Microwave-Assisted Synthesis of Nitro-Substituted Tetrahydropyridoazepines

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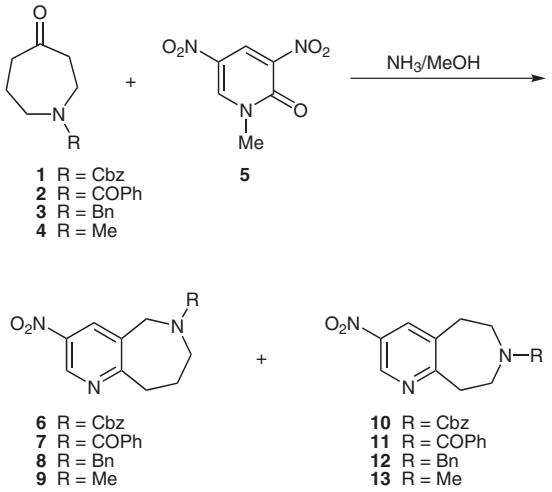
Abstract: The microwave-assisted condensation of azepan-4-ones with 3,5-dinitro-1-methylpyridin-2-one in the presence of ammonia was found to be a highly efficient method for the synthesis of nitro-substituted tetrahydropyridoazepines. Variation of the substituent at the amino group enables the regioselective synthesis of tetrahydropyrido[3,2-*c*]azepines and tetrahydropyrido[2,3-*d*]azepines.

Key words: ketones, condensation, regioselectivity, heterocycles, pyridines

While tetrahydroazepines are widely used in medicinal chemistry, and have been successfully applied for the synthesis of factor Xa inhibitors,[1] and antagonists of the 5-HT_{2C},[2] 5-HT_6,[3] H_3,[4] and the dopamine receptors,[5] the corresponding tetrahydropyridoazepine analogues are scarcely known. During our research program on novel heterocyclic structures we became interested in the synthesis of nitro-substituted tetrahydropyridoazepines, as the nitro group would provide a versatile handle for further functionalizations of these building blocks. Unfortunately, the synthetic routes reported so far for tetrahydropyridoazepines are not feasible for the synthesis of nitro-substituted derivatives.[6] In addition, the direct nitration of pyridines with nitric acid is difficult, and gives frequently low yields of the desired products.[7] To circumvent this problem, nitro-substituted pyridines have been synthesized by Diels–Alder reactions of 5-nitropyrimidine with enamines[8] or condensation of 3,5-dinitro-1-methyl-pyridin-2(1*H*)-one (**5**) with ketones and aldehydes in the presence of ammonia.[9] Both methods were shown to be efficient for the synthesis of nitro-substituted tetrahydronaphthyridines, but the desired tetrahydropyridoazepines were only formed in trace amounts.[8,10]

Microwave irradiation has been successfully applied in organic synthesis to increase the reaction rates of a wide range of transformations.[11] For this reason, we became interested to see if it could also improve the hitherto low-yielding formation of tetrahydropyridoazepines within the condensation reaction of cyclic ketones with 3,5-dinitro-1-methylpyridin-2(1*H*)-one (**5**) (Scheme 1).[10] We were very pleased to find that the benzyloxycarbonyl (Cbz)-protected azepan-4-one **1** was almost completely converted to the desired tetrahydropyridoazepine after heating the reaction mixture for 30 minutes at 60 °C in a microwave oven. After column chromatography, the product was isolated in 79% yield as a mixture of regioisomers **6** and **10** (Table 1, entry 4). Optimizing the reaction conditions, we were surprised to observe a decreased regioselectivity at higher temperatures, while the yield increased up to 92% at the same time (Table 1, entry 1). Further investigations revealed that **6** is preferentially formed at lower temperatures, while the product ratio is unaffected by the reaction time (Table 1, entries 5–7). The regioselectivity was significantly improved by stirring the reaction mixture for 48 hours at room temperature in a sealed tube without microwave irradiation, giving the desired tetrahydropyridoazepines **6** and **10** in 62% yield with an excellent selectivity (84:16, **6/10**) (Table 1, entry 9).



