One-step and solvent-free synthesis of terpene-fused pyrazines

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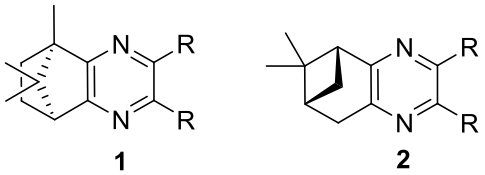
Abstract

Solvent-free condensation reactions were carried out by heating terpene-monooximes with an excess of amines. Employing camphor- and nopinone-derived monooximes, two classes of terpene-fused pyrazine derivatives were synthesized. Besides being solvent-free, the described one-step procedure can be directed towards terpene-fused imidazole or pyrazine derivatives. Whereas the reaction worked well with arylmethanamines bearing a (hetero)aromatic substituent at the α-carbon, alkylamines afforded only imino-oximes. A possible reaction path is presented.

Keywords: Pyrazine, terpenes, camphor, nopinone, condensation

Introduction

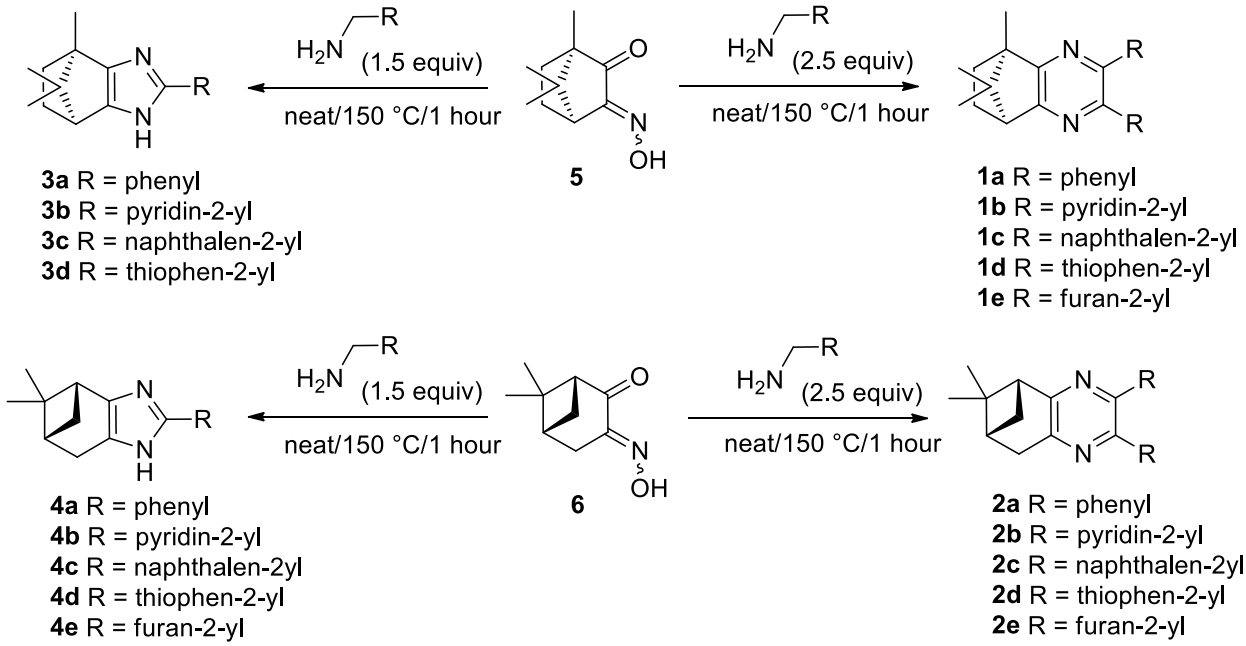
Pyrazines are important six-membered heterocyclic compounds.[1] For example, the 1,4-diazine structural motive can be found in compounds such as food flavors,[2] alkaloids,[3] low band gap conjugated materials,[4] and modern pyrazine phosphines.[5] Due to its two nitrogens, pyrazine can coordinate various transition metals and chiral pyrazine derivatives have thus found wide application in the areas of asymmetric catalysis, metal complexes, and metallosupramolecular assemblies. The most suitable synthesis of such chiral pyrazine derivatives utilizes commercially available and optically pure precursors such as α-amino acids or terpenes (chiral pool).[6] The synthesis and application of camphor-fused pyrazines as chelating and bridging ligands were mostly studied by Fitchett and Steel.[6a,7] However, despite the recent progress in the synthesis of pyrazines,[8] the most widely known synthetic procedure leading to pyrazines involves a reaction of α-diketones with 1,2-diamino compounds or a condensation reaction of α-aminoketones followed by (spontaneous) oxidation of the formed dihydropyrazines.[1,9] In the course of our recent research project aimed at the annulated terpene-imidazoles as optically active nitrogen ligands, we observed an unexpected formation of 2,3-disubstituted terpene-fused pyrazines.[10] Hence, we report herein a novel one-step and solvent-free synthesis of two classes of terpene-fused pyrazines **1** and **2** as well as their full spectral characterization.



