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Tetrahedron Letters 45 (2004) 5125–5129
Tetrahedron Letters

Stereocontrolled synthesis of hydroxyethylamine isosteres via chiral sulfoxide chemistry

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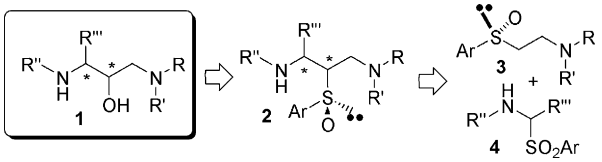
Received 8 March 2004; revised 27 April 2004; accepted 28 April 2004

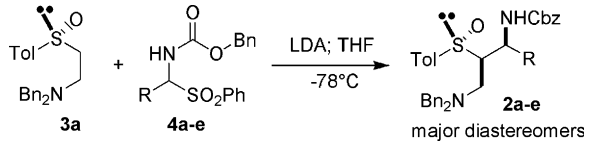
Abstract—A novel synthesis of enantiopure hydroxyethylamine isosteres **1** has been developed. Reaction of lithiated β-sulfinyl-ethylamines **3** with *N*-Cbz-imines generated in situ from α-amino-sulfones **4** afforded in good to excellent yields and moderate stereocontrol the 2-sulfinyl-1,3-diamines **2**. The latter were submitted to the nonoxidative Pummerer reaction (NOPR) in CH_2Cl_2, that produced the target compounds **1** in very good yields with inversion of configuration. In some cases, the use of acetonitrile as solvent resulted in a double-inversion pathway, leading for example to the oxazolidinone **5**. The total synthesis of an epimer of Saquinavir has been achieved by this method.

Among the most successful approaches to the development of potent enzyme inhibitors, modification of a peptide backbone through the incorporation of hydroxyethylamine dipeptide isosteres **1** (Scheme 1) has proven to be extremely valuable.[1] As an example, of the six FDA approved drugs that function as inhibitors for HIV protease, three (Saquinavir, Nelfinavir and Amprenavir) feature a hydroxyethylamine module.[2] Many routes to hydroxyethylamine isosteres **1** have been described,[3] but the syntheses on an industrial scale of Saquinavir,[4] Nelfinavir,[5] and Amprenavir[6] should be considered as benchmarks from the point of view of synthetic efficiency. In this communication we describe a conceptually new, two-step approach to hydroxy-ethylamine isosteres **1**, based on: (1) assembly of the hydroxyethylamine carbon framework through C–C bond forming reaction of chiral α-lithium β-sulfinyl-ethylamines **3** (Scheme 1) with the α-amino sulfones **4**, which are *N*-Cbz imines precursors; (2) stereoselective displacement of the sulfinyl by hydroxy group from the intermediate 2-sulfinyl-1,3-diamines **2** through the nonoxidative Pummerer reaction (NOPR).[7]



Scheme 1. Retrosynthetic strategy.

The enantiomerically pure sulfoxide (*R*)-**3a** (Scheme 2) was prepared by conjugate addition of dibenzylamine to vinyl *p*-tolylsulfoxide.[8] The Mannich-type reaction of α-lithium **3a** (2 equiv) with the α-amino-sulfones **4a–d**[9] occurred with very good yields and moderate stereocontrol (Table 1),[10] affording the 2-sulfinyl-1,3-diamines **2a–d** as the major diastereomers.[11] The only exception was the reaction involving **4e** (R = CH_2SPh), that took place with low yields due to partial degradation of **4e**



Scheme 2. Step 1: the condensation.

