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Stereoselective Michael additions of lithiated ortho-sulfinylbenzyl carbanions derived from α-amino nitriles

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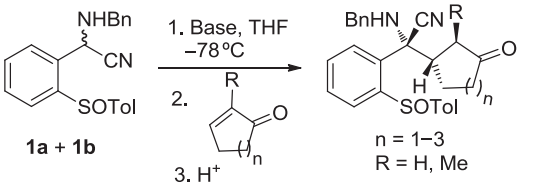
Enantiomerically pure α-substituted α-amino *ortho*-sulfinylphenylacetonitriles have been readily prepared by the reaction of diastereoisomeric mixtures of α-amino phenylacetonitriles with differently sized cycloalkenones and 2-methyl cyclopentenone in the presence of lithium bases. The reactions proceeded with high levels of stereoselectivity, generating molecules containing up to three asymmetric carbon centers in just one synthetic step.



Keywords: asymmetric synthesis; quaternary carbons; amino nitriles; Michael addition; remote stereocontrol by sulfoxides

1. Introduction

α, α-Disubstituted α-amino acids have been reported as glutamate agonists and antagonists (*1*), as compounds involved in enzymatic processes related with plant growth (*2*), and also as molecules capable of stabilizing protein secondary structures (*3*). Additionally, they are used as building blocks for the synthesis of peptide hormones and enzymatic inhibitors (*4*). As a consequence of their manifold applications, the search for new methods for their preparation is highly challenging. As α-amino nitriles are among the most useful precursors for synthesizing α-amino acids (among the reported methods for their preparation, a leading role is played by the reaction of aldimine-derived α-amino nitriles with electrophiles under basic conditions, see *e.g.* (*5*)), all those methods affording α, α-disubstituted α-amino nitriles also turn out to be of great interest (*6*). This prompted us several years ago to develop a highly competitive method for the stereoselective syntheses of a variety of α-substituted α-amino phenylacetonitriles (*7*), consisting in the completely stereoselective quaternization of the diastereoisomeric mixture resulting from the hydrocyanation of the 2-*p*-tolylsulfinylbenzaldimines, with different alkylating or acylating reagents in the presence of

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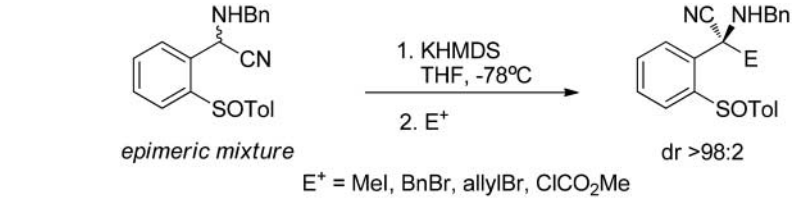
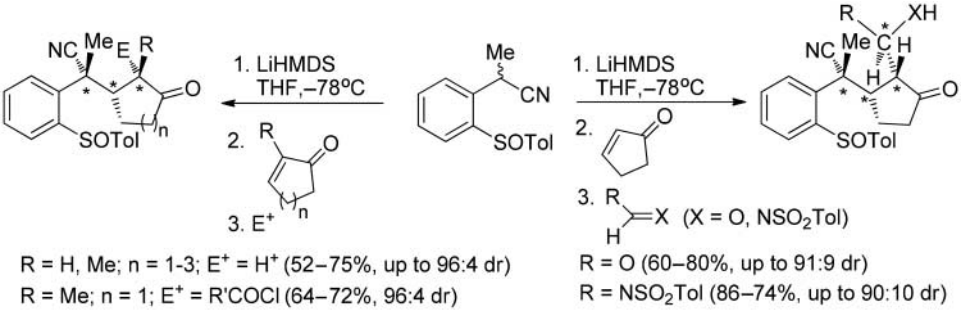
potassium hexamethyldisilazide (KHMDS) (Scheme 1). These results proved the high efficiency of the sulfinyl group as a remote chiral auxiliary capable of stabilizing the intervening carbanions in a totally diastereoconvergent process, the stereochemical outcome of which proved to be independent of the configuration at the benzylic carbon atom of the substrates.