Results and Discussion

We reported the synthesis of terpene-fused imidazoles **3** and **4** by reaction of bicyclic terpene monooximes (such as camphor-3-oxime or nopinone-3-oxime) with arylmethanamines.[10] Recently we found that pyrazines **1** and **2** were also formed (as by-products) in this reactions (Scheme 1). This fact prompted us to investigate such thermal condensation reactions in more details.

The starting camphor- and nopinone-derived monooximes **5** and **6** were synthesized by the nitrosation of the (+)-camphor and (+)-nopinone with *iso*-amylnitrite.[11] The initial reaction conditions optimized for the synthesis of imidazoles **3** and **4** involved heating of monooximes **5** and **6** with 1.5 equiv. of amine at 150 °C. Starting from the arylmethanamines such as phenylmethanamine (benzylamine), pyridin-2-ylmethanamine (picolinamine), naphthalen-1-ylmethanamine, thiophen-2-ylmethanamine, and furan-2-ylmethanamine (furfurylamine), imidazoles **3a**-**d** and **4a**-**e** were isolated in 33-55% yields (Table 1). These reactions also afforded the pyrazines **1** and **2** as minor products. However, increasing the amount of the amino component to 2.5 equiv. directed the reaction towards pyrazines **1** and **2**, which were isolated in 10-51% yields (Table 1).



Scheme 1. Syntheses of pyrazines **1** and **2** as well as imidazoles **3** and **4**.