Keywords: Peptidomimetics; Sulfoxides; Mannich reaction.
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doi:10.1016/j.tetlet.2004.04.160

Table 1. Step 1: addition of lithiated **3a** to **4a–e**

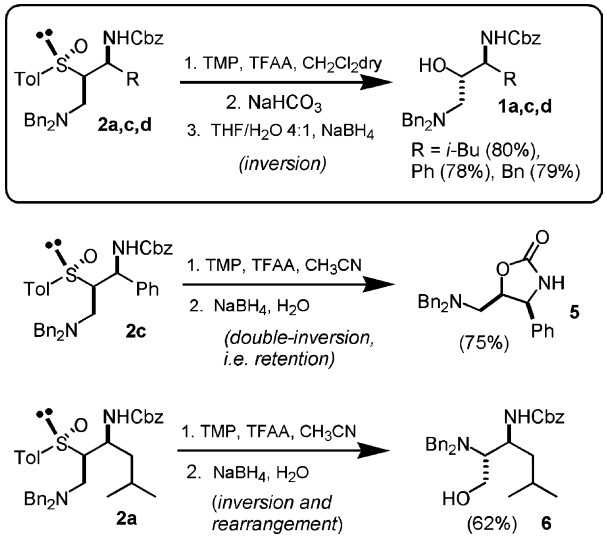
Product	R	Diastereom. ratio[a]	Yield (%)[b]
2a	Isobutyl	61:24:7.5:7.5	95
2b	C_2H_5	68.5:24:4.5:3[c]	86[d]
2c	C_6H_5	48:35:12:5	78
2d	$CH_2C_6H_5$	55:23:15:7	95
2e	CH_2SPh	39.5:26.5:21:13[c]	35

[a] Determined by HPLC analyses.
[b] Overall isolated yields.
[c] Stereochemistry not assigned.
[d] Determined by ^1H NMR analysis of the crude.

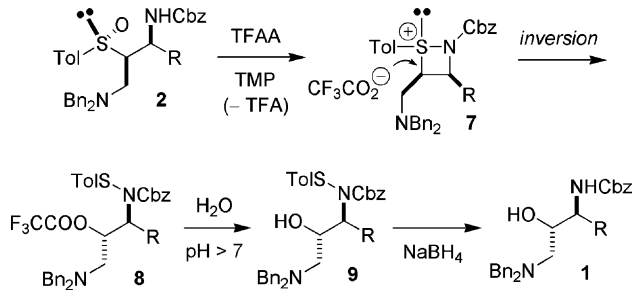
under the reaction conditions. The stereochemistries of **2c** and of one of the minor diastereomers of **2d** were determined by X-ray diffraction, whereas the other stereochemical assignments were made by chemical correlation and NMR spectroscopy.[12]

The second step of our strategy, namely the NOPR, has been studied in detail on the major diastereomers **2a**,**c** and **2d** (Scheme 3). The expected outcome, namely a formal S_N2-type displacement of the sulfinyl auxiliary by hydroxy group was observed upon treatment with trifluoroacetic anhydride (TFAA) (8 equiv) and *sym*-collidine (TMP) (3 equiv) in dry dichloromethane, followed by moderately basic aqueous work-up (typically $NaHCO_3$ or K_2CO_3) and finally by $NaBH_4$ reduction. This protocol afforded the hydroxyethylamine isosteres **1a**,**c** and **1d** in very good yields and total stereocontrol.[13]

However, the presence of the tertiary dibenzylamine function brought about a remarkable, and unexpected, modification of the standard NOPR reactivity, when acetonitrile was used as solvent.[14] In fact, **2c** afforded the *cis*-oxazolidinone **5** in good yield (Scheme 3) and overall retention of configuration (demonstrated by X-ray diffraction),[12] while **2a** gave the 2,3-diaminoalcohol **6** with inversion of configuration.[12] We next investigated the NOPR of **2d** in acetonitrile (reaction not shown in



Scheme 3. The stereodivergent 'nonoxidative' Pummerer reaction (NOPR).