Scheme 1 Condensation reaction of azepan-4-ones **1**–**4**

These results demonstrated that microwave irradiation is not necessary to perform the condensation reaction. Therefore, the observed temperature dependency of the regioselectivity could be in principle a thermal effect as well as a nonthermal microwave effect.[11] Heating the reaction mixture for 30 minutes at 60 °C in an oil bath gave the desired products **6** and **10** with a selectivity of 75:25 (**6/10**). The regioselectivity obtained by conventional heating is almost identical to the selectivity, which was obtained at 40 °C in the microwave (78:22, **6/10**) (Table 1, entry 5). This result was not completely unexpected as the microwave tends to overheat the reaction vessel at the beginning of the reaction, and the maximum temperature detected was usually up to 10 °C higher than intended.

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Table 1 Condensation Reaction of the Cbz-Protected Azepan-4-one **1**

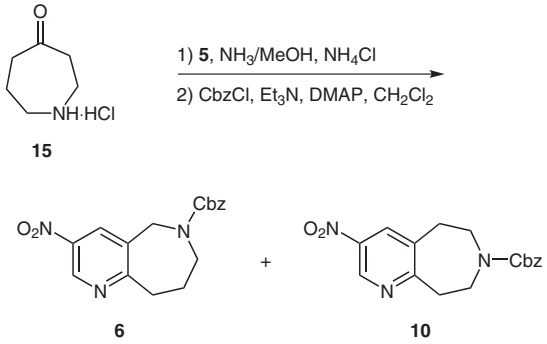
Entry	R	Temp (°C)	Time (h)	Selectivity (**6**/**10**)[a]	Yield (%)
1	Cbz	120[b]	0.5	64:36	92
2	Cbz	100[b]	0.5	64:36	90
3	Cbz	80[b]	0.5	65:35	79
4	Cbz	60[b]	0.5	68:32	79
5	Cbz	40[b]	0.5	78:22	37
6	Cbz	40[b]	1	78:22	43
7	Cbz	40[b]	2	77:23	73
8	Cbz	r.t.	24	86:14	56
9	Cbz	r.t.	48	84:16	62

[a] Determined by ^{1}H NMR spectroscopy.
[b] Heated by microwave irradiation.

Moreover, in contrast to an oil bath, microwave irradiation heats the reaction mixture from inside, while the temperature is detected at the outside of the reaction vessel. Therefore, we expect an even more pronounced temperature difference within reaction mixtures, which are heated by oil bath or microwave. For this reason, we believe that the observed temperature dependency is mainly a thermal effect, as a similar effect on the regioselectivity was observed by conventional heating as well.

To investigate the effect of the bulky Cbz-protecting group on the regioselectivity, the unprotected azepan-4-one hydrochloride **15** was reacted with 3,5-dinitro-1-methylpyridin-2(1*H*)-one (**5**) in the presence of ammonia, and the crude product was subsequently treated with Cbz-chloride to give the protected tetrahydropyridoazepines **6** and **10** in two steps (Scheme 2). In contrast to the Cbz-protected azepan-4-one **1**, the route starting from the unprotected ketone **15** gave preferentially the regioisomer **10** as the main product, and the best selectivity was observed at elevated temperature (Table 2, entries 1–4). An effect of the ammonium hydrochloride, present under these reaction conditions, was ruled out by reacting the Cbz-protected azepan-4-one **1** at 80 °C in the presence of one equivalent of ammonium chloride under otherwise identical conditions. No effect of the ammonium salt was detected, and the same regioselectivity was obtained as under salt-free conditions (65:35, **6**/**10**) (cf. Table 1, entry 2).

It is not easily rationalized, why the Cbz-protected azepan-4-one **1** and the unprotected azepan-4-one **15** preferentially give the opposite regioisomers. Based on the mechanism proposed by Thoda et al.,[9] the observed regioselectivity has to be controlled by the addition of the corresponding enolates **16** and **17** to pyridinone **5** (Scheme 3). Addition of ammonia gives the intermediates **18** and **19**, which will cyclize to the meta-bridged intermediates



Scheme 2 Condensation reaction and subsequent Cbz-protection of azepan-4-one **15**