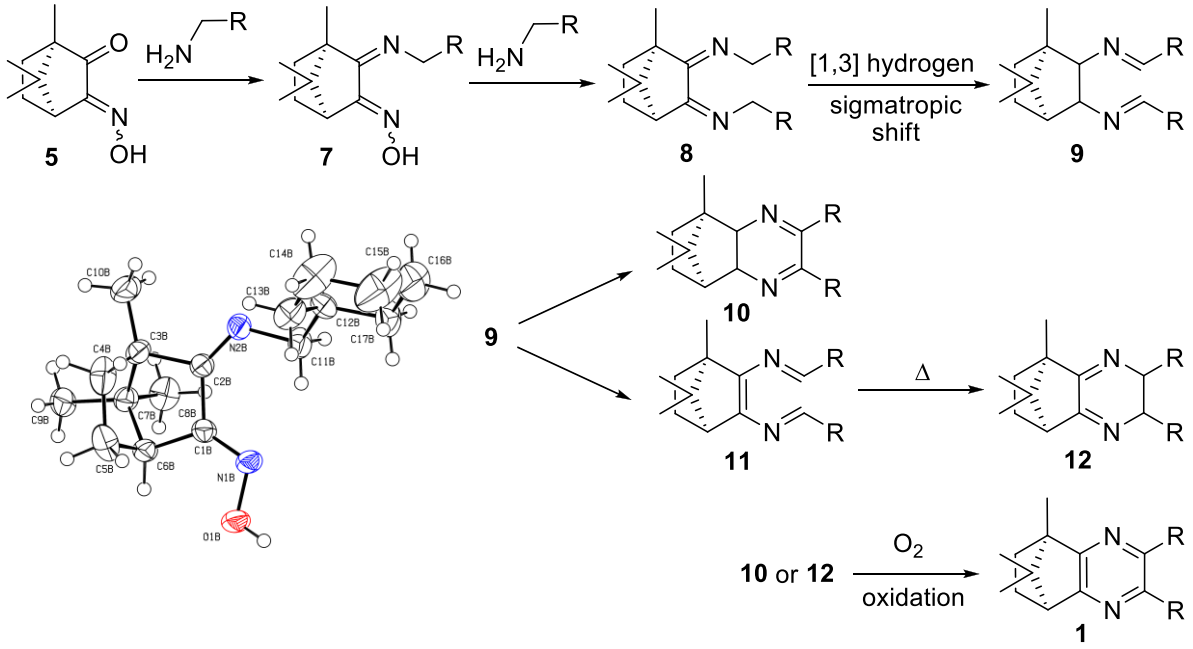
Table 1. Yields, melting points, and optical rotations of pyrazines **1** and **2**

Compound	R	Yield[a] [%] Pyrazine/Imidazole	Mp[c] [°C]	$[\alpha]_D^{20}$ (*c* 0.5, CH_3OH)[c]
1a/**3a**	phenyl	41/55	**1a:** 119-123	**1a:** +17.3
1b/**3b**	pyridin-2-yl	43/33	**1b:** 170-174	**1b:** +23.0
1c/**3c**	naphthalen-2-yl	2[b]/52	-	-
1d/**3d**	thiophen-2-yl	2[b]/41	-	-
1e/-	furan-2-yl	2[b]/0	-	-
2a/**4a**	phenyl	44/51	**2a:** 92-95	**2a:** +7.7
2b/**4b**	pyridin-2-yl	47/39	**2b:** 157-161	**2b:** +12.6
2c/**4c**	naphthalen-2-yl	12/50	**2c:** 90-94	**2c:** -15.7
2d/**4d**	thiophen-2-yl	51/42	**2d:** oil	**2d:** +20.8
2e/**4e**	furan-2-yl	10/41	**2e:** oil	**2e:** +15.7

[a] Isolated yields.

[b] GC/MS yields.

[c] See lit.[10] for the data of imidazoles **3** and **4**.



Scheme 2. Proposed reaction path of the condensation between monooximes and amines and the ORTEP plot of **7** (R = cyclohexyl).

According to the proposed mechanism of the condensation between the monooximes and amines to imidazoles **3** and **4**,[10] we were also curious how terpene-pyrazines **1** and **2** can be

formed. Hence, we have analyzed the crude reaction mixtures by GC/MS under different reaction conditions and times, which allowed us to propose a possible reaction path (Scheme 2). The reaction path in Scheme 2 is shown for camphor-derived monooxime **5**. Facile formation of "imino-oxime" **7** in the first reaction step was confirmed by X-ray analysis and the ORTEP plot in Scheme 2 shows the structure of "imino-oxime" with cyclohexyl residue as R (see lit.[10] or CCDC 686644). In the next step, an additional molecule of amine substitutes hydroxylamine in **7** affording **8**. Bisimine **8** undergoes [1,3] hydrogen sigmatropic shift to **9** in which the conjugation of the -N=CH- double bond and the (hetero)aromatic substituent R is ensured. The reaction with amines bearing bulky naphthalen-2-yl or thiophen-2-yl and furan-2-yl substituents featuring low aromaticity[12] provided only imino-oximes **7**, and, therefore, pyrazines **1c-e** were not isolated (only negligible amount was detected by GC/MS, see Table 1).

