 11) and extracted with ether (5x2 ml). Washing with brine (2x20 ml), drying ($Na_2SO_4$), and evaporating the solvents left an oil which was filtered on $NaHCO_3$-washed silica gel (ether); *ii) formation of the oxazinone*: A solution of CDI (10 mmol) in DMF (50 ml) was slowly added at room t. to a solution of the hydroxysulfone (10 mmol) in DMF (50 ml). After stirring overnight, the solvent was removed in a vacuum (0.5 τ). The pasty residue was taken up in ether (50 ml) and the resulting solution was washed with iced 0.1N HCl (10 ml) and brine (2x10 ml). Drying ($Na_2SO_4$) was followed by evaporation of the solvent and flash-chromatography on $NaHCO_3$-washed silica gel (ether/hexane; the oxazinones are slightly more polar than the starting hydroxysulfone); *iii) the reduction step*: To a cooled (-15°C) solution of the oxazinone (0.6 mmol) in methanol (4 ml) was sequentially added $Na_2HPO_4$ (250 mg; 2.5 eq.) and 5% sodium amalgam (675 mg; 5 eq.). After 30 mn, this addition was repeated. One hour later, ether (50 ml) was added and the mixture was washed with brine (3x10 ml), and dried ($K_2CO_3$). Evaporation was followed by flash-chromatography on $NaHCO_3$-washed silica gel (ether/hexane), what afforded the pure N-PMB-protected (*E*)-allylamine.

8- $^{13}C$ NMR data (50MHz, $CDCl_3$): **3a**: 51.22, 52.98, 55.38, 113.86, 113.91, 126.35, 128.63, 128.78, 129.52, 131.48, 132.4, 137.2, 158.75; **3c**: 18.08, 50.77, 52.63, 55.27, 113.77, 128.77, 129.12, 129.38, 131.13, 132.01, 132.34, 158.61; **3d**: 18.11, 24.42, 50.39, 51.47, 55.36, 114.07, 120.89, 128.78, 128.85, 128.92, 131.93, 136.08, 158.61; **3e**: 12.21, 13.87, 51.24, 52.70, 55.34, 113.84, 124.50, 126.31, 129.39, 130.30, 132.37, 136.70, 158.68.

(*Received in France* 21 *July* 1995; *accepted* 8 *September* 1995)