Scheme 1. Diastereoconvergent quaternization of amino nitriles derived from 2-p-tolulsulfinylbenzaldimines.

More recently we have demonstrated that this ability can be exploited for creating acyclic fragments containing up to four contiguous stereocenters, all of them controlled by the sulfinyl group, in one-pot reactions of lithiated chiral *ortho*-sulfinylbenzyl carbanions with prochiral Michael acceptors and subsequent attack of a variety of electrophiles (Scheme 2) (*8*).

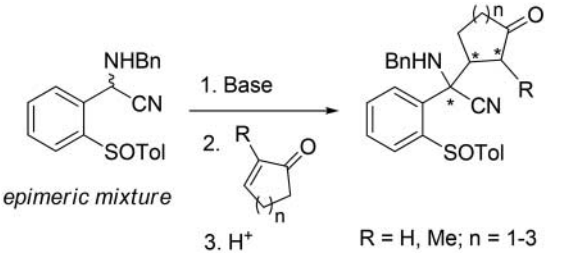


Scheme 2. Highly stereoselective Michael and tandem Michael-aldol reactions of ortho-sulfinylbenzyl carbanions.

With all these results in hand, and bearing in mind the potential interest of α, α-disubstituted α-amino nitriles with additional stereocenters in their framework, we initiated the study of the nucleophilic behavior of the carbanions derived from amino [2-(*p*-tolylsulfinyl) phenyl]acetonitriles in Michael-type addition reactions, which would broaden the scope of applicability of these substrates. We report herein the results obtained in the conjugate addition reactions of cycloalkenones with the anion derived from (benzylamino) [2-(*p*-tolylsulfinyl) phenyl]acetonitrile (**1**). Depending on the substitution pattern of the Michael acceptor employed in the reaction, up to three contiguous stereocenters could be generated in the process (Scheme 3).

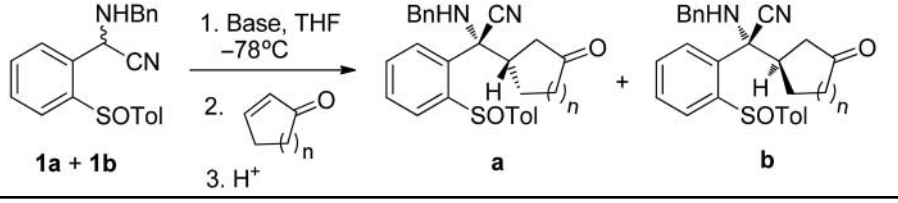
2. Results and discussion

The substrate of all the studied conjugate addition reactions, (benzylamino) [2-(*p*-tolylsulfinyl)phenyl]acetonitrile, was prepared by hydrocyanation of the corresponding 2-*p*-tolylsulfinylbenzaldimine, as previously reported (*7*). Initially, we studied the reaction



Scheme 3. Proposed strategy for the asymmetric synthesis of fragments containing up to three stereocenters from amino nitriles.

Table 1. Reactions of [2*S*,(S)*S*] and [2*R*,(S)*S*]-(benzylamino) [2-(*p*-tolylsulfinyl)phenyl] acetonitrile (**1a** + **1b**) with different cycloalkenones.



Entry	Base (additive)	*n*	Time	Product	Equiv. of E^{+a}	Yield (%)	dr (**a**:**b**)
1	KHMDS	1	2.5 h	**2a** + **2b**	3.0	37	90:10
2	KHMDS (18-crown-6 ether)	1	1.5 h	**2a** + **2b**	3.0	n.d.[b]	n.d.[b]
3	LiHMDS	1	0.5 h	**2a** + **2b**	3.0	60	> 98 : 2
4	LiHMDS	1	5 min	**2a** + **2b**	1.5	56	> 98 : 2
5	LiHMDS	2	5 min	**3a** + **3b**	1.5	87	> 98 : 2
6	LiHMDS	3	5 min	**4a** + **4b**	1.5	33	90:10

Note: [a]E^+ indicates cycloalkenone.
[b]Complex reaction mixture.