It is well-known that aminoxyl radicals of type $R'_2NO\cdot$ can easily be generated from hydroxylamine and oximes similar to **7** (lit.[13]). Thus, the plausible aminoxyl radicals formed in the reaction mixture (150 °C, neat) can initiate radical reactions (oxidation). An abstraction of the hydrogen from either -N=CH-R or -CH-N=C moieties and subsequent radical recombination leads to dihydropyrazine **10** or triene **11**. The later triene can undergo thermal cyclization to dihydropyrazine **12** as reported by Padwa[14] and others.[15] Dihydropyrazines **10** and **12** were detected by GC/MS (see Supplementary Material). Performing the reaction without exclusion of air, dihydropyrazines **10**/**12** were spontaneously oxidized to target pyrazine **1**. On the other hand, the reaction carried out under argon afforded only imidazole **3** as major product and traces of dihydropyrazines of type **10**/**12**.

Conclusions

The reported one-step and solvent-free synthetic procedure starts from commercially available or easily accessible compounds, is operationally very simple and offers efficient work-up (extraction followed by column chromatography). Moreover, the reaction can be directed towards fused imidazoles or pyrazines by simple changing the amount of the starting amine. Whereas the reaction worked well with arylmethanamines bearing an additional (hetero)aromatic substituent at the α-carbon, alkylamines afforded only imino-oximes.[10] Thus, the above-described procedure proved to be useful for the construction of (hetero)aryl 2,3-disubstituted terpene-fused pyrazines. Overall two new camphor-fused and five nopinone-fused pyrazines were synthesized and isolated this way.

Experimental Section

General. Reagents and solvents (reagent grade) were purchased from Aldrich and used as received. The starting monooximes **5** and **6** were synthesized according to the literature

procedures.[11] Evaporation and concentration *in vacuo* were performed at water aspirator pressure. The condensation reactions were carried out in a sealed glass pressure tube (Aldrich). Column chromatography was carried out with SiO_2 60 (particle size 0.040–0.063 mm, 230–400 mesh; Merck) and commercially available solvents. Thin-layer chromatography (TLC) was conducted on aluminum sheets coated with SiO_2 60 F254 obtained from Merck, with visualization by UV lamp (254 or 360 nm). Melting points (mp) were measured on a Buchi B-540 melting-point apparatus in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 360/400/500 MHz or 90/100/125 MHz, respectively, with Bruker AMX 360 or Bruker AVANCE 400/500 instruments at 25 °C. Chemical shifts are reported in ppm relative to the signal of Me_4Si. Residual solvent signal in the ^{1}H and ^{13}C NMR spectra was used as an internal reference ($CDCl_3$ - 7.25 and 77.23). Coupling constants (*J*) are given in Hertz. The apparent resonance multiplicity is described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet) and m (multiplet). Protons of the substituents at the pyrazine 2,3-positions are marked as follows: Ph (Phenyl), Np (naphthalen-1-yl), Py (pyridin-2-yl), Th (thiophen-2-yl), Fur (furan-2-yl). Additional NMR techniques such as ^{13}C APT, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC were used for regular signal assignment (see also Supplementary Material). Optical rotation values were measured on a Perkin Elmer 341 instrument, concentration *c* is given in g/100 mL CH_3OH. The mass spectra were measured on GC/MS configuration comprising Agilent Technologies 6890N gas chromatograph (HP-5MS column, length 30 m, I.D. 0.25 mm, film 0.25 lm) equipped with a 5973 Network MS detector (EI 70 eV, mass range 33-550 Da). Elemental analyses were performed on EA 1108 Fisons instrument.

General procedure for the condensation of monooximes with amines

A mixture of monooxime **5** or **6** (18 mmol) and amine (45 mmol) was heated in a sealed glass pressure tube for 1 h at 150 °C. The resulting mixture was taken up in CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (SiO_2 and indicated solvent system).

