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Tetrahedron Letters 45 (2004) 7231–7234
Tetrahedron Letters

Regio- and stereoselective transfer of *p*-toluenesulfonamido group from sulfur to carbon: preparation of aminoalcohol derivatives from allylalcohols☆

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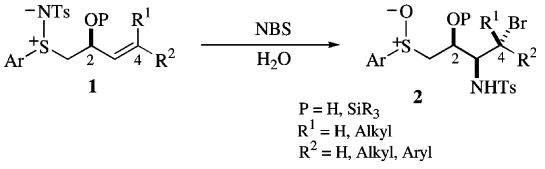
Received 21 July 2004; revised 4 August 2004; accepted 5 August 2004
Available online 21 August 2004

Abstract—A novel methodology for the regio- and stereoselective synthesis of amino alcohol derivatives from allylalcohols/ethers via intramolecular nucleophilic participation by the sulfilimine moiety is disclosed. The sulfilimine moiety is stereospecifically transformed to a sulfinyl moiety with an inverted configuration. The reaction is general and affords highly functionalised products.

Vicinal[1] and 1,3-amino alcohols[2] are structural motifs present in a variety of natural products and pharmaceutical agents. Interest in these structural units has led to the development of a variety of methods for their synthesis.[3] The addition of nucleophiles to double bonds, activated by complexation with electrophiles, affords highly functionalized products regio- and stereoselectively via asymmetric induction by allylic or homoallylic substituents.[4] We disclose herein an efficient, novel and a general method for the preparation of aminoalcohol derivatives **2** from readily accessible β-hydroxy (silyloxy) γ,δ-unsaturated sulfilimines **1** via intramolecular nucleophilic assistance,[5] by the sulfilimine group (Eq. 1).



(1)

The sulfilimines **4** were prepared[6] as a diastereomeric mixture in nearly equimolar quantities from the sulfide **3** and separated by column chromatography (Scheme 1).

The reaction of diastereomerically homogeneous sulfilimines **4a**–**e** with *N*-bromosuccinimide (NBS) was investigated with the aim of probing the influence of (a) the relative configuration of sulfur and C2, (b) the protecting group, (c) the geometry of the double bond and (d) the substituent at C4, on the regio- and stereoselectivity of product formation. The sulfilimines reacted at ambient temperature in toluene in the presence of water with NBS to yield the bromosulfonamides **5** (Table 1). Inspection of Table 1 reveals the following: (1) The sulfilimine moiety is stereospecifically transformed into a sulfoxide with an inverted configuration. (2) The reaction is general for a variety of substrates with different olefinic substitution patterns. (3) The reaction is clean and high yielding. (4) The reaction proceeds regioselectively affording products arising from a 5-*exo* nucleophilic attack by the sulfilimine group except for **4d**, which yields products resulting from 6-*endo* nucleophilic attack. This can be rationalized by the ability of the phenyl group to stabilize a partial positive charge at C4 leading to the nucleophilic attack at C4 in accordance with the Markonokov's rule.[7] (5) The reaction proceeds to afford the products with good to high stereoselectivity. The reaction probably proceeds via π complexed bromonium ion,[8] which on nucleophilic attack by the

Keywords: Sulfilimine; Bromosulfonamide; Intramolecular assistance; Sulfoxide.
☆IICT Communication No. 0408.
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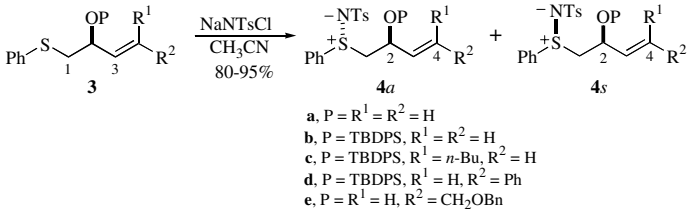
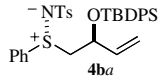
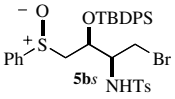
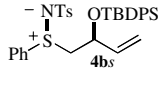
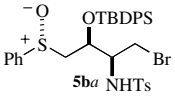
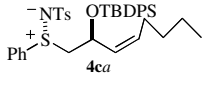
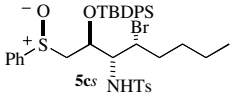
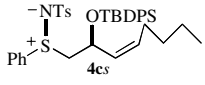
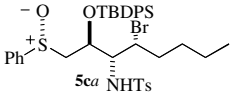
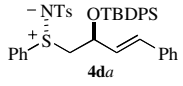
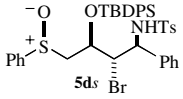
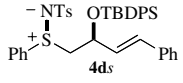
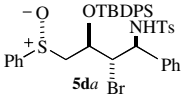
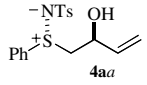
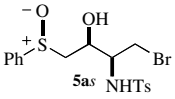
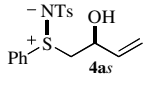
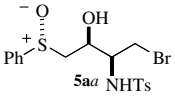
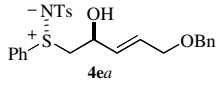
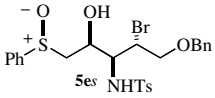
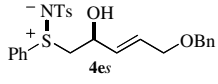
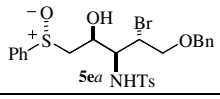
doi:10.1016/j.tetlet.2004.08.028



Scheme 1. Preparation of the diastereomeric mixture of sulfilimines.

