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Synthesis and antimicrobial activity of 4-hydroxy-4-(pyridyl)alk-3-en-2-ones

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ABSTRACT

4-Hydroxy-4-(pyridyl)alk-3-en-2-ones were prepared by base-mediated condensation of ketones with pyridinecarboxylates. Several derivatives show weak antimicrobial activity against Gram-positive and Gram-negative bacteria.

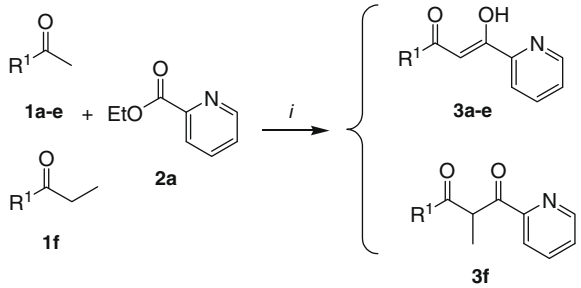
1. Introduction

Serious infections by resistant and multiresistant microbes are dramatically increased during the recent years[1,2] and represent the second leading cause of death.[3] Multiresistant strains of *Staphylococcus aureus*, such as MRSA (Methicillin resistant *S. aureus*), are often responsible for severe and life-threatening infections in patients during their stay in hospitals or in immunosuppressed persons. Therefore, the development of new antimicrobial agents represents an important task in medicinal chemistry. Its success crucially relies on the search for new chemical entities (NCEs). Unfortunately, pharmaceutical companies are more and more leaving this area, due to economic reasons.[4] Genomics, combinatorial synthesis, and high throughput screening (HTS) are used to identify new lead structures. However, success is limited as chemical companies have been unable to identify new and valid antimicrobial agents by random screening of compound libraries.[4] In fact no innovative antibiotics have been launched on the market for several decades. It was not before 2000 and 2003 that the first new NCEs, the oxazolidinone linezolid and the lipopeptide daptomycin, appeared on the market, respectively.[5,6] Recently, we have reported that 2-vinylchroman-4-ones show a remarkable activity against several humanpathogenic bacteria, including multiresistant strains.[7] Herein, we report the synthesis of 4-hydroxy-4-(pyridyl)alk-3-en-2-ones and their antimicrobial activity against Gram-positive and Gram-negative bacteria.

2. Results and discussion

2.1. Chemistry

We have earlier reported the synthesis of 4-hydroxy-4-(pyridyl)alk-3-en-2-ones by LDA-mediated condensation reactions.[8] We have found that better results (with respect to the purity of the compounds and in some cases regarding the yield) are obtained when sodium hydride (NaH)[9] is used as the base. The NaH-mediated condensation of ketones 1a-f with ethyl pyridine-2-carboxylate (2a) afforded the 4-hydroxy-4-(pyrid-2-yl)alk-3-en-2-ones **3a**–**f** (Scheme 1, Table 1). Products **3a**–**e** exclusively exist in their enol



Scheme 1. Synthesis of **3a**–**f**. Reagents and conditions: (i) NaH (4.0 equiv), **2a** (1.0 equiv), **1a**–**f** (2.0 equiv), Et_2O, reflux, 2 h.

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Table 1
Synthesis of **3a–f**

1,3	R^1	% (**3**)[a]
a	Me	65
b	Et	55
c	*n*Pr	66
d	*n*Bu	50
e	Ph	61
f	Et	55

[a] Yields of isolated products.

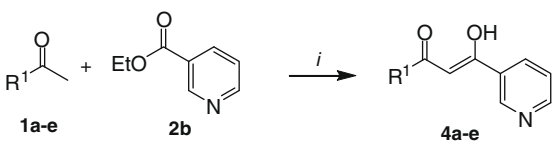
tautomeric form. Product **3f** exclusively resides in the keto form which is often the case for 2-substituted 1,3-diketones. The synthesis of **3a–c** and **3e** has been previously reported.[8]

The condensation of ketones **1a–e** with ethyl pyridine-3-carboxylate (**2b**) afforded the 4-hydroxy-4-(pyrid-3-yl)alk-3-en-2-ones **4a–e** (Scheme 2, Table 2). Products **4a–e** exclusively exist in their enol tautomeric form. The synthesis of **4a**,[8] **4b**,[10] **4d**,[11] and **4e**[11] has been previously reported. However, NMR and MS data of **4b**, **4d**, and **4e** have not yet been reported.

