Molbank **2014**, M834; doi:10.3390/M834

OPEN ACCESS

molbank

ISSN 1422-8599

www.mdpi.com/journal/molbank

Short Note

(*R*)-(−)-2-[(5-Oxido-5-phenyl-5λ^4-isoquino[4,3-*c*][2,1]benzothiazin-12-yl)amino]benzonitrile

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Received: 25 July 2014 / Accepted: 19 August 2014 / Published: 26 August 2014

Abstract: Copper-catalyzed cross-coupling between (*S*)-*S*-methyl-*S*-phenylsulfoximine (**1**) and 2-iodobenzonitrile (**2**) resulted in the discovery of an unprecedented one-pot triple arylation sequence to give (*R*)-(−)-2-[(5-oxido-5-phenyl-5λ^4-isoquino[4,3-*c*][2,1]benzothiazin-12-yl)amino]benzonitrile (**4**). Here, we describe the synthesis of the title compound (*R*)-**4** and the elucidation of its structure by means of various techniques.

Keywords: sulfoximines; benzothiazines; arylation; copper catalysis

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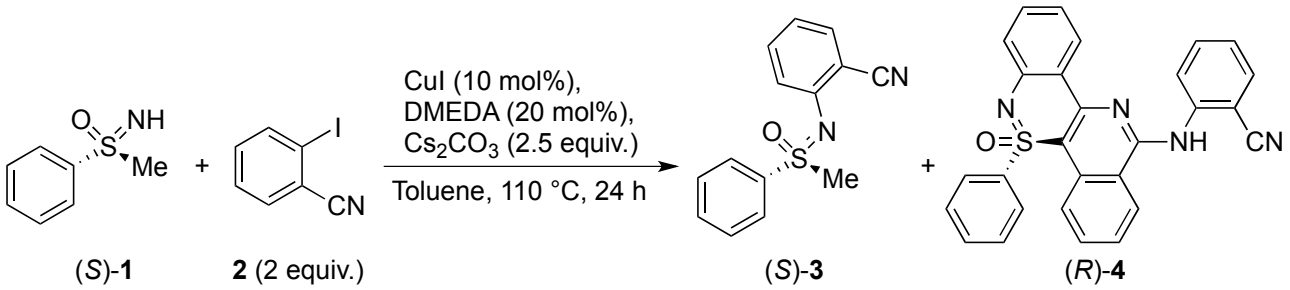
Introduction

Functionalized sulfoximines derived from (*S*)-*S*-methyl-*S*-phenylsulfoximine (**1**) are efficient chiral ligands in asymmetric metal catalysis [1–6]. Key step to access these compounds is the transition-metal catalyzed *N*-arylation reaction of (*S*)-**1** with a suitable aryl halide. For an ongoing project towards novel sulfonimidoyl-based ligands we required (*S*)-*N*-(2-cyanophenyl)-*S*-methyl-*S*-phenylsulfoximine (**3**) in larger quantities. Originally, syntheses of (*S*)- and (*R*)-**3** had only been achieved by palladium-catalyzed cross-couplings of the corresponding enantiopure sulfoximine **1** with 2-bromo- or 2-chlorobenzonitrile, respectively, [7–9]. Now it was envisaged to utilize a copper-catalyzed protocol [10] for the preparation of (*S*)-**3** starting from 2-iodobenzonitrile (**2**). To our surprise, application of this copper-based system also furnished a novel compound [(*R*)-(−)-2-[(5-oxido-5-phenyl-5λ^4-isoquino[4,3-*c*][2,1]benzothiazin-12-yl)amino]benzonitrile (**4**)], which was formed by an unexpected triple arylation cascade with aryl iodide **2** under these conditions.

Results and Discussion

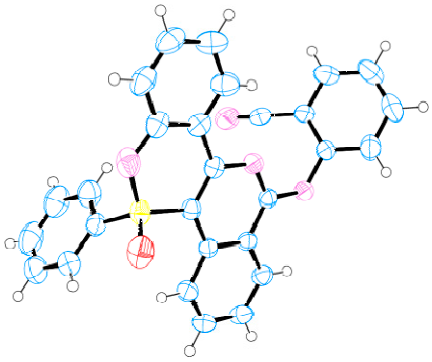
Following the reported procedure [10], the *N*-arylation of sulfoximine (*S*)-**1** was carried out with 2-iodobenzonitrile (**2**), cesium carbonate, and catalytic quantities of copper(I) iodide and *N*,*N*'-dimethylethylenediamine (DMEDA) in toluene (Scheme 1). However, arylation product (*S*)-**3** was only obtained in 61% yield and a considerable amount (23%) of an unknown second compound was isolated. By diligent examination of all analytical data this product was identified as title compound (*R*)-**4**.

Scheme 1. Synthesis of (*R*)-(−)-2-[(5-oxido-5-phenyl-5λ^4-isoquino[4,3-*c*][2,1]benzothiazin-12-yl)amino]benzonitrile (**4**).



