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Zolimidine Analogues: The Synthesis of Imidazo[1,2-α]pyridine-Based Sulfilimines and Sulfoximines

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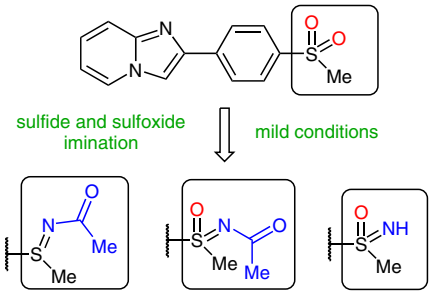

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Abstract Zolimidine is a methylsulfonyl-substituted drug with an imidazo[1,2-α]pyridine core used for the treatment of peptic ulcer. Herein, we report the synthesis of unprecedented *N*-acetylsulfilimine and -sulfoximine analogues under mild conditions. Deprotection of the *N*-acetylsulfoximine allows the preparation of the corresponding NH-sulfoximine.

Key words imidazo[1,2-α]pyridine, sulfoximine, sulfilimine, zolimidine, imination

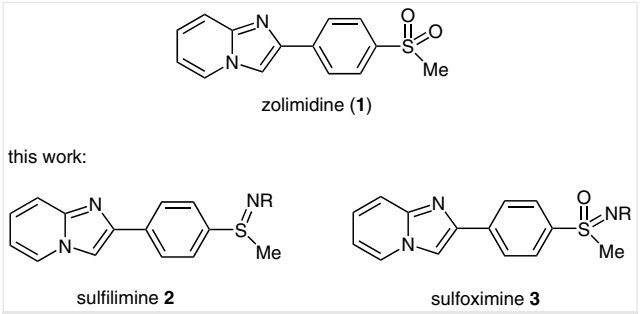

Figure 1 Zolimidine (**1**) and derivatives **2** and **3**, presented in this work

Imidazo[1,2-α]pyridines are widely applied in chemistry, biology, and materials science.[1–3] Incorporated in numerous natural products and pharmaceuticals,[4] they show an extraordinary variety of biological activities such as antifungal,[5] antiviral,[6] antibacterial,[7] anticancer,[8] and antiulcer.[9] As a consequence, several imidazo[1,2-α]pyridine-containing drugs exist, namely alpidem, zolpidem, necopidem, and saripidem (anxiolytic agents),[10] olprinone (treatment of heart failure),[11] GSK812397 (candidate for treatment of HIV),[12] rifaximin (antibiotic),[13] and zolimidine (**1**, used for treatment of peptic ulcer).[9a,b,14] Among them, the latter compound **1** caught our attention because it contains a methylsulfonyl moiety (Figure 1).

The mono-aza analogues of sulfones, namely sulfoximines,[15] have attracted much attention in crop protection[16] and drug development.[17] Recent studies revealed the change of a sulfone into a sulfoximine to induce interesting bioactivities.[18] Furthermore, in contrast to sulfones, sulfoximines can be modified at the nitrogen atom, which allows improving the solubility of the corresponding molecules.[18c,19] Sulfilimines, possessing a nitrogen substituent and a free electron pair at the sulfur atom, are intermediates in the sulfoximine synthesis and have shown interesting insecticidal activities.[16c,20]

Surprisingly, to our knowledge, no imidazo[1,2-α]pyridines with sulfoximidoyl and sulfilimidoyl substituents have been reported to date.[21] In order to fill this synthetic gap, we envisaged a sulfone-to-sulfoximine exchange on zolimidine and thereby the syntheses of analogues **2** and **3** (Figure 1). The preparation of these compounds would also allow an evaluation of the existing preparative approaches towards sulfoximines and sulfilimines and an analysis of their value in accessing heteroatom-containing derivatives.