2.2. Biological activity

The biological activity of compounds **3** and **4** was evaluated (Table 3). Especially the growth of the Gram-positive bacteria *S. aureus* and *Bacillus subtilis* and the Gram-negative *Escherichia coli* was inhibited. The results of these studies are summarized in Table 3. The antimicrobial activity of the 4-hydroxy-4-(pyridyl)alk-3-en-2-ones is much lower compared to the standard antibiotic Ampicillin, and shows an interesting influence of the substitution pattern.

The presence of the pyridine moiety is mandatory for the pharmacological activity. The antibacterial activities strongly depend on the substitution pattern of the pyridine moiety. The pyrid-2-yl derivatives **3d**, **3e** and **4d**, **4e** are the most active compounds in this study. Interestingly, only derivatives which exist in their enol tautomeric form exhibit weak antimicrobial activity. In contrast, **3f** (which exclusively resides in the keto form) shows no antibacterial activity against Gram-positive bacteria. Compound **3f** only shows a very weak activity against Gram-negative *E. coli*. This suggests that the formation of the enol tautomeric form is essential for the antibiotic activity of the pyridyl compounds. Considering the influence of substituent R^1 it was found that more bulky residues lead to a stronger growth inhibition. This is especially the case for *B. subtilis*. In *S. aureus* this tendency is also observable but to a lower extent. Beside this observation the highest antibacterial activity was found for the phenyl derivatives **4e** and **3e**. The latter showed the highest activity against all tested bacteria. The *n*-butyl-substituted derivatives **4d** and **3d** also show a growth inhibition. Thorarensen and coworkers reported the antibacterial activity of enolic compounds with possible influence on the cell wall or protein synthesis.[12] Investigation towards the mechanism of action will concentrate on the role of the substitution pattern of the 1,3-diketo moiety. Furthermore the investigation of possible alterations of the metabolism under influence of the pyridyl-derivatives in the tested bacteria is interesting and will be topic of future work.



Scheme 2. Synthesis of **4a–e**. Reagents and conditions: (i) NaH (4.0 equiv), **2b** (1.0 equiv), **1a–e** (2.0 equiv), Et_2O, reflux, 2 h.

Table 2
Synthesis of **4a–e**

1,4	R^1	% (**4**)[a]
a	Me	53
b	Et	67
c	*n*Pr	70
d	*n*Bu	62
e	Ph	65

[a] Yields of isolated products.

Table 3
Minimal inhibitory concentrations of selected compounds **3** and **4** (values given in μg/mL)[a]

Compound	*S. aureus ATCC 6538*	*B. subtilis ATCC 11229*	*E. coli ATCC 6051*
3a	46.90	190.03	378.52
3b	23.57	211.08	195.40
3c	191.57	97.25	97.84
3d	96.52	48.14	47.67
3e	47.36	24.49	24.09
3f	758.16	786.04	390.73
4a	392.30	397.18	401.66
4b	380.36	373.64	379.40
4c	192.82	200.40	94.11
4d	95.52	95.37	95.38
4e	95.13	94.64	95.80
Ampicillin	3.19	12.48	6.99

[a] Minimal inhibitory concentrations were determined by a dilution assay (results are averages of **3** independent experiments).

3. Conclusions

A variety of novel 4-hydroxy-4-(pyrid-2-yl)alk-3-en-2-ones were prepared by base-mediated condensation of ketones with pyridinecarboxylates. Some derivatives show weak antimicrobial activity against Gram-positive bacteria. Further investigations towards the understanding of the mode of action are in progress.

4. Experimental

4.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

4.2. Antibiotic susceptibility tests

Bacterial strains were obtained from the ATCC. The minimum inhibitory concentration (MIC) was determined by microdilution according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI).[13] The MIC was determined in 96 well microtiter plates in a final volume of 200 μl without agitation. The initial inoculum was 2×10^5 bacterial cells per well. The plates were incubated for 24 h at 37 °C.