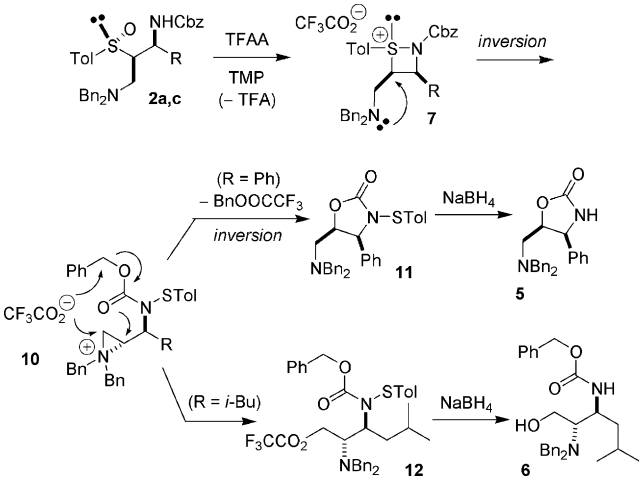
Scheme 4. Mechanism of the NOPR in dichloromethane.

Scheme 3). Surprisingly, in this case we observed the 'normal' NOPR outcome, with formation of the hydroxyethylamine isostere **1d** (79%), that was formed in CH_2Cl_2 as well.

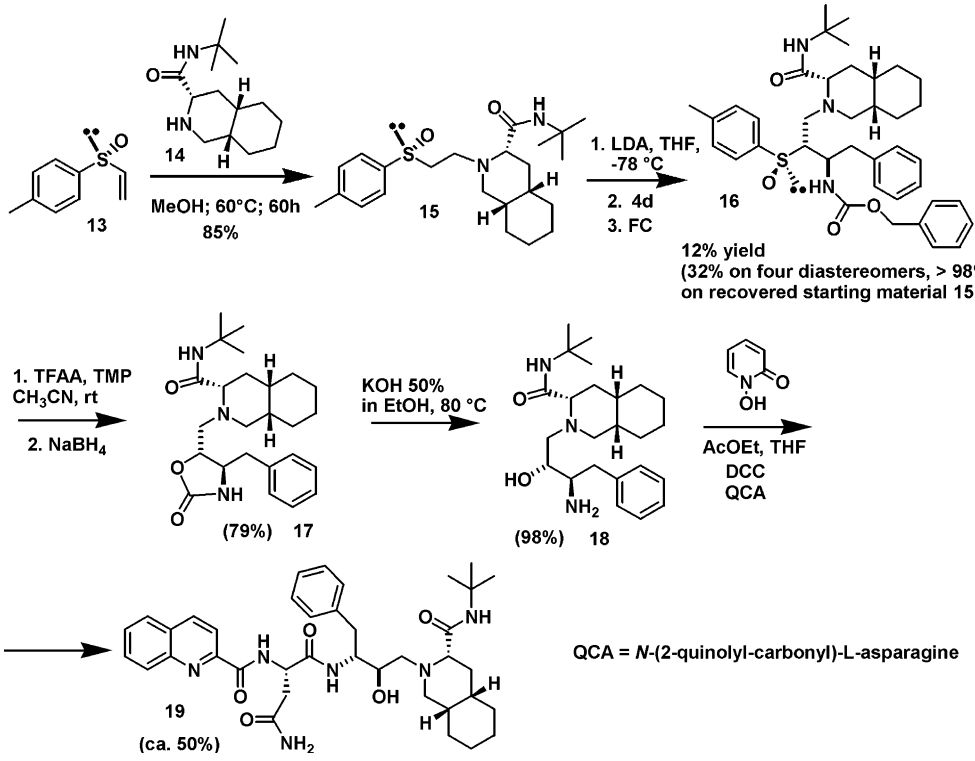
The results above can be interpreted as follows. The NOPR in dichloromethane follows the conventional mechanism (Scheme 4). One equivalent of TFAA acylates the sulfinyl oxygen of **2** providing, in the presence of TMP, the intermediate cyclic four membered sulfonium salt **7**, which is possibly in equilibrium with a σ-sulfurane form.

Recombination of **7** via S_N2-type attack of the trifluoroacetoxy anion to the sulfur-substituted stereogenic carbon, leads to the β-trifluoroacetoxy sulfenamide **8**, which is hydrolyzed to the alcohol **9** at pH > 7, and transformed into the final hydroxyethylamine isostere **1** upon reduction with $NaBH_4$. As a proof of this mechanism, compound **8c** could be isolated in 84% yield.