For the synthesis of sulfilimines **2** and sulfoximines **3** three different synthetic pathways were considered (Scheme 1). First, the sulfide **4** seemed a good starting point for an imination/oxidation sequence (route A) involving the synthesis of the desired sulfilimine **2** as an intermediate. Similarly, starting from **4** an oxidation/imination sequence (route B) would lead to sulfoximine **3** via sulfoxide **5**. Alternatively, it was considered to synthesize the imidazo[1,2-

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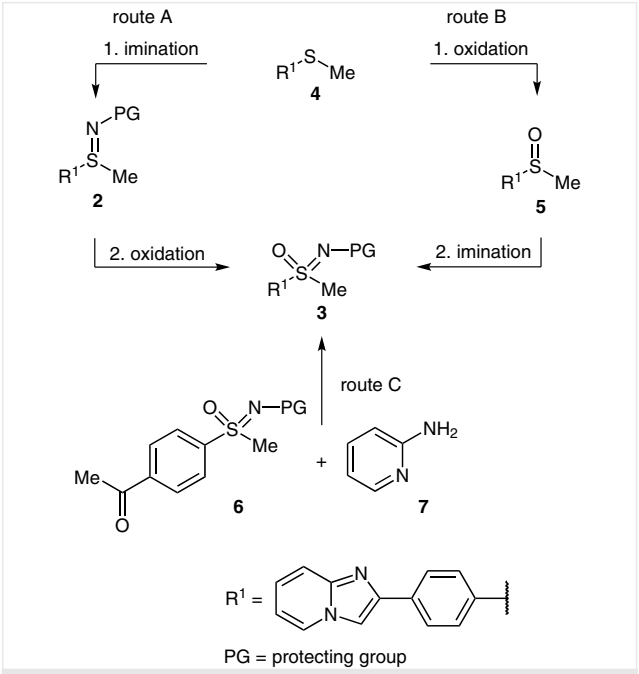
α]pyridine entity by a reaction of methyl ketone **6**, containing a sulfoximidoyl functionality, with 2-aminopyridine (**7**) (route C).[22]



Scheme 1 Synthetic pathways towards sulfilimine **2** and sulfoximine **3**

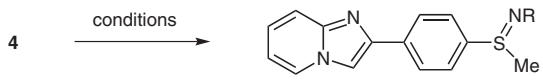
Initially, the imination of sulfide **4** was investigated (route A, Scheme 1). As *N*-cyanosulfilimines and *N*-cyanosulfoximines have previously shown interesting bioactivities,[18d,20b] the imination with cyanamide was attempted first. However, when applying transition metal-free conditions using potassium *tert*-butoxide and *N*-bromosuccinimide (NBS),[23] halogenation of the heterocycle solely occurred (Table 1, entry 1).[24]

Also the replacement of NBS and the strong base by iodobenzene diacetate,[25] did not allow sulfide imination with cyanamide (entry 2). Instead, traces of the corresponding sulfoxide **5** were observed. Further attempts to form *N*-cyanosulfilimines or *N*-cyanosulfoximines (route C, Scheme 1),[22a] by reaction of 1-[4-(*N*-cyanomethylsulfilimidoyl)phenyl]ethanone or 1-[4-(*N*-cyanomethylsulfoximidoyl)phenyl]ethanone with 2-aminopyridine, were ineffective.

Next, we focused on metal-catalyzed imination methods involving different protecting groups on the nitrogen atom. Unexpectedly, the frequently applied rhodium-catalyzed imination protocol[26] led to decomposition (entry 3). Likewise, the milder iron-catalyzed procedure useful in the imination of heterocyclic sulfoximines[27] did not afford the product (entry 4). Finally, a ruthenium-catalyzed photochemical approach, recently developed in our group, using 3-methyl-1,4,2-dioxazol-5-one as nitrene source, led to success (entry 5).[28] The mild reaction conditions allowed to obtain the desired *N*-acetylsulfilimine **2a** in 83% yield, thereby demonstrating the value of this method regarding heterocyclic substrates.

The first target compound in hand, following route A, the oxidation of **2a** to sulfoximine **3a** was investigated (Scheme 2). Initial attempts of using a one-pot procedure involving the aforementioned photochemical imination of **4**, and subsequent oxidation with sodium periodate remained unsuccessful not leading to sulfoximine **3a**.[28] Similarly, an oxidation with potassium permanganate, often used with heterocyclic starting materials,[27b] did not afford **3a**.

