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Oxidative reaction of 2-aminopyridine-3-sulfonyl chlorides with tertiary amines

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Abstract: 2-Aminopyridine-3-sulfonyl chlorides undergo a reaction with tertiary amines in the presence of air to produce sulfonylethenamines. The 2-aminopyridine-3-sulfonyl chloride apparently plays a dual role in the process promoting the aerobic oxidation of the amine and electrophilically trapping the resulting enamine.

Keywords: aerobic oxidation; amines; enamines; Hinsberg reaction; sulfonyl chlorides.

Introduction

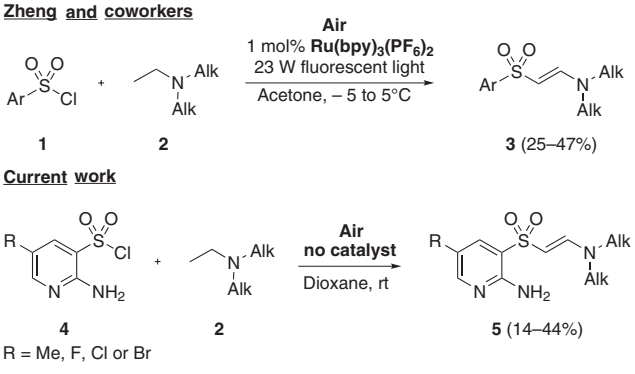
The reaction of arenesulfonyl chlorides with amines is known as the Hinsberg reaction or the Hinsberg test that can be used to distinguish primary, secondary and tertiary amines [1]. The reaction of primary and secondary amines with benzenesulfonyl chloride in the presence of base leads to the formation of sulfonamides. Tertiary alkyl amines react with benzenesulfonyl chloride to form *N*-benzenesulfonyl-*N*,*N*,*N*-trialkylammonium chloride adducts [2, 3] that in the presence of aquatic base (as in the Hinsberg test) undergo hydrolysis into parent amines and benzenesulfonic acid [4].

Recently, Zheng and coworkers have reported a visible-light induced oxidative reaction of arenesulfonyl chlorides **1** with tertiary alkyl amines **2** leading to sulfonylethenamines **3** in the presence of $Ru(bpy)_3(PF_6)_2$ photoredox catalyst (Scheme 1) [5]. In this paper, we would like to describe a related oxidative reaction of 2-aminopyridine-3-sulfonyl chlorides **4** with tertiary alkyl amines **2** that proceeds in the absence of any catalyst and provides access to sulfonylethenamines **5** (Scheme 1).

Results and discussion

This transformation was discovered accidently when the 2-amino-5-methylpyridine-3-sulfonyl chloride **4a** was exposed to an excess of triethylamine **2a** in the presence of air giving rise to the sulfonylethenamine product **5a**. The tentative pathway for the process is outlined on Scheme 2. We believe that **4a** and **2a** initially react to form the *N*-2-amino-5-methylpyridinyl-3-sulfonyl-*N*,*N*,*N*-triethylammonium chloride **A**. Next, the intermediate **A** undergoes oxidative degradation into the enamine **B** and 2-amino-5-methylpyridine-3-sulfonic acid **6**. Furthermore, **A** is also responsible for the electrophilic trapping of **B** that leads to the final sulfonylethenamine **5a** [6, 7]. Overall, the conversion of 2 equiv of 2-amino-5-methylpyridine-3-sulfonyl chloride **4a** can produce up to 1 equiv of desired sulfonylethenamine **5a** consuming in the course of reaction 3 equiv of triethylamine **2a** (Scheme 2).

Importantly, an attempted reaction of tosyl chloride **1a** failed to give the sulfonylethenamine product **3a** in the absence of $Ru(bpy)_3(PF_6)_2$, the photoredox catalyst (Scheme 3). However, treating the mixture of **1a** and **4a** with triethylamine **2a** led to the formation of both sulfonylethenamines **3a** and **5a** in 23% and 22% yields, respectively



Scheme 1 Oxidative reactions of arenesulfonyl chlorides with tertiary alkyl amines.