4.3. General procedure for the synthesis of 1,3-dicarbonyl compounds 3a–f and 4a–e

To a stirred suspension of NaH (4.0 equiv) in anhydrous diethyl ether (1.0 mL/2.5 mmol of **1**) at 0 °C was added **2a** or **2b** (1.0 equiv) and ketone **1a–f** (2.0 equiv) at 20 °C. The mixture was refluxed for

2 h, cooled and a diluted aqueous solution of NH_4Cl was added. The organic and the aqueous layer were separated and the latter was extracted with diethylether (3×20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, heptanes/EtOAc = 30:1→20:1) to give products **3** or **4**. Compounds **1a–f** and **2a–b** are commercially available. The synthesis of **3a–c** and **3e** has been previously reported.[8] The synthesis of **4a**,[8] **4b**,[10] **4d**,[11] and **4e**[11] has been previously reported. However, NMR and MS data of **4b**, **4d**, and **4e** have not yet been reported.

4.4. 4-Hydroxy-4-(pyrid-2-yl)but-3-en-2-one (3a)

Starting with NaH (2.30 g, 96.0 mmol), diethyl ether (18 mL), acetone (3.5 mL, 48.0 mmol) and **2a** (3.3 mL, 24.0 mmol), **3a** was isolated as a yellowish solid, mp = 48–50 °C (2.055 g, 65%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), 6.82 (s, 1H, CH), 7.38–7.43 (m, 1H, CH_{py}), 7.80–7.86 (m, 1H, CH_{py}), 8.06–8.09 (m, 1H, CH_{py}), 8.65–8.66 (m, 1H, CH_{py}), 15.69 ($s_{(br)}$, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.1 (CH_3), 97.2 (CH), 122.1, 126.2, 137.0, 149.0 (CH_{py}), 152.1 (C_{py}), 180.7 (COH), 195.0 (CO). IR (KBr, cm^{-1}): $\tilde{\nu} = 3117$ (w), 3066 (w), 2957 (w), 2870 (w), 1605 (m), 1579 (m), 1463 (m), 1416 (m), 1353 (m), 1284 (m), 1245 (m), 1183 (m), 1158 (m), 1079 (m), 1043 (w) 990 (m), 907 (m), 848 (m), 784 (s), 746 (m), 620 (m), 584 (w), 545 (m). GC–MS (EI, 70 eV): *m/z* (%) = 163 (M^+, 46), 148 (84), 134 (8), 121 (28), 106 (64), 96 (14), 85 (15), 79 (75), 78 (100), 52 (25), 51 (31), 50 (10), 43 (35), 39 (10). HRMS (EI): Calcd for $C_9H_9O_2N$: 163.06278; found: 163.063192.

4.5. 1-Hydroxy-1-(pyrid-2-yl)pent-1-en-3-one (3b)

Starting with NaH (2.30 g, 96.0 mmol), diethyl ether (18 mL), 2-butanone (4.37 mL, 48.0 mmol) and **2a** (3.3 mL, 24.0 mmol), **3b** was isolated as a yellowish oil (2.10 g, 55%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.21 (t, ^3J = 7.4 Hz, 3H, CH_2CH_3), 2.50 (q, ^3J = 7.7, 2H, CH_2CH_3), 6.82 (s, 1H, CH), 7.37–7.42 (m, 1H, CH_{py}), 7.79–7.86 (m, 1H, CH_{py}), 8.05–8.08 (m, 1H, CH_{py}), 8.64–8.66 (m, 1H, CH_{py}), 15.69 ($s_{(br)}$, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.4 (CH_2CH_3), 32.4 (CH_2CH_3), 96.2 (CH), 122.0, 126.1, 137.2, 149.5 (CH_{py}), 152.3 (C_{py}), 180.4 (COH), 199.6 (CO). IR (neat, cm^{-1}): $\tilde{\nu} = 2976$ (w), 2879 (w), 1601 (m), 1577 (s), 1577 (s), 1460 (m), 1413 (m), 1312 (m), 1241 (m), 1044 (m), 993 (m), 829 (m), 781 (s), 742 (s), 689 (m), 543 (w). GC–MS (EI, 70 eV): *m/z* (%) = 177 ([M^+], 12), 162 (4), 148 (100), 106 (68), 79 (25), 78 (77), 52 (10), 51 (15). HRMS (EI): Calcd for $C_{10}H_{11}O_2N$: 177.07843; found: 177.078306.