In acetonitrile, a highly polar solvent, formation of aziridinium ions **10** (Scheme 5) through nucleophilic attack of the dibenzylamino group on the electrophilic sulfur-substituted carbon of **7** became competitive.[15] The aziridinium ion **10c** (R = Ph), formed with inversion of configuration at carbon, can undergo intramolecular S_N2 ring-opening by action of a Cbz oxygen affording the *N*-*p*-tolylsulfanyl oxazolidin-2-one **11** (it could be isolated in 43% yield), which is easily transformed into



Scheme 5. Mechanism of the NOPR of **2a** and **2c** in acetonitrile.



Scheme 6. Total synthesis of a Saquinavir stereoisomer **19**.

the final product **5** upon reducing treatment. A different reaction pathway was observed for the aziridinium ion **10a** (R = *i*-Bu), that underwent intermolecular attack at the less hindered position by the trifluoroacetoxy counter-ion, affording the rearranged product **12**.

One-pot trifluoroacetate hydrolysis and sulfenamide reduction afforded the final 2,3-diaminoalcohol **6** in satisfactory overall yield and total stereocontrol. Ring openings of aziridinium ions **10a**,**c** to **12** and **11** were found to be fast-rated processes, and attempts to achieve intermolecular ring-opening by other amine nucleophiles have been hitherto unsuccessful.

Although it is currently not clear why in acetonitrile three structurally similar substrates **2a**,**c** and **2d** react following three totally different pathways under the same conditions, it is apparent that the NOPR in acetonitrile is dramatically influenced by the nature of the R group.[16]

We next studied the application of this synthetic methodology to the synthesis of a model hydroxyethylamine target, such as Saquinavir. The β-decahydroisoquinoline sulfoxide precursor **15** (Scheme 6) was prepared in good yields via aza-Michael-reaction of (*S*)-vinyl-*p*-tolylsulfoxide **13** with the decahydroisoquinoline-3-carboxylamide **14**. Condensation of lithiated **15** with the imine precursor **4d** afforded a mixture of the four possible diastereomers (32% overall isolated yield, >98% yield of recovery of unreacted **15**) in a 8.0:7.5:3.5:1.0 ratio. The second most abundant diastereomer **16** was crystallized and analyzed by X-ray diffraction,[12] that allowed us to assess its absolute stereochemistry. We therefore decided to use **16**, obtained in 12% yield by FC, for the completion of the synthesis.

Disappointingly, the planned NOPR in CH_2Cl_2 did not produce the desired outcome, affording instead complex mixtures of products.[17] However, using acetonitrile as solvent the reaction occurred in good yields, albeit with the double-inversion (retention) mechanism, providing the *trans*-oxazolidinone **17**. Saponification to the β-amino-alcohol **18** was achieved quantitatively, then coupling with *N*-(2-quinolyl-carbonyl)-L-asparagine, according to the conditions described by Hoffmann–La Roche scientists,[18] afforded the epimer **19** of Saquinavir having opposite configuration at the amine carbon of the hydroxyethylamine unit.[19]

In conclusion, we have developed a very direct and stereocontrolled approach to hydroxyethylamine dipeptide isosteres, based on sulfoxide chemistry. The total synthesis of an epimer of Saquinavir has been achieved. Further synthetic applications of the methodology and mechanistic studies are in progress.

Acknowledgements

MIUR (Cofin 2002, Project 'Peptidi Sintetici Bioattivi'), and CNR are gratefully acknowledged for economic support.