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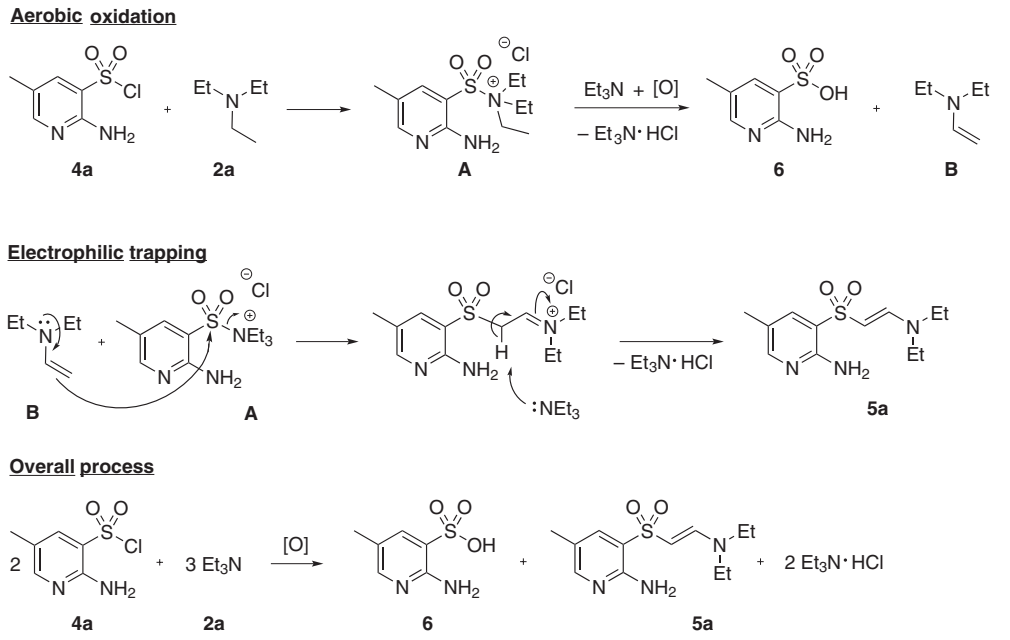
Huiping Wei, Gaigai Wang, Binbin Li, Jianjun Huang and Haiyan Li: College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Dushu Lake Campus, Suzhou, 215123, China

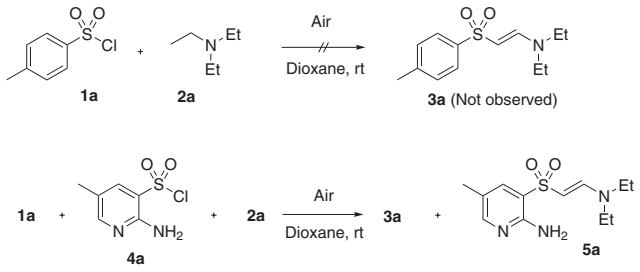


Scheme 2 Tentative reaction pathway.

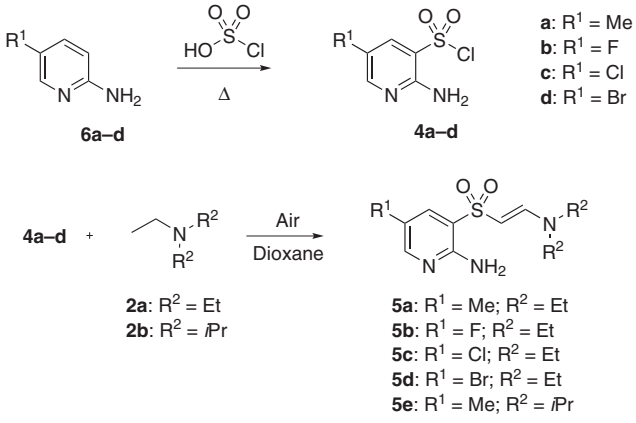
(Scheme 3). These control experiments confirm the crucial role of 2-aminopyridine-3-sulfonyl chloride **4** as the promotor of the catalyst-free aerobic oxidation.

It is worth to note that the oxidations of tertiary amines into iminium cations followed by the reactions with nucleophiles constitute a well-known approach to the α-functionalization of amines [8–17] while our reaction presumably belongs to a relatively more rare class of complementary processes where the amine is oxidized into enamine with the subsequent trapping by a suitable electrophile [18–23].