Table 1 Imination of Sulfide **4** Following Route A



2
2a (R = acetyl)

Entry	Conditions	R	Yield (%) of **2**[a]
1	NH_2CN, *t*-BuOK, NBS, MeOH, r.t., 30 min	CN	–[b]
2	NH_2CN, $PhI(OAc)_2$, MeOH, r.t., 4 h	CN	–[c]
3	$Rh_2(OAc)_4$ (2.5 mol%), trifluoroacetamide, MgO, $PhI(OAc)_2$, CH_2Cl_2, r.t., 24 h	$COCF_3$	–[d]
4	$Fe(OTf)_2$ (15 mol%), PhI=NNS, 4 Å molecular sieves, MeCN, 50 °C, 20 h	nosyl	–[e]
5	Ru(TPP)CO (0.5 mol%), 3-methyl-1,4,2-dioxazol-5-one, toluene, *hv*, r.t., 1 h	COMe	83

[a] After purification by column chromatography.
[b] Formation of 3-bromo-2-[4-(methylthio)phenyl]imidazo[1,2-α]pyridine.
[c] Formation of traces of sulfoxide **5**.
[d] Decomposition.
[e] No conversion.

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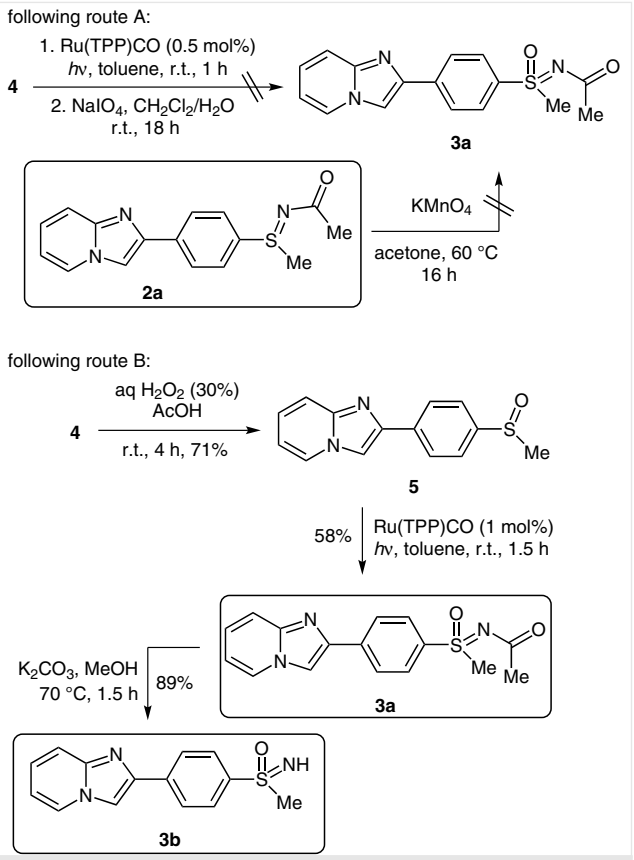

Scheme 2 Different routes towards sulfoximines **3a** and **3b**

Changing the strategy, we switched to synthetic route B (Scheme 1). To our delight, oxidation of sulfide **4** with an aqueous dihydrogen peroxide solution in acetic acid[29] proceeded well, giving sulfoxide **5** in 71% yield (Scheme 2). The previously proven mild ruthenium-catalyzed light-promoted conditions allowed obtaining sulfoximine **3a** in a yield of 58%.[28] Finally, the acetyl protecting group was removed using potassium carbonate in methanol at 70 °C,[30] leading to NH-sulfoximine **3b** in 89% yield (Scheme 2).