References and notes

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10. (a) Attempts to improve the stereocontrol by modification of base, solvent or reaction conditions have been so far unsuccessful. (b) Condensation reactions. General procedure. A solution of (R_S)-β-sulfinyl amine **3a** (5.5 mmol) in THF (20 mL) was added to a solution of LDA (6.6 mmol) in THF (40 mL) stirred under nitrogen at −75 °C. The slurry cleared up to a clean solution. Ten minutes later, a solution of sulfonyl derivative **4** (2.75 mmol) in THF (20 mL) was added dropwise to the orange solution. The reaction mixture was left under stirring at the same temperature for 5 min. The reaction progress was monitored by TLC (*n*-hexane/ethyl acetate = 7:3). A saturated NH_4Cl solution was added, the organics were extracted with AcOEt (3 × 30 mL), the combined extracts were dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography (FC) affording the products **2**.
11. (a) Pure compounds **2a**,**c**,**d** were isolated by standard flash chromatography on silica gel. (b) The following additional stereochemical assignments have been made based on X-ray diffraction, NMR studies and chemical correlations: in the reaction with **4a** the major diastereomer is (1*S*,1′*R*,R_S)-{1-[2′-dibenzylamino-1′-(toluene-4-sulfinyl)-ethyl]-3-methyl-butyl}-carbamic acid benzyl ester (**2a**), whereas the second (in abundance) diastereomer has (1*R*,1′*S*,R_S)-stereochemistry; in the reaction with **4c** the major diastereomer is (1*S*,2*R*,R_S)-[3-dibenzylamino-1-phenyl-2-(toluene-4-sulfinyl)-propyl]-carbamic acid benzyl ester (**2c**), whereas the second (in abundance) diastereomer has (1*R*,2*S*,R_S)-stereochemistry; in the reaction with **4d** the major diastereomer is (1*S*,2*R*,R_S)-[1-benzyl-3-dibenzylamino-2-(toluene-4-sulfinyl)-propyl]-carbamic acid benzyl ester (**2d**), whereas the second (in abundance) diastereomer has (1*R*,2*S*,R_S)-stereochemistry.
12. Experimental details of X-ray diffraction and ^1H NMR stereochemical assignments will be published in a full paper.
13. The stereochemistry of **1c** was unambiguously assigned by X-ray diffraction of a *N*-Bn oxazolidinone derivative (see Note 12), whereas the configurations of **1a**,**d** were determined on the basis of spectroscopic analogies with **1c**. (b) Pummerer reaction. General procedure in CH_2Cl_2. To a solution of (R_S)-sulfinyl substrate **2** (2.00 mmol) in anhydrous CH_2Cl_2 (70 mL) stirred at 0 °C, neat TMP (6.0 mmol, 900 μL) and TFAA (10.0 mmol, 1.4 mL) were added dropwise and temperature was allowed to reach rt. The reaction progress was monitored by TLC (*n*-hexane/ethyl acetate, 7:3) until completion. A 5% aqueous $NaHCO_3$ solution was then added up to pH 7. The organics were extracted with AcOEt (3 × 30 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was dissolved in a THF/H_2O 4:1 mixture (12 mL) and treated portionwise with solid $NaBH_4$. Gas evolution occurred and the reaction mixture was left under stirring overnight. The reaction progress was monitored by TLC (*n*-hexane/ethyl acetate, 7:3) until completion. A saturated NH_4Cl solution was then added, the resulting mixture was diluted with water and the organics were extracted with ethyl acetate (3 × 50 mL), dried over anhydrous sodium sulfate, filtered and the solvent evaporated at reduced pressure to give a residue, that was purified by FC.
14. Acetonitrile has been so far used as the solvent of choice for the NOPR.
15. For some key studies on the application of aziridinium ions in synthesis see: (a) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555–3557; (b) Weber, K.; Kuklinski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647–649; (c) O'Brxien, P.; Towers, T. D. *J. Org. Chem.* **2002**, *67*, 304–307.

16. The influence of stereochemistry on the NOPR of substrates **2** is currently under investigation.
17. The main side-process, according to ^{1}H NMR analysis of the mixtures, was the cleavage of the *N*-*tert*-butyl group on the decahydroisoquinoline-3-carboxylamide residue.
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19. Indeed, ^{1}H NMR analysis showed that **19** is a diastereomer of Saquinavir, according to the spectra accurately described in: Gilbert, J. C.; Redshaw, S.; Simmonite, H. S.; Thomas, W. A.; Whitcombe, I. W. A. *J. Chem. Soc., Perkin Trans. 2* **1993**, 475–479.