In order to briefly assess the scope of the discovered process, a series of 2-aminopyridine-3-sulfonyl chlorides **4a–d** were prepared by reacting appropriate 2-aminopyridines **6a–d** with chlorosulfuric acid (Scheme 4) [24, 25]. Next, the reactions of **4a–d** with triethylamine (**2a**) and *N*,*N*-diisopropylethylamine (**2b**) to prepare sulfonylethenamines **5a-e** were studied (Scheme 4). At first, we evaluated



Scheme 3 Control experiments.



Scheme 4 Synthesis of 2-aminopyridine-3-sulfonyl chlorides **4** and sulfonylethenamines **5**.

the reaction of 2-amino-5-methylpyridine-3-sulfonyl chloride (**4a**) with triethylamine (**2a**) under various conditions. These trial reactions were run on 0.6 mmol scale in 2 mL of solvent for 1–1.5 h. Treatment of **4a** with 2.2 equiv of **2a** under the air atmosphere in dioxane as solvent provided sulfonylethenamine **5a** in the isolated yield of 31%. The use of 3 equiv of **2a** resulted in a slight improvement furnishing **5a** in 36% yield.[1] Importantly, no **5a** was formed when the attempted reaction was conducted under the inert atmosphere, which was clearly seen by TLC analysis. Introducing

1 Analogous reaction on 0.75 mmol scale in 2.5 mL of dioxane afforded **5a** in 35% yield.

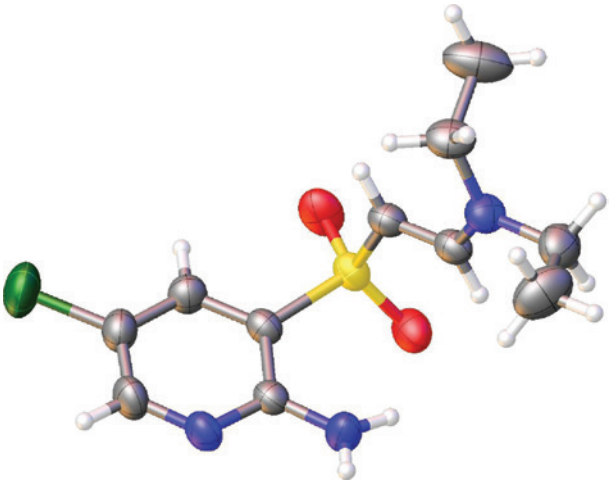


Figure 1 X-ray crystallographic structure of compound **5c.**

1 equiv of water in the reaction media as a competitive electrophile impaired the reaction outcome leading to a diminished 25% yield of **5a**. The use of THF or DMF instead of dioxane also resulted in the decreased yields of 28% and 25%, respectively.

The reaction of 2-amino-5-fluoropyridine-3-sulfonyl chloride (**4b**) with **2a** required extended reaction time and delivered sulfonylethenamine **5b** in only 17% isolated yield. The analogous transformations involving 2-amino-5-chloropyridine-3-sulfonyl chloride (**4c**) and 2-amino-5-bromopyridine-3-sulfonyl chloride (**4d**) proceeded more efficiently yielding sulfonylethenamines **5c** and **5d** in 44% and 41%, respectively. The structure of (*E*)-5-chloro-3-[2-(diethylamino)vinylsulfonyl]pyridin-2-amine (**5c**) was ascertained by X-ray crystallographic analysis (Figure 1, CCDC 1478486 contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html). Finally, the reaction of 2-amino-5-methylpyridine-3-sulfonyl chloride (**4a**) with a bulky *N*,*N*-diisopropylethylamine (**2b**) furnished sulfonylethenamine **5e** in 14% yield.

Conclusion

A novel catalyst-free process for the oxidative β-functionalization of tertiary amines with 2-aminopyridine-3-sulfonyl chlorides was discovered and documented.

Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz and 100 MHz, respectively, using Bruker Avance III HD instrument. High resolution mass spectra (HR-MS) were obtained on a Bruker micrOTF-Q III instrument. Melting points were measured using an Inesa WRR apparatus. Infrared (FT-IR) spectra were recorded neat on a Bruker Vertex 70 spectrometer. All starting materials and solvents were purchased from commercial sources and used as received.