The unknown second compound was optically active which evidenced the retention of a stereogenic center at sulfur whose full stereochemical integrity could be confirmed by CSP-HPLC analysis. The IR spectrum unambiguously demonstrated the presence of a sulfonimidoyl moiety by displaying classificatory absorption bands at 1241 and 1149 cm^{-1} for the S=O and S=N vibration, respectively [11]. Absorption bands at 3258 and 2221 cm^{-1} were attributed to an amino and a nitrile group, respectively. Furthermore, three typical absorption bands at 1601, 1572 and 1515 cm^{-1} showed vibrations of aromatic C=C bonds with diagnostic bands at 754 and 681 cm^{-1} indicating both mono-substitution and 1,2-disubstitution of aromatic rings. The ^{1}H NMR spectrum taken in $CDCl_3$ consisted of 18 largely coupled sharp signals in the region of 7.11–8.81 ppm for carbon- and nitrogen-bound protons (the latter resonating at 10.51 ppm in d_6-DMSO). Importantly, the S-C*H*$_3$ singlet, typically around 3.20 ppm, was not present anymore, indicating a full substitution of the corresponding carbon atom. The ^{13}C NMR spectrum recorded in $CDCl_3$ showed 11 quaternary carbons (with the nitrile carbon at 117.5 ppm) and 17 aromatic *C*-H groups. Consequently, the NMR data suggested a notably asymmetric molecular structure. All available mass spectrometric techniques provided a molar mass of 458 g mol^{-1} for the unknown compound. From a combustion analysis an elemental composition of $C_{28}H_{18}N_4OS$ was deduced which also supported the result of the MS experiments. Based on all these individual findings, the unknown compound was proposed to be (*R*)-(−)-2-[(5-oxido-5-phenyl-5λ^4-isoquino[4,3-*c*][2,1]benzothiazin-12-yl)amino]benzonitrile (**4**). Finally, this assumption was unequivocally confirmed by X-ray crystal structure analysis of (*R*)-**4** after recrystallization from acetonitrile (Figure 1).

Figure 1. ORTEP projection of (*R*)-**4** obtained by single-crystal X-ray diffraction with ellipsoids shown at 50% probability level (one associated molecule of acetonitrile omitted for clarity) [12].



Experimental

A large, flame-dried Schlenk tube under argon was charged with sulfoximine (*S*)-**1** (0.897 g, 5.78 mmol), 2-iodobenzonitrile (**2**, 2.730 g, 11.56 mmol, 2.0 equiv.), Cs_2CO_3 (4.710 g, 14.45 mmol, 2.5 equiv.), CuI (0.110 g, 0.578 mmol, 10 mol%), dry toluene (12 mL) and DMEDA (126 µL, 1.16 mmol, 20 mol%) in the order given. After the Schlenk tube was tightly sealed with a stopper, the reaction mixture was stirred at 110 °C for 24 h and then cooled down to room temperature. DCM and aqueous HCl (c = 2 mol/L) were added. The organic phase was separated and the product was extracted from the aqueous layer with DCM three times. The combined organic phases were dried with $MgSO_4$ and filtered. After evaporation of solvents, the oily residue was subjected to column chromatography (SiO_2, *n*-pentane/EtOAc = 2/1). Product (*R*)-**4** was isolated as a yellow solid. Additionally, sulfoximine (*S*)-**3** was separately obtained as a yellow oil (61% yield, 0.899 g, 3.51 mmol).