4.6. 1-Hydroxy-1-(pyrid-2-yl)hex-1-en-3-one (3c)

Starting with NaH (2.30 g, 96.0 mmol), diethyl ether (18 mL), 2-pentanone (5.1 mL, 48.0 mmol) and **2a** (3.26 mL, 24.0 mmol), **3c** was isolated as a yellowish oil (3.04 g, 66%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.98 (t, ^3J = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.66–1.80 (m, 2H, $CH_2CH_2CH_3$), 2.44 (t, ^3J = 7.2 Hz, 2H, $CH_2CH_2CH_3$), 6.81 (s, 1H, CH), 7.36–7.42 (m, 1H, CH_{py}), 7.78–7.85 (m, 1H, CH_{py}), 8.05–8.09 (m, 1H, CH_{py}), 8.63–8.66 (m, 1H, CH_{py}), 15.77 ($s_{(br)}$, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 ($CH_2CH_2CH_3$), 19.3 ($CH_2CH_2CH_3$), 41.6 ($CH_2CH_2CH_3$), 97.0 (CH), 122.3, 126.4, 137.3, 149.5 (CH_{py}), 152.7 (C_{py}), 180.6 (COH), 198.3 (CO). IR (neat cm^{-1}): $\tilde{\nu} = 2962$ (w), 2873 (w), 1720 (w), 1601 (m), 1577 (s), 1577 (s), 1458 (m), 1430 (m), 1333 (m), 1283 (m), 1086 (m), 993 (m), 827 (w), 785 (s), 742 (s), 690 (m), 618 (m). GC–MS (EI, 70 eV): *m/z* (%) = 191 ([M^+], 9), 163 (13), 148 (100), 121 (17), 106 (78), 93 (15), 79 (30), 78 (87), 52 (11), 51 (16), 43 (13). HRMS (EI): Calcd for $C_{11}H_{13}O_2N$: 191.09408; found: 191.093919.

4.7. 1-Hydroxy-1-(pyrid-2-yl)hept-1-en-3-one (3d)

Starting with NaH (2.30 g, 96.0 mmol), diethyl ether (18 mL), 2-hexanone (5.9 mL, 48.0 mmol) and **2a** (3.3 mL, 24.0 mmol), **3d** was isolated as a light yellow oil (2.46 g, 50%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.86 (t, ^3J = 7.3 Hz, 3H, $(CH_2)_3CH_3$), 1.25–1.40 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.56–1.67 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.40 (t, ^3J = 7.5 Hz, 2H, $CH_2CH_2CH_2CH_3$), 6.75 (s, 1H, CH), 7.30–7.36 (m, 1H, CH_{py}), 7.72–7.79 (m, 1H, CH_{py}), 8.99–8.02 (m, 1H, CH_{py}), 8.57–8.60 (m, 1H, CH_{py}), 15.66 ($s_{(br)}$, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.5, 28.0, 39.17 (CH_2), 96.8 (CH), 122.1, 126.2, 137.1, 149.3 (CH_{py}), 152.3 (C_{py}), 180.8 (COH), 198.5 (CO). IR (neat cm^{-1}): $\tilde{\nu} = 2956$ (w), 2871 (w), 1720 (w), 1720 (m), 1578 (m), 1563 (m), 1461 (m), 1430 (m), 1378 (w), 1281 (m), 1146 (w), 1087 (m), 1043 (w), 991 (w), 825 (w), 785 (s), 742 (m), 692 (w), 618 (m). GC–MS (EI, 70 eV): *m/z* (%) = 205 ([M^+], 7), 163 (30), 149 (12), 148 (100), 135 (13), 122 (11), 121 (35), 120 (18), 106 (78), 93 (27), 79 (37), 78 (100), 52 (12), 51 (16), 41 (12). HRMS (EI): Calcd for $C_{12}H_{15}O_2N$: 205.11029; found: 205.110456.