Synthesis of 2-aminopyridine-3-sulfonyl chlorides 4a–d

An appropriate 2-aminopyridine **6** (20–30 mmol) was added portionwise to a cooled (0–5°C) chlorosulfonic acid (12–18 mL) under vigorous stirring. The mixture was heated under reflux for 3 h, then cooled and carefully poured into ice (25–40 g) with stirring. The resulting mixture was diluted with water up to 120–150 mL total volume (for **4a** it was additionally neutralized with solid $NaHCO_3$) and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated.

2-Amino-5-methylpyridine-3-sulfonyl chloride (4a) This compound was synthesized from 2-amino-5-methylpyridine (**6a**, 30 mmol); yield 58%; white solid; mp 160–162°C; IR: υ_{max} 3464, 3303, 3127, 1645, 1545, 1492, 1358, 1358, 1238, 1153, 758, 695 cm^{-1}; ^{1}H NMR: δ 8.21 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 1.7 Hz, 1H), 5.96 (bs, 2H), 2.27 (s, 3H); ^{13}C NMR: δ 156.8, 152.6, 138.0, 123.3, 121.3, 17.2. HR-MS. Calcd for $C_6H_8ClN_2O_2S^+$ ([M + H]$^+$): *m/z* 206.9990. Found: *m/z* 206.9991.

2-Amino-5-fluoropyridine-3-sulfonyl chloride (4b) This compound was synthesized from 2-amino-5-fluoropyridine (**6b**, 20 mmol); yield 40%; beige solid; mp 124–126°C; ^{1}H NMR: δ 8.30 (d, *J* = 2.9 Hz, 1H), 7.84 (dd, *J* = 7.0, 2.9 Hz, 1H), 5.96 (bs, 2H); ^{13}C NMR: δ 151.4 (d, *J* = 249.7 Hz), 151.3, 144.9 (d, *J* = 25.0 Hz), 124.6 (d, *J* = 22.7 Hz), 120.3 (d, *J* = 2.9 Hz). HR-MS. Calcd for $C_5H_5ClFN_2O_2S^+$ ([M+H]$^+$): *m/z* 210.9739. Found: *m/z* 210.9728.

2-Amino-5-chloropyridine-3-sulfonyl chloride (4c) This compound was synthesized from 2-amino-5-chloropyridine (**6c**, 20 mmol); yield 51%; beige solid; mp 134–136°C; ^{1}H NMR: δ 8.33 (d, *J* = 2.4 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H), 6.00 (bs, 2H); ^{13}C NMR: δ 155.1, 152.6, 137.1, 121.6, 120.2. HR-MS. Calcd for $C_5H_5Cl_2N_2O_2S^+$ ([M + H]$^+$): *m/z* 226.9443. Found: *m/z* 226.9448.

2-Amino-5-bromopyridine-3-sulfonyl chloride (4d) This compound was synthesized from 2-amino-5-bromopyridine (**6d**, 20 mmol); yield 54%; yellowish solid; mp 142–143°C; ^{1}H NMR: δ 8.40 (d, *J* = 2.3 Hz, 1H), 8.17 (d, *J* = 2.3 Hz, 1H), 6.02 (bs, 2H); ^{13}C NMR: δ 156.7, 152.7, 139.9, 122.4, 106.7. HR-MS. Calcd for $C_5H_5ClBrN_2O_2S^+$ ([M + H]$^+$): *m/z* 270.8938. Found: *m/z* 270.8928.

Synthesis of sulfonylethenamines 5

An appropriate 2-aminopyridine-3-sulfonyl chloride (**4**, 0.75 mmol) was dissolved in dry dioxane (2.5 mL) followed by addition of amine **2** (2.25 mmol). The resulting mixture was vigorously stirred under the air atmosphere at room temperature for a period of time indicated below.[2] Upon completion of the reaction time, the mixture was

2 Additionally, every 10–15 min a vial with reaction mixture was shaken. Shaking the reaction mixture is essential for saturating the reaction mixture with the oxygen from the air that is the oxidant in our process.

diluted with ethyl acetate, treated with silica gel and concentrated. Column chromatography eluting with petroleum ether/ethyl acetate (4 : 1 to 1 : 1) delivered **5**. Product **5c** was additionally washed with diethyl ether after chromatography.