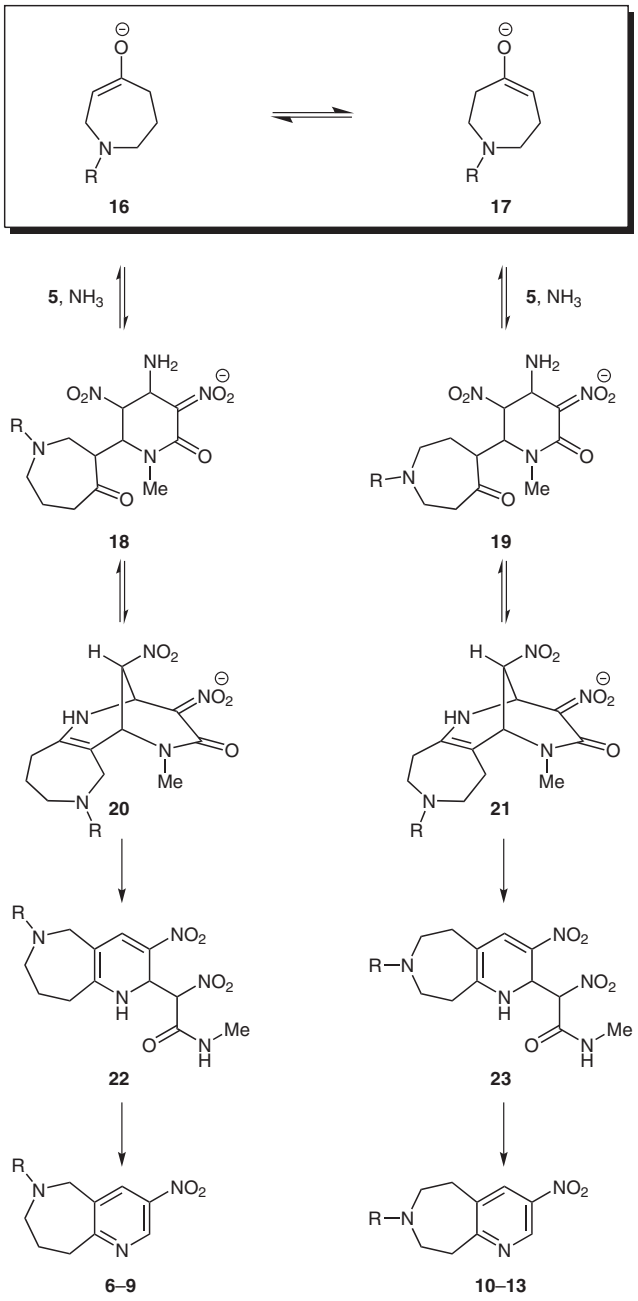
Table 2 Condensation Reaction and Subsequent Cbz-Protection of Azepan-4-one **15**

Entry	Temp (°C)	Time (h)	Selectivity (**6**/**10**)[a]	Yield (%)
1	100[b]	0.5	34:66	38
2	80[b]	0.5	34:66	38
3	80[b]	2	35:65	40
4	60[b]	0.5	34:66	41
5	r.t.	24	44:56	40

[a] Determined by ^{1}H NMR spectroscopy.
[b] Heated by microwave irradiation.

20 and **21**. Consecutive elimination of the ammonium salt of *N*-methyl-α-nitroacetamide finally leads to the tetrahydropyridoazepine regioisomers **6**–**9** and **10**–**13** (Scheme 3). Therefore, the two main factors determining the product ratio should be the equilibrium constant between the two enolates **16** and **17**, and the difference between the reaction rates of their addition to the pyridinone **5**.

To get a better insight into the steric and electronic effects of the protecting group on the regioselectivity, benzyl 4-oxoazepane-1-carboxylate (**1**), 1-benzoylazepan-4-one (**2**), 1-benzylazepan-4-one (**3**), and 1-methylazepan-4-one hydrochloride (**4**) were treated with pyridinone **5** in the presence of ammonia at room temperature and 100 °C (Scheme 1). Azepan-4-ones **1** and **2**, with a carbonyl-group attached to the nitrogen, preferentially gave the tetrahydropyrido[3,2-*c*]azepines **6** and **7**, and the best selectivity was observed at room temperature (Table 3, entries 1–4). While almost no regioselectivity was observed at room temperature for azepan-4-ones **3**, **4** (Table 3, entries 6 and 8), and **15** (Table 2, entry 5), the tetrahydropyrido[2,3-*d*]azepines **12**, **13** (Table 3, entries 5 and 7) and **10** (Table 2, entry 1) were formed as the major products at 100 °C. These observations led to the conclusion, that the carbonyl group present in the Cbz and the benzoyl group efficiently stabilizes the enolate **16** at room temperature, while elevated temperatures generally facilitate the reaction of the corresponding enolate **17** (Scheme 3).