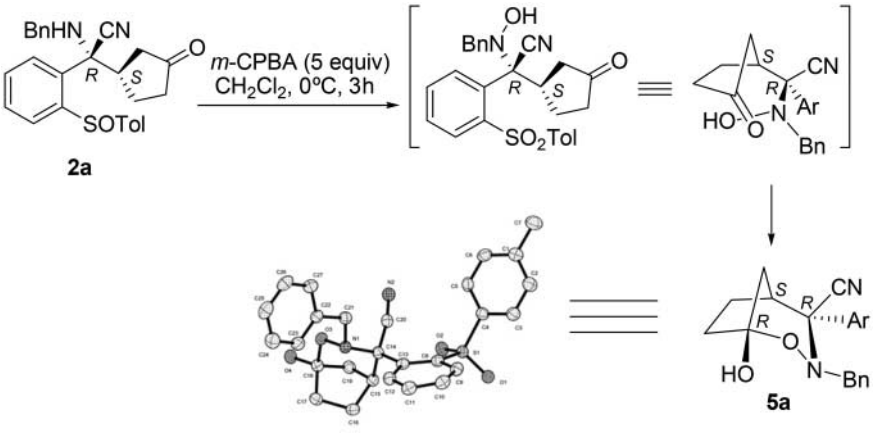
of the diastereoisomeric mixture (dr 48:52) of [2*S*,(S)*S*] and [2*R*,(S)*S*]-(benzylamino) [2-(*p*-tolylsulfinyl)phenyl]acetonitrile (**1a** + **1b**) with cyclopent-2-enone under different experimental conditions (Table 1, Entries 1–5).

In all the cases, a complete conversion of the substrate was observed by NMR of the crude reaction mixtures, the adduct [2*R*,3*S*,(S)*S*]-**2a** being the major or only isolated product. When the reaction was accomplished with KHMDS and 3 equiv. of cyclopentenone were used, the mixture **2a** and **2b** (dr 90:10, Table 1, Entry 1) was isolated in 37% yield after 2.5 h. The addition of 18-crown-6 ether for enhancing the reactivity of the anion led to the formation of complex mixtures (Entry 2). Fortunately, both stereoselectivity and yield were improved by using lithium hexamethyldisilazide (LiHMDS) as the base, yielding diastereomerically pure **2a** in 60% yield (Table 1, Entry 3). The reactivity with the lithium base was also higher and the reaction was almost instantaneous by using only 1.5 equiv. of cyclopentenone (Table 1, Entry 4). These results proved that all these reactions are diastereoconvergent regardless of the configuration of the benzylic carbon of the substrate and the employed counterion.

The reaction of the carbanion generated from **1a** + **1b** with LiHMDS and cyclohex-2-enone also proved to be completely diastereoselective affording only adduct **3a** in good yield (Table 1, Entry 5). The use of the larger cyclohept-2-enone (Table 1, Entry 6) produced erosion in the diastereoselectivity (dr 90:10) giving the major isomer **4a** in a lower yield, presumably due to its high instability, which hindered its isolation and purification.

The absolute configuration of **2a** was unequivocally determined as [2*R*,3*S*,(S)*S*] by X-ray diffraction analysis of the compound **5a** (crystallographic data (excluding structure factors) of

5a have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 921152. Copies of the data can be obtained, free of charge, on application to CCDC, Cambridge, UK (deposit@ccdc.cam.ac.uk)), obtained by treatment of **2a** with *m*-chloroperoxybenzoic acid. This compound was formed by the simultaneous *m*-CPBA oxidation of the sulfinyl (into sulfonyl) and the NH (into N−OH) groups, followed by attack of the OH to the carbonyl group, affording the hemiacetal **5a** (Scheme 4). As this sequence does not affect the configuration of the stereogenic carbon atoms present in the starting sulfoxide **2a**, the absolute configuration of the latter should be identical to that unequivocally determined for **5a**. Absolute configurations of compounds **3a** and **4a**, respectively, obtained as the only and major diastereoisomer starting from cyclohexenone and cycloheptenone, were assigned as that of **2a**.