Yield: 23% (0.616 g, 1.34 mmol); mp = 211–212 °C (racemate: 263–265 °C); $[\alpha]$ = −57.7 (c = 0.6 g, 100 mL^{-1}, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.11 (ddd, J = 8.2 Hz, 7.1 Hz, 1.2 Hz, 1H, Ar-H), 7.25 (dd, J = 8.0 Hz, 1.1 Hz, 1H, Ar-H), 7.27 (td, J = 7.6 Hz, 1.0 Hz, 1H, Ar-H), 7.42–7.50 (m, 3H, Ar-H), 7.50–7.58 (m, 3H, Ar-H), 7.70 (dd, J = 7.8 Hz, 1.5 Hz, 1H, Ar-H), 7.78 (ddd, J = 8.8 Hz, 7.5 Hz, 1.6 Hz, 1H, Ar-H), 7.87–7.90 (m, 2H, Ar-H), 8.07 (dd, J = 7.6 Hz, 1.6 Hz, 1H, Ar-H), 8.19–8.24 (m, 2H, Ar-H and NH), 8.50 (dd, J = 8.1 Hz, 1.5 Hz, 1H, Ar-H), 8.81 (d, J = 8.4 Hz, 1H, Ar-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 103.4 (C), 105.5 (Ar-C), 116.9 (Ar-C), 117.5 (C), 118.4 (Ar-C), 120.3 (Ar-CH), 121.8 (Ar-CH), 122.3 (Ar-CH), 123.6 (Ar-CH), 123.8 (Ar-CH), 124.8 (Ar-CH), 125.9 (Ar-CH), 127.6 (Ar-CH), 127.7 (2 Ar-CH), 129.0 (2 Ar-CH), 132.0 (2 Ar-CH), 132.4 (Ar-CH), 132.5 (Ar-C), 132.8 (Ar-CH), 133.9 (Ar-CH), 141.7 (Ar-C), 144.0 (Ar-C), 144.2 (Ar-C), 148.0 (C), 153.2 (C) ppm; ^{1}H NMR [600 MHz, $(CD_3)_2SO$]: δ = 6.98 (ddd, J = 8.2 Hz, 7.2 Hz, 1.1 Hz, 1H, Ar-H), 7.11 (dd, J = 8.1 Hz, 0.8 Hz, 1H, Ar-H), 7.40 (ddd, J = 8.6 Hz, 7.2 Hz, 1.6 Hz, 1H, Ar-H), 7.53 (td, J = 7.7 Hz, 1.0 Hz, 1H, Ar-H), 7.56–7.60 (m, 2H, Ar-H), 7.60–7.64 (m, 1H, Ar-H), 7.67–7.73 (m, 2H, Ar-H), 7.80 (d, J = 8.0 Hz, 1H, Ar-H), 7.84–7.88 (m, 3H, Ar-H), 8.04 (dd, J = 7.8 Hz, 1.4 Hz, 1H, Ar-H), 8.12 (dd, J = 7.7 Hz, 1.8 Hz, 1H, Ar-H), 8.18 (dd, J = 8.1 Hz, 1.5 Hz, 1H, Ar-H), 8.68 (dd, J = 7.5 Hz, 1.7 Hz, 1H, Ar-H), 10.51 (s, 1H, NH) ppm; ^{13}C NMR [150 MHz, $(CD_3)_2SO$]: δ = 103.5 (C), 110.2 (Ar-C), 117.0 (Ar-C), 117.4 (C), 118.0 (Ar-C), 119.7 (Ar-CH), 122.6 (Ar-CH), 123.6 (Ar-CH), 124.5 (Ar-CH), 125.6 (Ar-CH), 126.2 (Ar-CH), 127.1 (2 Ar-CH), 127.3 (Ar-CH), 127.4 (Ar-CH), 129.3 (2 Ar-CH),

131.7 (Ar-C), 131.8 (Ar-CH), 132.2 (Ar-CH), 133.0 (Ar-CH), 133.1 (Ar-CH), 133.9 (Ar-CH), 141.9 (Ar-C), 143.7 (Ar-C), 144.0 (Ar-C), 147.4 (C), 155.6 (C) ppm; IR (ATR): ν = 3640, 3258, 2324, 2221, 2020, 1980, 1936, 1601, 1572, 1546, 1515, 1484, 1459, 1422, 1376, 1333, 1277, 1241, 1206, 1149, 1092, 1038, 1009, 976, 844, 794, 754, 720, 681 cm^{-1}; EI-MS: *m*/*z* (%) = 458 (100) $[M]^+$, 410 (15), 381 (22), 357 (9), 333 (62), 102 (6), 77 (12), 51 (10); CI-MS: *m*/*z* (%) = 499 (3) $[M+C_3H_5]^+$, 487 (16) $[M+C_2H_5]^+$, 459 (100) $[M+H]^+$, 358 (7); ESI-MS: *m*/*z* (%) = 939 (9) $[2M+Na]^+$, 497 (8) $[M+K]^+$, 481 (24) $[M+Na]^+$, 459 (42) $[M+H]^+$, 358 (100); ESI-HRMS: *m*/*z* calcd for $C_{28}H_{19}N_4OS$: 459.12741; found 459.12793 with Δ = 1.14 ppm; anal. calcd for $C_{28}H_{18}N_4OS$ (458.54): C, 73.34; H, 3.96; N, 12.22; found C, 73.44; H, 4.09; N, 12.30; HPLC: t_r = 16.8 min [major], t_r = 25.2 min [minor] (Chiralpak AD-H, 0.6 mL min^{-1}, *n*-heptane/isopropanol = 60/40, λ = 230 nm, 20 °C); >99% ee.

Crystallographic data were collected with a Bruker Kappa APEX II CCD-diffractometer with monochromatic Mo–Kα radiation (λ = 0.71073 Å) and a CCD detector. The structure was solved by direct methods using SHELXS-97 and refined against F2 on all data by full-matrix least-squares methods using SHELXL-97 [13,14].

Acknowledgments

Ingo Schiffers, Wolfgang Bettray and Christoph Räuber (all RWTH Aachen University) are kindly acknowledged for stimulating discussions.

Author Contributions

M.F. performed the experimental work and product characterization. I.A. collected the X-ray data and determined the structure. M.F. prepared the manuscript with contributions from all authors. The overall project management was done by C.B.

Conflicts of Interest

The authors declare no conflict of interest.

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