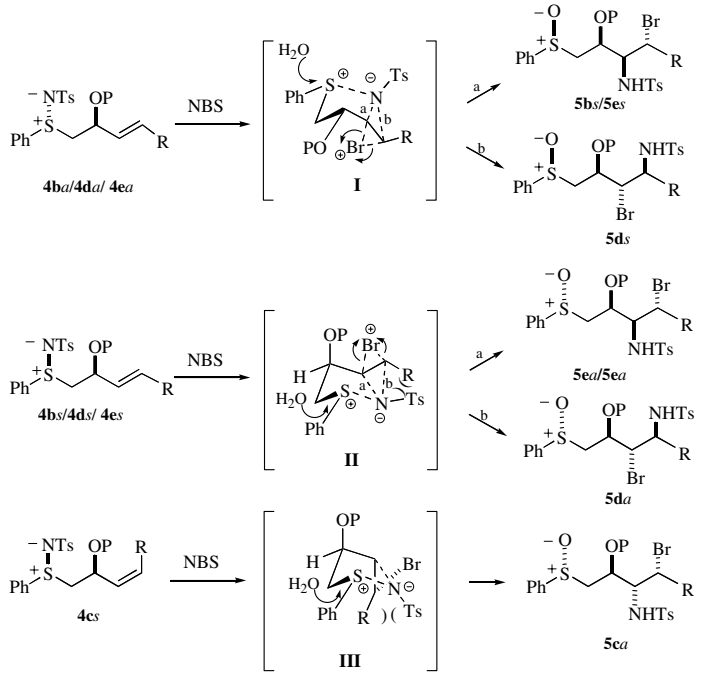
Table 1. Preparation of bromosulfonamides from unsaturated sulfilimines[a]

S. No.	Sulfilimine	Bromosulfonamide	Yield % C2–C3 (*syn:anti*)
1	 **4b*a***	 **5b*s***	80 >95:<5
2	 **4b*s***	 **5b*a***	82 >95:<5
3	 **4c*a***	 **5c*s***	90 <5:>95
4	 **4c*s***	 **5c*a***	85 1:2[b,c,d]
5	 **4d*a***	 **5d*s***	86 1:3[b,c,d]
6	 **4d*s***	 **5d*a***	82 <5:>95
7	 **4a*a***	 **5a*s***	86 >95:<5
8	 **4a*s***	 **5a*a***	85 >95:<5
9	 **4e*a***	 **5e*s***	90 >95:<5
10	 **4e*s***	 **5e*a***	86 3:1[b,c,d]

[a] All reactions were done on 0.5 mmol scale in toluene as the solvent in the presence of 1.3 equiv of NBS and 1.2 equiv of H_2O.
[b] The yield refers to the combined yield of both the products.
[c] The major product is depicted.
[d] The isomers are inseparable.

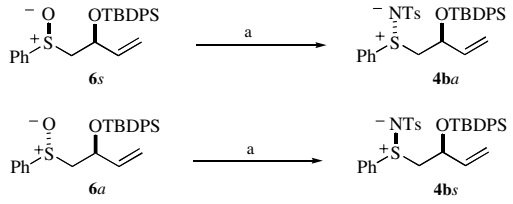
sulfilimine (pathway a or b) would afford the intermediates **I**, **II/III**, from the *anti* and the *syn* sulfilimines, respectively. Further hydrolysis of the salts by the attack of water at the sulfur atom would yield the inverted sulfoxide/the 1,2- (pathway a) or the 1,3-aminoalcohol derivatives (pathway b, Scheme 2).