In conclusion, we have synthesized unprecedented *N*-acetylsulfilimidoyl- and *N*-acetylsulfoximidoyl-substituted derivatives of zolimidine. The evaluation of various synthetic pathways revealed that only the recently introduced light-promoted ruthenium catalysis using 3-methyl-1,4,2-dioxazol-5-one as *N*-acylnitrene source allowed an efficient imination of the sulfur atom at the imidazo[1,2-α]pyridine core. Finally, the NH-sulfoximine was obtained in good yield by deprotection of the acetyl group.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VNMRS 600 spectrometer in $CDCl_3$, DMSO-d_6, or acetone-d_6. Chemical shifts (δ) are given in ppm relative to solvent residual peaks ($CDCl_3$, δ = 7.26; DMSO-d_6, δ = 2.50; acetone-d_6, δ = 2.05). Coupling constants *J* are reported in Hz. Standard abbreviations were used to denote coupling patterns. IR spectra were recorded on a PerkinElmer FT-IR Spectrum 100 (KBr disk). Wave numbers are given in reciprocal centimeters (cm^{-1}). Mass spectra were recorded on a Finnigan SSQ 7000 spectrometer and HRMS on a Thermo Scientific LTQ Orbitrap XL spectrometer. Elementary analyses were performed on an Elementar Vario El instrument. Melting points were determined in open-end capillary tubes on a Büchi B-540 melting point apparatus. Irradiation was conducted with a Philips HPK 125 W high-pressure mercury vapor lamp cooled with water. Reactions were carried out under air if not described differently. Solvents were distilled prior to use. Chemicals were purchased from commercial suppliers and used without further purification. 2-[4-(Methylthio)phenyl]imidazo[1,2-α]pyridine (**4**)[22a] and 3-methyl-1,4,2-dioxazol-5-one were prepared according to reported procedures.[28a] Flash column chromatography was carried out with Merck silica gel 60 (35–70 mesh). Analytical TLC was performed with aluminum sheets silica gel 60 F254 (Merck), and the products were visualized by UV detection and/or staining solutions.

Imination Reaction;[28] General Procedure

To a solution of **4** or **5** (1 equiv) and 3-methyl-1,4,2-dioxazol-5-one (1 equiv) in anhydrous toluene under argon was added Ru(TPP)CO (0.5 or 1 mol%). After stirring at r.t. under irradiation with a 125 W high-pressure mercury lamp, the solvent was removed under reduced pressure. Purification by flash column chromatography afforded product **2** or **3**, respectively.

2-[4-(*N*-Acetyl-*S*-methylsulfilimidoyl)phenyl]imidazo[1,2-α]pyridine (2a)

Following the general procedure using **4** (120 mg, 0.5 mmol), 3-methyl-1,4,2-dioxazol-5-one (51 mg, 0.5 mmol), Ru(TPP)CO (1.9 mg, 0.5 mol%), and anhydrous toluene (5 mL) for 1 h, the product was obtained after flash column chromatography (EtOAc); yield: 123 mg (83%); light brown solid; mp 176–179 °C.

IR (KBr): 3004, 1739, 1568, 1359, 1293 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 6.7 Hz, 1 H), 8.07 (d, *J* = 8.3 Hz, 2 H), 7.91 (s, 1 H), 7.78 (d, *J* = 8.3 Hz, 2 H), 7.60 (d, *J* = 9.1 Hz, 1 H), 7.20–7.17 (m, 1 H), 6.79 (t, *J* = 6.7 Hz, 1 H), 2.82 (s, 3 H), 2.13 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 182.0, 145.8, 143.7, 137.9, 134.1, 127.2, 127.1, 125.7, 125.3, 117.7, 112.9, 109.2, 34.5, 24.3.

MS (EI): *m*/*z* (%) = 297 ([M]$^+$, 2), 207 (28), 190 (74), 179 (27), 166 (33), 155 (35), 146 (26), 120 (25), 103 (43), 78 (100).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{16}N_3OS$ [M + H]$^+$: 298.1009; found: 298.1010.

2-[4-(*N*-Acetyl-*S*-methylsulfoximidoyl)phenyl]imidazo[1,2-α]pyridine (3a)

Following the general procedure using **5** (64 mg, 0.25 mmol), 3-methyl-1,4,2-dioxazol-5-one (25 mg, 0.25 mmol), Ru(TPP)CO (1.9 mg, 1 mol%), and anhydrous toluene (3 mL) for 1.5 h, the product was obtained after flash column chromatography (acetone–EtOAc, 1:5); yield: 45 mg (58%); light brown solid; mp 198–200 °C (dec.).