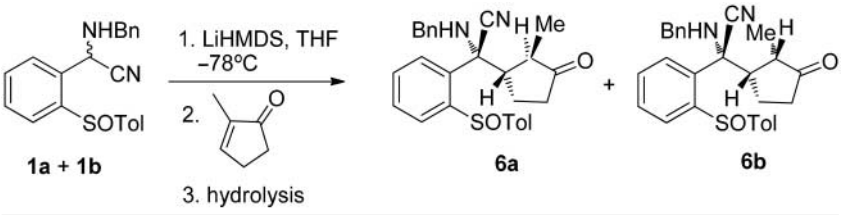


Scheme 4. Synthetic transformations for configurational assignment of **2a**.

Next we studied the reaction of 3-methylcyclopent-2-enone with the **1a** + **1b** mixture, in order to obtain compounds containing two vicinal quaternary stereocenters, but it was unsuccessful since the unaltered starting material was recovered after long reaction times. By contrast, the reaction of **1a** + **1b** with 2-methylcyclopent-2-enone under LiHMDS was complete affording a mixture of only two diastereoisomers (**6a** and **6b**) containing three stereocenters, two of them simultaneously created in the process (Table 2). The stereoselectivity was observed to be closely dependent on the quenching conditions. It was only moderate by using an aqueous solution of ammonium chloride (Table 2, Entries 1 and 2) and was improved by the addition of MeOH (Entry 3). The best results (dr 95:5) were achieved when a saturated HCl solution in MeOH was added to the reaction mixture at −78°C (Table 2, Entry 4). The loss of stereoselectivity when different quenching conditions were employed was attributed to changes in the temperature during the hydrolysis step. When 10% HCl–MeOH was added onto the reaction mixture at −78°C, protonation should occur on the rigid chelated enolate (*vide infra*). Other quenching conditions took place at higher temperatures which probably caused erosion in the stereoselectivity of the process.

Both diastereoisomers should differ only in the configuration of the stereogenic center next to the carbonyl group (the other two will exhibit the same configurations as those at compound **2a**). Thus, taking into account that this must be a consequence of the equilibration of the intermediate anion, we have assigned the configuration S to this center (Table 2) because this corresponds to the most stable situation where the methyl group and the quaternary carbon are in a trans arrangement in the cyclopentanone ring.

Table 2. Reaction of [2*S*,(S)*S*] and [2*R*,(S)*S*]-(benzylamino) [2-(*p*-tolylsulfinyl)phenyl] acetonitrile (**1a** + **1b**) with 2-methylcyclopent-2-enone.



Entry	Time (h)	Hydrolysis conditions	Equiv. E^{+a}	Yield (%)	dr (**a**:**b**)
1	0.5	Aq. sat. NH_4Cl	3.0	54	73:27
2	0.5	Aq. sat. NH_4Cl^b	3.0	54	70:30
3	1.0	Sat. NH_4Cl–MeOH	3.0	53	86:14
4	1.0	10% HCl–MeOH	1.5	53	95:5
5	0.5	10% HCl–MeOH[c]	1.5	53	55:45

Note: [a]E^+ indicates cycloalkenone.
[b]Inverse addition (carbanion was added onto the Michael acceptor).
[c]The reaction mixture was added onto the methanolic solution.