When R = H and P = H/TBDPS, the reaction proceeds with excellent regio- and stereoselectivity to afford the 1,2-aminoalcohols. The intermediate **II** from **4e*s*** would experience steric interactions between the substituent R (CH_2OBn) and the *N*-Ts group thus explaining for the erosion of stereoselectivity in the reaction; inter-



Scheme 2. Proposed probable pathway for the regio- and stereoselective formation of bromosulfonamides.

mediate **I** from **4e***a* does not suffer from such steric repulsions. Likewise the intermediate **I** from **4d***a* has a boat-like structure, while the intermediate **II** from **4d***s* has a chair-like structure explaining for the excellent stereoselectivity observed with the latter. The poor stereoselectivity observed in the reaction of **4c***s* can be rationalized by invoking the intermediacy of **III**, which suffers from steric repulsions between the butyl chain and *N*-Ts. (6) The outcome of the reaction is the same for the substrates wherein the hydroxy group is protected or is free (compare entries 1, 2 with 7, 8). The silyl ether protected sulfilimines were chosen for study mostly due to the ease of their preparation and for the ease of isolation and purification of the products resulting from them. It is thereby apparent that the regio- and stereoselectivity of the reaction is influenced by the nature of the substituent R at C4, the olefin geometry and the relative configurations of sulfur and C2. The isomeric nature of the products **5a***s* and **5a***a* was proven by oxidation individually, to yield an identical sulfone. A similar exercise proved the isomeric character of sulfoxides **5b***s*/**5b***a*, **5c***s*/**5c***a*, **5d***s*/**5d***a* and **5e***s*/**5e***a*. The structure of **4d***a* with an *anti* orientation of the sulfilimine moiety and the silyloxy group was confirmed by single crystal X-ray diffraction.[9] The structure of sulfilimines **4a***a*, **4b***a*, **4c***a* and **4e***a* were assigned by comparison, which revealed similarities in the chemical shifts of C1, C2 protons to those in **4d***a*. The sulfilimines **4a***s*–**4e***s* also revealed similarities in their ^{1}H NMR spectra. The difference in chemical shifts (Δ^{δ}) between the methylene protons is lesser and the methine proton resonates downfield in **4a***a*–**4e***a* compared to **4a***s*–**4e***s*. The structure of the bromosulfonamide **5d***s* was secured by X-ray crystallography.[9] The X-ray structure established beyond doubt the inversion of sulfur configuration in going from the starting material to the product and also relative configuration at C2,



Scheme 3. Stereoselective preparation of sulfilimines from sulfoxides. Reagents and conditions: (a) TsNCO, *t*-BuSMe, CH_3CN, rt, 48–72 h, 70–75%.

C3 and C4. The structure of the product from **4c***a* was deduced by X-ray crystallography on the derived sulfone.[9] The *syn* disposition of the hydroxy and sulfonamido groups in **5a***a* was confirmed by NOE studies on the derived acetonide. The structures assigned to **5b***s* and **5b***a* were confirmed by deprotection to yield **5a***s* and **5a***a*, respectively. The structure assigned to **5e***s* was confirmed by transformation to the corresponding acetonide, which revealed a value of 2.9 Hz[10] for the coupling between C2H and C3H indicating the *trans* orientation of these protons in the acetonide.

Finally for exploiting the full potential of the methodology, it is clear from the results disclosed herein that the β-hydroxy sulfilimines be available as single diastereomers. Cram and co-workers[11] have shown that *N*-Ts-methyl-*p*-tolyl sulfilimine can be obtained with inversion of configuration from methyl-*p*-tolyl sulfoxide. Thus diastereomerically pure sulfoxides **6***s* and **6***a*[12] were readily transformed using the Cram protocol to yield **4b***a* and **4b***s*,[13] respectively (Scheme 3). Similarly the other sulfilimines used in the study should be accessible from the corresponding β-hydroxy sulfoxides, which can be

readily elaborated as single diastereomers by diastereoselective reduction of the corresponding β-keto sulfoxides.[14]

In conclusion, we have disclosed herein a novel protocol for the elaboration of aminoalcohol derivatives from allyl ethers via intramolecular nucleophilic sulfilimine group participation. The reaction has been shown to proceed highly regio- and stereoselectively. The sulfinyl group in the product can be utilized for C–C bond formation and the bromine atom for introducing other heteroatoms. The potential of the methodology for the synthesis of bioactive molecules is presently under progress and shall be reported in due course.

References and notes

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8. In the case of halogen additions, onium intermediates are generally freely reversible. See: Guindon, Y.; Slassi, A.; Ghiro, E.; Bantle, G.; Jung, G. *Tetrahedron Lett.* **1992**, *33*, 4257, and references cited therein.
9. Crystallographic data (excluding structure factors) for **4d***a*, **5d***s* and sulfone from **5c***s* have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers 233344-233346. Copy of the data can be obtained free of charge, on application to CCDC, 12, Union Road, Cambridge CB2 11EZ, UK [fax: +44(0)-1223-336033] or deposit@ccdc.cam.ac.uk.
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12. The sulfoxides **6***a* and **6***s* were readily obtained by $NaIO_4$ oxidation of **3a** to yield an inseparable mixture of hydroxy sulfoxides followed by treatment with *tert*-butyldiphenylchlorosilane and separation.
13. Sulfilimine **4b***a* was obtained along with small quantities of **4b***s* from **6***s*, while **4b***s* was obtained from **6***a* as a single compound.
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