(*E*)-3-((2-(Diethylamino)vinyl)sulfonyl)-5-methylpyridin-2-amine (5a) This compound was synthesized from 2-amino-5-methylpyridine-3-sulfonyl chloride (**4a**) and triethylamine (**2a**); reaction time 1 h; yield 35%; beige solid; mp 153–154°C; IR: υ_{max} 3466, 3298, 3139, 3074, 2972, 2921, 1609, 1486, 1251, 1118, 879, 696 cm^{-1}; ^1H NMR: δ 7.94 (d, J = 1.5 Hz, 1H), 7.86 (d, J = 1.9 Hz, 1H), 7.28 (d, J = 12.7 Hz, 1H), 5.86 (bs, 2H), 4.90 (d, J = 12.6 Hz, 1H), 3.25 (bs, 2H), 3.10 (bs, 2H), 2.23 (s, 3H), 1.15 (bs, 6H); ^{13}C NMR: δ 152.9, 151.7, 149.1, 137.2, 123.0, 122.1, 89.9, 50.1, 42.8, 17.3, 14.7, 11.1. HR-MS. Calcd for $C_{12}H_{20}N_3O_2S^+$ ($[M+H]^+$): *m/z* 270.1271. Found: *m/z* 270.1277.

(*E*)-3-((2-(Diethylamino)vinyl)sulfonyl)-5-fluoropyridin-2-amine (5b) This compound was synthesized from 2-amino-5-fluoropyridine-3-sulfonyl chloride (**4b**) and triethylamine (**2a**); reaction time 1 h 40 min; yield 17%; beige solid; mp 98–100°C; IR: υ_{max} 3440, 3303, 3169, 3071, 2985, 2922, 1613, 1473, 1287, 1237, 1115, 877, 692 cm^{-1}; ^1H NMR: δ 8.02 (d, J = 2.2 Hz, 1H), 7.74 (dd, J = 7.4, 2.4 Hz, 1H), 7.28 (d, J = 12.5 Hz, 1H), 5.57 (bs, 2H), 4.91 (d, J = 12.5 Hz, 1H), 3.25 (bs, 2H), 3.10 (bs, 2H), 1.19 (bs, 3H), 1.11 (bs, 3H); ^{13}C NMR: δ 152.9 (d, J = 246.3 Hz), 151.5 (d, J = 1.2 Hz), 149.9, 139.1 (d, J = 24.8 Hz), 123.9 (d, J = 22.1 Hz), 122.8 (d, J = 1.7 Hz), 88.9, 50.4 (bs), 43.0 (bs), 14.7 (bs), 11.2 (bs). HR-MS. Calcd for $C_{11}H_{17}FN_3O_2S^+$ ($[M+H]^+$): *m/z* 274.1020. Found: *m/z* 274.1028.

(*E*)-5-Chloro-3-((2-(diethylamino)vinyl)sulfonyl)pyridin-2-amine (5c) This compound was synthesized from 2-amino-5-chloropyridine-3-sulfonyl chloride (**4c**) and triethylamine (**2a**); reaction time 30 min; yield 44%; beige solid; mp 150–152°C; IR: υ_{max} 3415, 3302, 3173, 2977, 2933, 1608, 1473, 1282, 1235, 1114, 881, 770, 696 cm^{-1}; ^1H NMR: δ 8.08 (d, J = 2.4 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.27 (d, J = 12.5 Hz, 1H), 5.78 (bs, 2H), 4.90 (d, J = 12.6 Hz, 1H), 3.26 (bs, 2H), 3.10 (bs, 2H), 1.19 (bs, 3H), 1.11 (bs, 3H); ^{13}C NMR: δ 153.1, 150.2, 149.8, 136.2, 123.4, 120.5, 89.1, 50.4 (bs), 43.0 (bs), 14.7 (bs), 11.2 (bs). HR-MS. Calcd for $C_{11}H_{17}ClN_3O_2S^+$ ($[M+H]^+$): *m/z* 290.0725. Found: *m/z* 290.0723.