Pyrazine 1a. Off-white solid. Yield 2.51 g (41%); mp 119-123 °C; $[\alpha]_D^{20}$ = +17.3 (*c* 0.5, CH_3OH); R_f = 0.33 (SiO_2; CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.70 (s, 3H, C*H*$_3$), 1.08 (s, 3H, C*H*$_3$), 1.39 (d, *J* = 8.4 Hz, 2H, C*H*$_2$), 1.40 (s, 3H, C*H*$_3$), 1.97-2.04 (m, 1H, C*H*$_2$), 2.22-2.30 (m, 1H, C*H*$_2$), 3.06 (d, *J* = 4.2 Hz, 1H, C*H*), 7.24-7.26 (m, 6H, Ph), 7.37-7.44 (m, 4H, Ph); ^{13}C NMR (90 MHz, $CDCl_3$): δ 10.14, 19.02, 20.38, 24.96, 32.07, 53.19, 53.89, 56.21, 127.95, 128.01, 128.24, 128.31, 130.10, 130.28, 139.90, 140.01, 148.64, 148.85, 160.65, 162.39; EI-MS (70 eV) *m*/*z* (rel. int.): 340 (M^+, 100), 325 (27), 311 (19), 297 (75), 283 (15); Anal. Calcd for $C_{24}H_{24}N_2$ (340.46): C, 84.67; H, 7.11; N, 8.23. Found: C, 84.77; H, 7.18; N, 8.16.

Pyrazine 1b. Off-white solid. Yield 2.65 g (43%); mp 170-174 °C; $[\alpha]_D^{20}$ = +23.0 (*c* 0.5, CH_3OH); R_f = 0.18 (SiO_2; Hexane/EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.67 (s, 3H, C*H*$_3$), 1.05 (s, 3H, C*H*$_3$), 1.36 (d, *J* = 8.4 Hz, 2H, C*H*$_2$), 1.39 (s, 3H, C*H*$_3$), 1.97-2.00 (m, 1H, C*H*$_2$), 2.21-2.26 (m, 1H, C*H*$_2$), 3.08 (d, *J* = 4.2 Hz, 1H, C*H*), 7.11-7.15 (m, 2H, Py), 7.50 (d, *J* =

8.7 Hz, 1H, Py), 7.59-7.67 (m, 3H, Py), 8.40 (dd, *J* = 16.2 Hz, *J* = 4.8 Hz, 2H, Py); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.08, 18.93, 20.30, 24.79, 31.88, 53.19, 54.04, 56.24, 122.49, 122.63, 124.75, 124.86, 136.30, 136.45, 148.62, 148.82, 148.97, 149.12, 158.05, 161.67, 163.29 (one signal missing); EI-MS (70 eV) *m*/*z* (rel. int.): 342 (M^+, 35), 327 (17), 313 (30), 299 (100), 264 (13), 207 (15), 78 (15); Anal. Calcd for $C_{22}H_{22}N_4$ (342.44): C, 77.16; H, 6.48; N, 16.36. Found: C, 77.11; H, 6.57; N, 16.33.

Pyrazine 1c. Not isolated (~2% yield by GC/MS); EI-MS (70 eV) *m*/*z* (rel. int.): 440 (M^+, 100), 425 (15), 411 (13), 397 (55), 207 (35), 191 (15), 153 (15), 91 (14).

Pyrazine 1d. Not isolated (~2% yield by GC/MS); EI-MS (70 eV) *m*/*z* (rel. int.): 352 (M^+, 100), 337 (30), 323 (14), 309 (80), 259 (18), 97 (54).

Pyrazine 1e. Not isolated (~2% yield by GC/MS); EI-MS (70 eV) *m*/*z* (rel. int.): 320 (M^+, 100), 305 (32), 291 (15), 277 (90), 263 (15), 207 (17), 102 (11).