4.8. 3-Hydroxy-1-phenyl-3-(pyrid-2-yl)prop-2-en-1-one (3e)

Starting with NaH (2.30 g, 96.0 mmol), diethyl ether (18 mL), acetophenone (5.6 mL, 48.0 mmol) and **2a** (3.3 mL, 24.0 mmol), **3e** was isolated as a light yellow solid mp = 81–83 °C (3.30 g, 61%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.44–7.55 (m, 4H, CH_{Ar}), 7.59 (s, 1H, CH), 7.82–7.89 (m, 1H, CH_{Ar}), 8.05–8.09 (m, 2H, CH_{Ar}), 8.14–8.18 (m, 1H, CH_{Ar}), 8.69–8.72 (m, 1H, CH_{Ar}), 16.59 ($s_{(br)}$, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 93.6 (CH), 122.1, 126.2 (CH_{Ar}), 127.3 ($2 \times CH_{Ar}$), 128.5 ($2 \times CH_{Ar}$), 132.7 (CH_{Ar}), 135.4 (C_{Ph}), 137.1, 149.3 (CH_{Ar}), 152.6 (C_{py}), 183.6 (COH), 186.3 (CO). IR (neat cm^{-1}): $\tilde{\nu} = 3120$ (w), 3055 (w), 2959 (w), 2872 (w), 1681 (w), 1598 (m), 1455 (m), 1417 (m), 1278 (m), 1250 (m), 1212 (m), 1178 (m), 1145 (m), 1086 (m), 1041 (w) 992 (m), 908 (m), 831 (w), 770 (s), 749 (m), 686 (m), 608 (m). GC–MS (EI, 70 eV): *m/z* (%) = 225 (M^+, 53), 208 (10), 198 (9), 197 (20), 196 (49), 180 (29), 168 (15), 147 (37), 120 (11), 105 (100), 98 (16), 96 (23), 92 (19), 89 (10), 84 (43), 79 (41), 78 (51), 77 (46), 75 (11), 72 (23), 69 (62), 65 (17). HRMS (EI): Calcd for $C_{14}H_{11}O_2N$: 225.07843; found: 225.078442.

4.9. 2-Methyl-1-(pyrid-2-yl)pentane-1,3-dione (3f)

Starting with NaH (2.30 g, 96 mmol), diethyl ether (18 mL), 3-pentanone (5.1 mL, 48.0 mmol) and **2a** (3.3 mL, 24.0 mmol), **3f** was isolated as a light red oil (2.52 g, 55%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.08 (t, ^3J = 7.4 Hz, 3H, CH_2CH_3), 1.39 (d, ^3J = 7.6 Hz, 3H, CH_3), 2.70 (q, ^3J = 7.0, 2H, CH_2CH_3), 4.86 (q, ^3J = 7.1, 1H, $CHCH_3$), 7.42–7.47 (m, 1H, CH_{py}), 7.79–7.86 (m, 1H, CH_{py}), 8.03–8.07 (m, 1H, CH_{py}), 8.60–8.63 (m, 1H, CH_{py}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.8, 12.7 (CH_3), 35.3 (CH_2), 54.1 (CH), 122.4, 127.3, 137.1, 148.7 (CH_{py}), 152.3 (C_{py}), 198.5, 208.9 (CO). IR (neat cm^{-1}): $\tilde{\nu} = 2978$ (w), 2877 (w), 1716 (s), 1697 (s), 1584 (m), 1569 (w), 1455 (m), 1410 (w), 1324 (m), 1286 (w), 1223 (m), 1113 (w), 1038 (w), 995 (m), 950 (m), 790 (w), 781 (w), 742 (m), 667 (w), 618 (m). GC–MS (EI, 70 eV): *m/z* (%) = 191 ([M^+], 1), 163 (10), 162 (93), 135 (91), 134 (30), 107 (27), 106 (69), 80 (11), 79 (67), 78 (100), 57 (25), 52 (15), 51(24), 29 (19). HRMS (EI): Calcd for $C_{11}H_{13}O_2N$: 191.09408; found: 191.093912.

