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Short Note

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (*R*)-4-methylbenzenesulfonimidate

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Abstract: (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*R*)-4-methylbenzenesulfonimidate was synthesized via the stereoselective NH-transfer to (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*S*)-4-methylbenzenesulfinate. The reaction employed diacetoxyiodobenzene (DIB) and ammonium carbamate, and occurred in acetonitrile at room temperature. The imidation of sulfur proceeded with complete stereocontrol, and the reaction afforded the desired product as a single diastereoisomer and with high enantiocontrol (*e.r.* = 97:3) in 70% yield. The product was characterized by ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, IR spectroscopy, HRMS, and the enantiomeric ratio was established by HPLC analysis at the chiral stationary phase.

Keywords: sulfonimidate; asymmetric synthesis; iodonitrene; sulfur imidation

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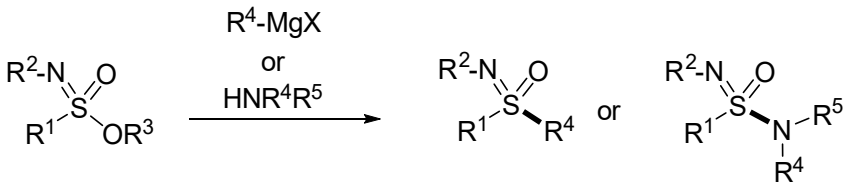
1. Introduction

Sulfonimidates, the mono-aza analogues of sulfonamides, are useful reagents in organic synthesis. These compounds have been efficiently exploited as alkyl transfer reagents and as precursors of other pharmaceutically relevant S(VI) motifs [1]. Moreover, the stereogenic sulfur of sulfonimidates can be also harnessed as a template for asymmetric synthesis. For example, the reaction of carbon nucleophiles with sulfonimidates, which involves the formation of a new S-C bond with the concurrent loss of the alkoxy group, proceeds with the inversion of the configuration of sulfur in a S_N2 fashion (Scheme 1) [2]. Consequently, the reaction of the stereodefined sulfonimidates enabled the preparation of valuable optically active sulfoximines, as was recently reported by Stockman and co-workers [3]. Similarly, the reaction of sulfonimidates with amines produced relevant sulfonimidamides, again, by using a formal nucleophilic substitution process [4].



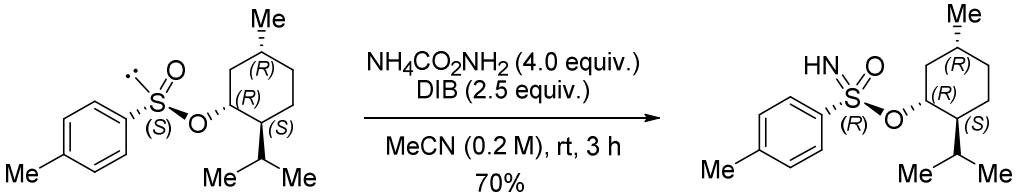
Scheme 1. Reaction of sulfonimidates with organomagnesium compounds and amines.

The synthesis of chiral optically active sulfonimidates is highly valuable in an asymmetric synthesis, but it is still poorly explored. The preparation of enantioenriched sulfonimidates is essentially limited to cyclic compounds that are accessible by the intramolecular oxidative cyclization of sulfinamides derived from chiral amino alcohols [2,5]. Alternatively, optically active sulfonimidates can be prepared from chiral sulfonimidoyl halides by using sodium alkoxides [6,7]. Hence, the preparation of acyclic optically active sulfonimidates is rather limited. Recently, in collaboration with Bull's research group (Imperial

College London), we have been involved in the development of new synthetic strategies for the chemoselective transfer of electrophilic nitrogen to sulfur [8–10] and nitrogen [11] atoms using hypervalent iodine reagents [12]. In this context, we recently reported the synthesis of sulfinimidate esters from thiols, diacetoxyiodobenzene (DIB) and ammonium carbamate [13]. This transformation is supposed to proceed thorough the generation of sulfinate esters, through the oxidation of thiols, and the subsequent imidation of such sulfinates by a transient iodonitrene. Based on the evidence that the sulfur imidation via iodonitrene can occur on sulfinate ester, we report herein the synthesis of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*R*)-4-methylbenzenesulfonimidate from commercially available (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*S*)-4-methylbenzenesulfinate, which is known as the Andersen's reagent [14].