Pyrazine 2a. Off-white solid. Yield 2.60 g (44%); mp 92-95 °C; $[\alpha]_D^{20}$ = +7.8 (*c* 0.5, CH_3OH) [lit.[16] $[\alpha]_D$ = +22.0 (*c* 0.33, CH_2Cl_2)]; R_f = 0.61 (SiO_2; CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (s, 3H, C*H*$_3$), 1.44 (d, *J* = 10.0 Hz, 1H, C*H*$_2$), 1.48 (s, 3H, C*H*$_3$), 2.45-2.49 (m, 1H, C*H*), 2.81-2.87 (m, 1H, C*H*$_2$), 3.14 (t, *J* = 5.5 Hz, 1H, C*H*), 3.20 (d, *J* = 2.5 Hz, 2H, C*H*$_2$), 7.25-7.28 (m, 6H, Ph), 7.40-7.43 (m, 4H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.66, 26.19, 31.21, 34.93, 40.15, 40.24, 49.07, 128.18, 128.21, 128.34, 128.38, 129.91, 129.97, 139.33, 139.41, 148.04, 149.63, 150.48, 159.56; EI-MS (70 eV) *m*/*z* (rel. int.): 326 (M^+, 100), 311 (37), 297 (11), 283 (53), 180 (19), 77 (12); Anal. Calcd for $C_{23}H_{22}N_2$ (326.43): C, 84.63; H, 6.79; N, 8.58. Found: C, 84.68; H, 6.86; N, 8.63.

Pyrazine 2b. Off-white solid. Yield 2.78 g (47%); mp 157-161 °C; $[\alpha]_D^{20}$ = +12.6 (*c* 0.5, CH_3OH); R_f = 0.21 (SiO_2; Hexane/EtOAc 2:1); ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.75 (s, 3H, C*H*$_3$), 1.41 (d, *J* = 10.1 Hz, 1H, C*H*$_2$), 1.45 (s, 3H, C*H*$_3$), 2.44-2.48 (m, 1H, C*H*), 2.80-2.86 (m, 1H, C*H*$_2$), 3.19 (t, *J* = 5.8 Hz, 1H, C*H*), 3.23 (s, 2H, C*H*$_2$), 7.13-7.19 (m, 2H, Py), 7.53 (d, *J* = 7.5 Hz, 2H, Py), 7.60-7.66 (m, 2H, Py), 8.44-8.47 (m, 2H, Py); ^{13}C NMR (90 MHz, $CDCl_3$): δ 21.24, 25.75, 30.73, 34.68, 39.68, 39.70, 48.83, 122.42, 122.44, 124.29, 124.35, 136.04, 136.06, 147.35, 148.94, 148.98, 151.48, 157.00, 157.10, 160.43 (one signal missing); EI-MS (70 eV) *m*/*z* (rel. int.): 328 (M^+, 100), 313 (46), 287 (53), 285 (61), 250 (41), 181 (42), 78 (31); Anal. Calcd for $C_{21}H_{20}N_4$ (328.41): C, 76.80; H, 6.14; N, 17.06. Found: C, 76.79; H, 6.24; N, 17.00.

Pyrazine 2c. Off-white solid. Yield 0.92 g (12%); mp 90-95 °C; $[\alpha]_D^{20}$ = -15.7 (*c* 0.5, CH_3OH); R_f = 0.28 (SiO_2; Hexane/EtOAc 2:1); ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.93 (s, 3H, C*H*$_3$), 1.54 (s, 3H, C*H*$_3$), 1.62 (d, *J* = 2.5 Hz, 1H, C*H*$_2$), 2.55-2.58 (m, 1H, C*H*), 2.91-2.97 (m, 1H, C*H*$_2$), 3.23 (t, *J* = 5.5 Hz, 1H, C*H*), 3.32 (d, *J* = 2.6 Hz, 2H, C*H*$_2$), 7.07-7.13 (m, 4H, Np), 7.35-7.45 (m, 2H, Np), 7.61-7.64 (m, 2H, Np), 7.74-7.77 (m, 2H, Np), 7.82-7.85 (m, 2H, Np); ^{13}C NMR (90 MHz, $CDCl_3$): δ 21.79, 26.20, 31.19, 35.17, 40.23, 40.26, 49.22, 124.92, 124.96, 125.69, 125.72, 125.84, 125.87, 126.42, 126.46, 127.86, 127.91, 128.44, 128.45, 128.65, 128.66, 131.99, 133.89, 136.17, 136.28, 149.61, 150.96, 151.19, 159.88 (two signals missing); EI-MS (70 eV) *m*/*z* (rel. int.): 426 (M^+, 100), 411 (24), 383 (22), 230 (25), 153 (15), 77 (12); Anal. Calcd for $C_{31}H_{26}N_2$ (426.55): C, 87.29; H, 6.14; N, 6.57. Found: C, 87.20; H, 6.19; N, 6.44.