4.10. 4-Hydroxy-4-(pyrid-3-yl)but-3-en-2-one (4a)

Starting with NaH (2.30 g, 96.0 mmol), diethyl ether (18 mL), acetone (3.5 mL, 48.0 mmol) and **2b** (3.3 mL, 24.0 mmol), **4a** was isolated as a light orange solid, mp = 50–52 °C (2.07 g, 53%). ^{1}H

NMR (250 MHz, $CDCl_3$): δ 2.17 (s, 3H, CH_3), 6.13 (s, 1H, CH), 7.32–7.37 (m, 1H, CH_{py}), 8.08–8.12 (m, 1H, CH_{py}), 8.66–6.68 (m, 1H, CH_{py}), 9.01 (s, 1H, CH_{py}), 15.92 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0 (CH_3), 97.2 (CH), 123.7, 128.5, 148.4, 152.7, (CH_{Ar}), 134.5 (C_{py}), 181.2 (*C*OH), 194.6 (CO). IR (neat, cm^{-1}): $\tilde{\nu} = 2952$ (w), 2919 (w), 1926 (w), 1584 (s), 1411 (m), 1371 (s), 1204 (m), 1077 (s), 824 (m), 872 (s), 695 (s), 543 (w). GC–MS (EI, 70 eV): *m/z* (%) = 163 ([M^+], 67), 162 (100), 148 (97), 106 (66), 104 (9), 85 (25), 79 (26), 78 (53), 69 (18), 65 (10), 51 (29), 50 (13), 43 (33), 39 (11). HRMS (EI): Calcd for $C_9H_9O_2N$: 163.06278; found: 163.062897.

4.11. 1-Hydroxy-1-(pyrid-3-yl)pent-1-en-3-one (4b)

Starting with NaH (2.30 g, 96.0 mmol), diethyl ether (18 mL), 2-butanone (4.4 mL, 48.0 mmol) and **2b** (3.3 mL, 24.0 mmol), **4b** was isolated as a yellowish oil (2.86 g, 67%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.21 (t, ^3J = 7.4 Hz, 3H, CH_2CH_3), 2.48 (q, ^3J = 8.5, 2H, CH_2CH_3), 6.17 (s, 1H, CH), 7.38−7.41 (m, 1H, CH_{py}), 8.13−8.18 (m, 1H, CH_{py}), 8.71–8.73 (m, 1H, CH_{py}), 9.06 (s, 1H, CH_{py}), 15.94 ($s_{(br)}$, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.6 (CH_2CH_3), 32.5 (CH_2CH_3), 95.9 (CH), 123.4 (CH_{py}), 130.7 (C_{py}), 134.4, 148.2, 152.6 (CH_{py}), 180.5 (COH), 198.6 (CO). IR (neat cm^{-1}): $\tilde{\nu} = 2975$ (w), 2879 (w), 1720 (w), 1587 (s), 1461 (m), 1412 (m), 1320 (m), 1268 (m), 1153 (w), 1087 (w), 1022 (m), 993 (w), 907 (w), 804 (w), 710 (m), 620 (w), 543 (w). GC–MS (EI, 70 eV): *m/z* (%) = 177 ([M^+], 37), 176 (11), 149 (14), 148 (100), 106 (43), 78 (27), 69 (12), 51 (14). HRMS (EI): Calcd for $C_{10}H_{11}O_2N$: 177.07843; found: 177.078509.

4.12. 1-Hydroxy-1-(pyrid-3-yl)hex-1-en-3-one (4c)

Starting with NaH (2.30 g, 96.0 mmol), diethyl ether (18 mL), 2-pentanone (5.1 mL, 48.0 mmol) and **2b** (3.3 mL, 24.0 mmol), **4c** was isolated as a light yellow oil (3.20 g, 70%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.93 (t, ^3J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.58–1.73 (m, 2H, $CH_2CH_2CH_3$), 2.36 (t, ^3J = 7.2 Hz, 2H, $CH_2CH_2CH_3$), 6.10 (s, 1H, CH), 7.30–7.35 (m, 1H, CH_{py}), 8.07−8.12 (m, 1H, CH_{py}), 8.64–8.67 (m, 1H, CH_{py}), 9.0 (s, 1H, CH_{py}), 15.96 ($s_{(br)}$, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 ($CH_2CH_2CH_3$), 19.3 ($CH_2CH_2CH_3$), 41.0 ($CH_2CH_2CH_3$), 96.2 (CH), 123.4 (CH_{py}), 130.8 (C_{py}), 134.3, 148.5, 152.6 (CH_{py}), 181.4 (COH), 197.4 (CO). IR (neat cm^{-1}): $\tilde{\nu} = 3041$ (w), 2963 (w), 2873 (w), 1720 (w), 1587 (s), 1462 (m), 1410 (m), 1380 (w), 1339 (w), 1264 (m), 1193 (m), 1090 (w), 1021 (m), 906 (m), 825 (w), 773 (m), 700 (s), 649 (w), 563 (w). GC–MS (EI, 70 eV): *m/z* (%) = 191 ([M^+], 26), 163 (15), 149 (12), 148 (100), 106 (38), 78 (25), 69 (12), 51 (11). HRMS (EI): Calcd for $C_{11}H_{13}O_2N$: 191.09408; found: 191.093962.