3. Mechanistic proposal

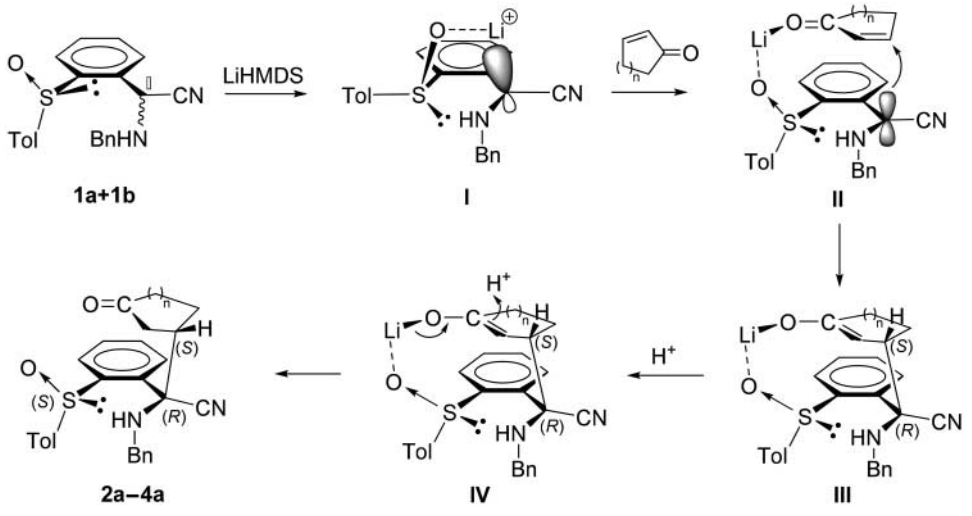
The stereochemical results obtained in the above described reactions can be explained as follows. The reaction of the epimeric mixture of amino nitriles (**1a** and **1b**) with LiHMDS initially generates the boat-like chelated sp^3 carbanionic species **Ia** (Scheme 5), with the metal associated with both the sulfinyl oxygen and the benzylic carbon atom. The favored arrangement of the substituents around the carbanionic carbon had been previously established as that indicated for **I** in Scheme 5 by theoretical calculations (*7*). This arrangement minimizes the dipolar repulsion between S→O and C:N bonds and is stabilized by the n^2–d^0 interactions between the lone electron pair at nitrogen and the empty d orbitals at sulfur (*9*). Such as it had been postulated for the acylation processes of other sulfinylbenzyl carbanions (*10*), the carbonyl oxygen atom of cycloalkenones may coordinate with the cation Li^+, thus breaking the initial boat-like chelate **I** and generating a new intermediate species **II**. Intramolecular addition from **II** would afford **III** with the *R* configuration at the benzylic stereocenter, coincident with that observed for the major or exclusive diastereoisomers obtained in these reactions. Simultaneously, the *S* configuration of the C-β atom at the cycloalkenone ring can also be predicted from this approach (Scheme 5).

From the above results, we can conclude that the *ortho*-sulfinyl group has proved to be a highly efficient chiral auxiliary for the Michael addition of tertiary benzylic carbanions derived from benzyl α-amino nitriles, affording enantiomerically pure α,α-disubstituted α-amino nitriles connected to additional stereocenters. Currently, we are developing the *in situ* trapping of the enolates formed in the conjugate addition with different types of electrophiles. The results will be reported in due course.

4. Experimental section

4.1. *Typical procedure for Michael addition reaction of (benzylamino) [2-(p-tolylsulfinyl)phenyl]acetonitrile*

To a solution of diastereoisomeric 48:52 mixture of [2*S*,(S)*S*] and [2*R*,(S)*S*]-(benzylamino) [2-(*p*-tolylsulfinyl)phenyl]acetonitrile (**1a** + **1b**, 36.1 mg, 0.1 mmol) in anhydrous THF (1.5 ml)



Scheme 5. Mechanistic proposal accounting for the stereochemical outcome of Michael additions of carbanions derived from **1a** + **1b** to cycloalkenones.

at −78°C under argon was added LiHMDS (1M in THF) (120 µl, 0.12 mmol). The mixture was stirred at −78°C for 5 min and then 0.15 mmol of the corresponding Michael acceptor was added dropwise. The reaction was monitored by TLC. Upon transformation of the starting material, the reaction was hydrolyzed using the method indicated in each case. The mixture was extracted with CH_2Cl_2 (3 × 5 ml), dried (Na_2SO_4), and the solvent was evaporated. The diastereoisomeric mixture was purified by flash column chromatography or by *Combiflash* system using a normal phase column (ISCO®); the used eluent was indicated in each case.

5. Supporting information

Characterization data for sulfinyl derivatives **2a**, **3a**, **4a**, **4b**, **6a**, **6b**, and compound **5a** are described in the supporting information.

Acknowledgements

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