IR (KBr): 3022, 1627, 1360, 1268, 1201, 1032 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.60 (s, 1 H), 8.57 (d, *J* = 5.9 Hz, 1 H), 8.24 (d, *J* = 8.6 Hz, 2 H), 8.00 (d, *J* = 8.6 Hz, 2 H), 7.63 (d, *J* = 9.1 Hz, 1 H), 7.31–7.28 (m, 1 H), 6.95–6.93 (m, 1 H), 3.47 (s, 3 H), 2.00 (s, 3 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 178.8, 145.5, 142.8, 139.3, 137.6, 128.1, 127.6, 126.6, 126.1, 117.4, 113.2, 111.5, 43.6, 26.9.

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MS (EI): *m*/*z* (%) = 313 ([M]$^+$, 2), 296 (5), 240 (19), 238 (19), 208 (98), 206 (100), 192 (19), 190 (17), 180 (16), 178 (17).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{16}N_3O_2S$ [M + H]$^+$: 314.0958; found: 314.0956.

2-[4-(NH-*S*-methylsulfoximidoyl)phenyl]imidazo[1,2-α]pyridine (3b)

A mixture of **3a** (69 mg, 0.22 mmol) and K_2CO_3 (152 mg, 1.10 mmol) in MeOH (3.65 mL) was stirred at 70 °C[30] for 1.5 h. The solvent was removed under reduced pressure and the product was obtained after purification by flash column chromatography (EtOAc–MeOH, 9:1); yield: 53 mg (89%); white solid; mp 200–202 °C.

IR (KBr): 3207, 1596, 1406, 1213, 1096 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.56–8.55 (m, 2 H), 8.17 (d, *J* = 8.4 Hz, 2 H), 7.98 (d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 9.1 Hz, 1 H), 7.30–7.27 (m, 1 H), 6.94–6.92 (m, 1 H), 4.24 (s, 1 H), 3.10 (s, 3 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 145.0, 142.7 (2 C), 137.7, 127.8, 127.1, 125.7, 125.5, 116.8, 112.6, 110.6, 45.8.

MS (EI): *m*/*z* (%) = 271 ([M]$^+$, 4), 207 (61), 178 (99), 164 (100), 138 (78), 127 (65), 113 (44), 101 (36).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{14}N_3OS$ [M + H]$^+$: 272.0852; found: 272.0851.

2-[4-(Methylsulfinyl)phenyl]imidazo[1,2-α]pyridine (5)[14]

To a solution of **4** (70 mg, 0.29 mmol) in AcOH (1.39 mL) at 0 °C was added 30% aq H_2O_2 (0.13 mL, 0.29 mmol).[29] After stirring for 4 h at r.t., the reaction mixture was quenched by the addition of concd aq NaOH (0.5 mL). H_2O (5 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were removed under reduced pressure. The product was obtained after purification by flash column chromatography (acetone–EtOAc, 1:1 to acetone–MeOH, 20:1); yield: 53 mg (71%); light brown solid; mp 160–163 °C.

IR (KBr): 3134, 1633, 1499, 1404, 1088, 1038 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 8.50 (d, *J* = 6.8 Hz, 1 H), 8.40 (s, 1 H), 8.22 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 9.1 Hz, 1 H), 7.28–7.25 (m, 1 H), 6.90 (dt, *J* = 6.7, 1.0 Hz, 1 H), 2.74 (s, 3 H).

^{13}C NMR (151 MHz, acetone-d_6): δ = 146.2, 145.6, 144.1, 136.9, 126.7, 126.4, 125.0, 123.8, 117.1, 112.4, 109.6, 43.4.

MS (EI): *m*/*z* (%) = 256 ([M]$^+$, 41), 238 (100), 224 (9), 206 (12), 192 (31), 190 (17), 180 (8).

Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.41; H, 4.68; N, 10.64.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380109.

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