(*E*)-5-Bromo-3-((2-(diethylamino)vinyl)sulfonyl)pyridin-2-amine (5d) This compound was synthesized from 2-amino-5-bromopyridine-3-sulfonyl chloride (**4d**) and triethylamine (**2a**); reaction time 40 min; yield 41%; beige solid; mp 154–156°C; IR: υ_{max} 3414, 3301, 3166, 2975, 2924, 2853, 1607, 1471, 1236, 1110, 1070, 887, 767, 696 cm^{-1}; ^1H NMR: δ 8.16 (d, J = 2.4 Hz, 1H), 8.04 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 12.6 Hz, 1H), 5.71 (bs, 2H), 4.90 (d, J = 12.6 Hz, 1H), 3.25 (bs, 2H), 3.10 (bs, 2H), 1.19 (bs, 3H), 1.11 (bs, 3H); ^{13}C NMR: δ 153.4, 152.3, 149.8, 138.7, 123.9, 107.4, 89.1, 50.4, 43.0, 14.7, 11.2. HR-MS. Calcd for $C_{11}H_{17}BrN_3O_2S^+$ ($[M+H]^+$): *m/z* 334.0219. Found: *m/z* 334.0209.

(*E*)-3-((2-(Diisopropylamino)vinyl)sulfonyl)-5-methylpyridin-2-amine (5e) This compound was synthesized from 2-amino-5-methylpyridine-3-sulfonyl chloride (**4a**) and *N*,*N*-diisopropylethylamine (**2b**); reaction time 1.5 h; yield 14%; beige solid; mp 138–139°C; IR: υ_{max} 3423, 3335, 3293, 3165, 3079, 2974, 2919, 2850, 1603, 1469, 1275, 1114, 921, 886, 848, 693 cm^{-1}; ^1H NMR: δ 7.95 (d, J = 1.7 Hz, 1H), 7.85 (d, J = 1.7 Hz, 1H), 7.35 (d, J = 12.7 Hz, 1H), 5.75 (bs, 2H), 4.95 (d, J = 12.7 Hz, 1H), 3.58 (bs, 2H), 2.22 (s, 3H), 1.19 (bs, 12H); ^{13}C NMR: δ 152.7, 150.3, 145.6, 137.9, 123.2, 122.9, 89.8, 49.6, 47.5, 23.5, 19.6, 17.4. HR-MS. Calcd for $C_{14}H_{24}N_3O_2S^+$ ($[M+H]^+$): *m/z* 298.1584. Found: *m/z* 298.1528.

Control experiments

A mixture of 4-toluenesulfonyl chloride (**1a**, 95 mg, 0.5 mmol) and triethylamine (**2a**, 152 mg, 1.5 mmol) in dry dioxane (2 mL) was vigorously stirred under the air atmosphere at room temperature for 1 h.[2] No formation of **3a** was observed by TLC analysis or by ^1H NMR of concentrated crude mixture.

A mixture of 2-amino-5-methylpyridine-3-sulfonyl chloride (**4a**, 103 mg, 0.5 mmol), 4-toluenesulfonyl chloride (**1a**, 95 mg, 0.5 mmol) and trimethylamine (**2a**, 202 mg, 2 mmol) in dry dioxane (2 mL) was vigorously stirred under the air atmosphere at room temperature for 1 h [1]. Upon completion of the reaction time, the mixture was diluted with ethyl acetate, treated with silica gel and concentrated. Column chromatography eluting with petroleum ether/ethyl acetate (4 : 1 to 1 : 1) delivered **3a** (23%) and **5a** (22%) contaminated with minor impurities.

(*E*)-*N*,*N*-Diethyl-2-tosylethenamine (3a) ^1H NMR: δ 7.72 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 12.7 Hz, 1H), 7.24 (d, J = 8.2 Hz, 2H), 4.88 (d, J = 12.7 Hz, 1H), 3.15 (bs, 4H), 2.39 (s, 3H), 1.13 (bs, 6H); ^{13}C NMR: δ 148.9, 142.6, 142.1, 129.5, 126.3, 91.9, 50.1, 42.8, 21.6, 14.8, 11.3. HR-MS. Calcd for $C_{13}H_{19}NO_2SNa^+$ ($[M+Na]^+$): *m/z* 276.1029. Found: *m/z* 276.1037.

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