2. Results

A solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*S*)-4-methylbenzenesulfinate (0.2 M in MeCN) was treated with 4.0 equivalents of ammonium carbamate and 2.5 equivalents of diacetoxyiodobenzene, and the mixture was stirred for 3 h at room temperature (Scheme 2). The ^{1}H NMR analysis of the crude evidenced the total consumption of the starting sulfinate and the formation of the desired product as a single diastereoisomer. The formation of sulfonimidate **2** was first assumed by the appearance of a broad proton signal at 3.14 ppm which was assigned to the NH group ($CDCl_3$). The product was obtained in 70% yield (*e.r.* = 97:3) after column chromatography on neutral alumina. The HRMS analysis confirmed the empirical formula for sulfonimidate **2**. To assign the enantiomeric ratio of sulfonimidate **2**, the starting menthyl sulfinate (±)-**1** was synthesized from racemic menthol, obtaining a 1:1 mixture of diastereoisomer to sulfur, which was subsequently transformed under the reported conditions into racemic sulfonimidate (±)-**2**. The HPLC analysis at the chiral stationary phase of the product revealed the expected four peaks for the four steroisomers used as the reference against the optically active compound **2** (see Supplementary Materials). Although the X-ray analysis could not be performed because of the waxy nature of sulfonimidate **2**, the imidation step was performed stereoselectively towards (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*R*)-4-methylbenzenesulfonimidate according to precedent results observed in the imidation of chiral optically active sulfoxides [15,16].



1 (*e.r.*= 97:3) **2** (*e.r.* = 97:3)

Scheme 2. Synthesis of sulfonimidate **2**.

3. Materials and Methods

General. All of the chemicals were purchased from Fluorochem (Hadfield, UK) and TCI Europe (Zwijndrecht, Belgium), and they were used without further purification. The infrared spectrum was recorded in reciprocal centimeters (cm^{-1}) using a PerkinElmer 283 Spectrometer (FT-IR, Waltham, MA, USA) with a KBr disc. The NMR spectra were recorded using a Varian Mercury 300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C, Santa Clara, CA, USA). The peaks of the residual solvents were used as the internal standards which were related to TMS at δ 7.26 ppm (^{1}H in CDCl3) and δ 77.00 ppm (^{13}C in CDCl3). The NMR data are reported as follows: the chemical shift (multiplicity (s = singlet, d = doublet, t = triplet and q = quartet)), the spin–spin coupling constants (*J*) which are reported in Hertz, and the integration and signal assignment. High resolution mass analysis was performed using an Agilent 6530 accurate mass Q-TOF (Santa Clara,

CA, USA) with electrospray ion source (ESI) which was operated in a positive ion mode. Flash column chromatography was performed using neutral alumina according to the standard techniques. The solutions were concentrated under reduced pressure with a rotary evaporator. For the thin layer chromatography (TLC), aluminium sheets precoated with silica gel 60 F254 (Merck KGaA, Darmstadt, Germany) were used, and the spots were visualized under UV light (λ = 254 nm) and/or from oxidation with KMnO4 (aq.).

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl (R)-4-methylbenzenesulfonimidate. To a solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*S*)-4-methylbenzenesulfinate (1 g, 3.4 mmol) in MeCN (17 mL), ammonium carbamate (1.06 g, 13.6 mmol, 4.0 equiv.) and diacetoxyiodobenzene (2.74 g, 8.5 mmol, 2.5 equiv.) were added in one portion, and the mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, then, 100 mL of $NaHCO_3$ (aq.) solution was added and the mixture was extracted with 3 × 50 mL of AcOEt. The organic layers were collected, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The reaction crude was purified by column chromatography on neutral alumina (R_f = 0.5, 20% AcOEt in hexane) to afford the desired product as a white waxy solid (740 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H, Ar–H), 7.29 (d, *J* = 8.2 Hz, 2H, Ar–H), 4.21 (td, *J* = 10.8, 4.5 Hz, 1H, CH), 3.14 (s, 1H, NH), 2.41 (s, 3H, CH_3), 2.13–2.03 (m, 1H, C*H*H), 1.85 (dtd, *J* = 13.7, 6.8, 2.1 Hz, 1H, CH), 1.66–1.55 (m, 2H, 2 × C*H*H), 1.41–1.21 (m, 2H, 2 × CH), 1.15–1.08 (m, 1H, C*H*H), 0.94–0.76 (m, 7H), 0.39 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, CDCl3) δ 143.7, 136.9, 129.5, 127.6, 82.2, 47.8, 42.4, 34.0, 31.8, 25.5, 23.1, 22.1, 21.6, 21.1, 15.3. IR (KBr) = 3271, 2923, 2851, 1454, 1328, 1158, 1093, 814. HRMS (ESITOF) *m*/*z* $(2M + Na)^+$ calcd for $C34H54N_2NaO_4S_2$ 641.3423; found 641.3416. $[\alpha]_D^{20} = -45.8^\circ$ ($CDCl_3$, c 0.1).

Supplementary Materials: Copies of 1H, 13C, COSY, HSQC spectra. HPLC analysis.

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Conflicts of Interest: The authors declare no conflict of interest.

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