Pyrazine 2d. Oil. Yield 3.11 g (51%); $[\alpha]_D^{20}$ = +20.8 (*c* 0.5, CH_3OH); R_f = 0.82 (SiO_2; Hexane/EtOAc 2:1); ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.82 (s, 3H, C*H*$_3$), 1.45 (d, *J* = 10.1 Hz, 1H, C*H*$_2$), 1.52 (s, 3H, C*H*$_3$), 2.48-2.51 (m, 1H, C*H*), 2.84-2.89 (m, 1H, C*H*$_2$), 3.16 (t, *J* = 5.6 Hz, 1H, C*H*), 3.19 (d, *J* = 2.6 Hz, 2H, C*H*$_2$), 7.01-7.06 (m, 2H, Th), 7.16-7.20 (m, 2H, Th), 7.42-7.45 (t, *J* = 5.2 Hz, 2H, Th); ^{13}C NMR (90 MHz, $CDCl_3$): δ 21.61, 26.08, 31.04, 34.69, 40.02, 40.11, 48.85, 127.68, 127.83, 127.92, 128.04, 135, 24, 136.18, 141.48, 141.66, 141.72, 142.78, 150.42, 159.53; EI-MS (70 eV) *m*/*z* (rel. int.): 338 (M^+, 100), 323 (30), 295 (52), 211 (13), 186 (15), 77 (12); Anal. Calcd for $C_{19}H_{18}N_2S_2$ (338.49): C, 67.42; H, 5.36; N, 8.28; S, 18.95. Found: C, 67.38; H, 5.33; N, 8.22; S, 18.79.

Pyrazine 2e. Oil. Yield 0.55 g (10%); $[\alpha]_D^{20}$ = +15.7 (*c* 0.5, CH_3OH); R_f = 0.75 (SiO_2; Hexane/EtOAc 2:1); ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.70 (s, 3H, C*H*$_3$), 1.35 (d, *J* = 10.1 Hz, 1H, C*H*$_2$), 1.42 (s, 3H, C*H*$_3$), 2.39-2.43 (m, 1H, C*H*), 2.75-2.81 (m, 1H, C*H*$_2$), 3.10 (t, *J* = 5.6 Hz, 1H, C*H*), 3.13 (d, *J* = 2.9 Hz, 2H, C*H*$_2$), 6.44-6.46 (m, 2H, Fur), 6.47-6.51 (m, 2H, Fur), 7.48-7.50 (m, 2H, Fur); ^{13}C NMR (90 MHz, $CDCl_3$): δ 21.50, 26.03, 29.80, 30.96, 34.92, 39.99, 40.11, 49.06, 111.22, 111.47, 111.76, 111.78, 137.91, 139.31, 143.33, 143.43, 150.90, 151.03, 151.06, 159.93; EI-MS (70 eV) *m*/*z* (rel. int.): 306 (M^+, 100), 291 (23), 277 (10), 263 (45), 206 (10), 77 (10); Anal. Calcd for $C_{19}H_{18}N_2O_2$ (306.36): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.42; H, 5.92; N, 9.13.

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