4.13. 1-Hydroxy-1-(pyrid-3-yl)hept-1-en-3-one (4d)

Starting with NaH (2.30 g, 96.0 mmol), diethyl ether (18 mL), 2-hexanone (5.9 mL, 48.0 mmol) and **2b** (3.3 mL, 24.0 mmol), **4d** was isolated as a yellowish oil (3.05 g, 62%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.94 (t, ^3J = 7.2 Hz, 3H, $(CH_2)_3CH_3$), 1.32–1.47 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.61–1.73 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.45 (t, ^3J = 7.3 Hz, 2H, $CH_2CH_2CH_2CH_3$), 6.17 (s, 1H, CH), 7.36–7.42 (m, 1H, CH_{py}), 8.13−8.18 (m, 1H, CH_{py}), 8.71–8.73 (m, 1H, CH_{py}), 9.06 (s, 1H, CH_{py}), 16.02 ($s_{(br)}$, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (CH_3), 22.3, 27.7, 39.1 (CH_2), 96.5 (CH), 123.4 (CH_{py}), 130.8 (C_{py}), 134.3, 148.5, 152.6 (CH_{py}), 181.1 (COH), 197.7 (CO). IR (neat cm^{-1}): $\tilde{\nu} = 3041$ (w), 2957 (w), 2871 (w), 1586 (s), 1464 (m), 1410 (m), 1378 (w), 1270 (m), 1128 (w), 1093 (m), 1021 (m), 946 (w), 853 (w), 770 (s), 699 (s), 620 (w), 565 (w). GC–MS (EI, 70 eV): *m/z* (%) = 205 ([M^+], 5), 176 (12), 163 (65), 162 (28), 149 (10), 148 (100), 121 (13), 106 (67), 78 (33), 69 (15), 51 (14), 41 (8). HRMS (EI): Calcd for $C_{12}H_{15}O_2N$: 205.11029; found: 205.110456.

4.14. 3-Hydroxy-1-phenyl-3-(pyrid-3-yl)prop-2-en-1-one (4e)

Starting with NaH (2.30 g, 96.0 mmol), diethyl ether (18 mL), acetophenone (5.6 mL, 48.0 mmol) and **2b** (3.3 mL, 24.0 mmol), **4e** was isolated as a light yellow solid, mp = 118–120 °C (3.50 g, 65%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.86 (s, 1H, CH), 7.41–7.62 (m, 4H, CH_{Ar}), 7.98–8.01 (m, 2H, CH_{Ar}), 8.25–8.28 (m, 1H, CH_{Ar}), 8.76–8.78 (m, 1H, CH_{Ar}), 9.19 (s, 1H, CH_{Ar}), 16.50 ($s_{(br)}$, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 93.65 (CH), 123.5 (CH_{Ar}), 127.3 ($2 \times CH_{Ar}$), 128.8 ($2 \times CH_{Ar}$), 131.2 (C_{Ph}), 132.8, 133.4 (CH_{Ar}), 135.1 (C_{py}), 148.4, 152.9 (CH_{Ar}), 183.5 (COH), 186.4 (CO). IR (neat cm^{-1}): $\tilde{\nu} = 3108$ (w), 3056 (w), 2917 (w), 1587 (m), 1519 (m), 1463 (m), 1404 (m), 1279 (m), 1240 (m), 1188 (m), 1154 (m), 1115 (m), 1063 (m), 1036 (w) 963 (m), 841 (w), 804 (m), 769 (s), 717 (m), 683 (s), 607 (m). GC–MS (EI, 70 eV): *m/z* (%) = 225 ([M^+], 83), 224 (100), 196 (24), 148 (23), 147 (24), 106 (25), 105 (40), 79 (19), 78 (30), 77 (46), 69 (40), 51 (29). HRMS (EI): Calcd for $C_{14}H_{11}O_2N$: 225.07843; found: 225.078866.

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