Scheme 3 Proposed reaction mechanism

In summary, microwave irradiation was shown to have a beneficial effect on the rate of the reaction of azepan-4-ones with pyridinone **5** in the presence of ammonia. The condensation reaction was performed under elevated pressure, at temperatures exceeding the boiling point of the solvent, giving the desired tetrahydropyridoazepines in excellent yield (up to 95%) and with short reaction times. Substituents at the nitrogen of the azepan-4-one, containing a carbonyl group, were found to stabilize the intermediate enolate **16**, enabling the regioselective synthesis of tetrahydropyrido[3,2-*c*]azepines.

The condensation reactions were performed using a CEM Discover microwave equipped with an Explorer autosampler. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer. IR spectra were recorded on a PerkinElmer Paragon 500 FTIR-spectrometer. LC/MS analyses were conducted using the Agilent 1100 HPLC system equipped with a mass-selective detector and a GROM-SIL 80 ODS-7pH column. Separation of regioisomers were performed with an Agilent 1100 preparative HPLC system equipped with autosampler, fraction collector, and a ProntoSil Prep012 120-C18 ace-EPS column.

Table 3 Influence of Different Residues on the Condensation Reaction

Entry	R	Temp (°C)	Time (h)	Selectivity[a]	Yield (%)
1	Cbz	100[b]	0.5	64:36 (**6**/**10**)	90
2	Cbz	r.t.	24	86:14 (**6**/**10**)	56
3	COPh	100[b]	0.5	55:45 (**7**/**11**)	95
4	COPh	r.t.	24	79:21 (**7**/**11**)	60
5	Bn	100[b]	0.5	42:58 (**8**/**12**)	43
6	Bn	r.t.	24	53:47 (**8**/**12**)	54
7	Me	100[b]	0.5	31:69 (**9**/**13**)	34
8	Me	r.t.	24	44:56 (**9**/**13**)	57

[a] Determined by ^{1}H NMR spectroscopy.
[b] Heated by microwave irradiation.

Nitro-Substituted Tetrahydropyridoazepines; Benzyl 3-Nitro-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine-6-carboxylate (6) and Benzyl 3-Nitro-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*d*]azepine-7-carboxylate (10); Typical Procedure

Benzyl 4-oxoazepane-1-carboxylate (**1**; 49 mg, 0.20 mmol) and 1-methyl-3,5-dinitropyridin-2(1*H*)-one (**5**; 44 mg, 0.22 mmol) were dissolved in a solution of ammonia in MeOH (2.0 mL, 7.0 M). The reaction mixture was stirred in a sealed tube at r.t. for 24 h or heated in a microwave to 100 °C for 30 min. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, cyclohexane–EtOAc) to give the desired product as a mixture of regioisomers **6** and **10** (see below). Unreacted benzyl-4-oxoazepane-1-carboxylate (**1**) could not be separated by column chromatography. The purity of the product and the ratio of regioisomers was determined by ^{1}H NMR spectroscopy.

The yield of benzyl 3-nitro-6,7,8,9-tetrahydro-5*H*-pyridoazepine-carboxylates **6** and **10** was calculated on the basis of purity. The regioisomers **6** and **10** were separated by preparative HPLC, while the regioisomers **9** and **13** were separated by column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3).

Benzyl 3-Nitro-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine-6-carboxylate (6) and Benzyl 3-Nitro-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*d*]azepine-7-carboxylate (10); Two-Step Procedure

Azepane-4-one hydrochloride (**15**; 30 mg, 0.20 mmol) and 1-methyl-3,5-dinitropyridin-2(1*H*)-one (**5**; 44 mg, 0.22 mmol) were dissolved in a solution of ammonia in MeOH (2.0 mL, 7.0 M). The reaction mixture was stirred in a sealed tube at r.t. for 24 h or heated in a microwave to 100 °C for 30 min. The solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (10 mL); the EtOAc layer was washed with H_2O (3 × 2.0 mL) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2.0 ml) together with Et_3N (0.04 mL, 0.26 mmol) and 4-dimethylaminopyridine (3 mg, 0.02 mmol). At 0 °C, a solution of benzyl chloroformate in toluene (50 wt%,

0.08 mL, 81 mg, 0.24 mmol) was added. The reaction mixture was warmed to r.t. overnight. A solution of $NaHCO_3$ (4.0 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 5.0 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, cyclohexane–EtOAc) to afford the desired product as a mixture of regioisomers.

6

IR (ATR): 2934w, 1694s, 1581m, 1514m, 1424s, 1337s, 1257m, 1242m, 1213m, 1185m, 1107s, 1085m, 1042m, 976m, 935m, 914m, 886w, 822w, 771m, 742s, 698s, 677w, 605m cm^{-1}.

^1H NMR (400.1 MHz, $CDCl_3$): δ = 9.18 (s, 0.45 H, CH_{arom}, rotamer), 9.13 (s, 0.55 H, CH_{arom}, rotamer), 8.39 (s, 0.45 H, CH_{arom}, rotamer), 8.05 (s, 0.55 H, CH_{arom}, rotamer), 7.30 (m, 4 H, CH_{arom}, Bn), 7.21 (m, 1 H, CH_{arom}, Bn), 5.04 (br, 2 H, PhCH_2), 4.55 (s, 0.9 H, CH_2, rotamer), 4.50 (s, 1.1 H, CH_2, rotamer), 3.84 (br, 2 H, CH_2), 3.33 (m, 2 H, CH_2), 1.90 (m, 2 H, CH_2).

^{13}C {^1H} NMR (125.8 MHz, $CDCl_3$): δ = 169.6 (C_{arom}), 169.3 (C_{arom}), 156.4 (C=O), 156.1 (C=O), 144.0 (CH_{arom}), 143.9 (C_{arom}), 143.5 (C_{arom}) 137.4 (C_{arom}), 137.1 (C_{arom}), 135.9 (C_{arom}), 135.8 (C_{arom}), 132.7 (CH_{arom}) 132.2 (CH_{arom}), 129.9 (CH_{arom}), 129.8 (CH_{arom}), 129.7 (CH_{arom}), 129.6 (CH_{arom}), 129.5 (CH_{arom}), 129.2 (CH_{arom}), 69.7 (Ph*C*H_2), 69.4 (Ph*C*H_2), 53.1 (CH_2), 52.8 (CH_2), 52.6 (CH_2), 52.1 (CH_2), 40.6 (CH_2), 40.5 (CH_2), 29.03 (CH_2), 28.4 (CH_2).

LC/MS (MeCN–H_2O–TFA, 0.5 mL/min, 60 °C, 20 V): t_R = 6.55 min; *m*/*z* = 328.1 $[M + H]^+$, 350.1 $[M + Na]^+$.

10

IR (ATR): 3064w, 2962w, 1686s, 1596m, 1579m, 1512s, 1463w, 1454m, 1426s, 1346s, 1332s, 1282w, 1232s, 1181m, 1094s, 1038w, 988m, 947s, 915m, 806m, 766m, 746s, 696s, 600m, 563s cm^{-1}.

^1H NMR (400.1 MHz, $CDCl_3$): δ = 9.17 (s, 1 H, CH_{arom}), 8.26 (br, 1 H, CH_{arom}), 7.35 (m, 5 H, CH_{arom}), 5.18 (s, 2 H, PhCH_2), 3.73 (br, 4 H, CH_2), 3.32 (br, 2 H, CH_2), 3.06 (br, 2 H, CH_2).

^{13}C {^1H} NMR (125.8 MHz, $CDCl_3$): δ = 166.8 (C_{arom}), 155.5 (C=O), 143.0 (C_{arom}), 141.5 (CH_{arom}), 137.6 (C_{arom}), 136.3 (C_{arom}), 132.4 (CH_{arom}), 128.6 (CH_{arom}), 128.3 (CH_{arom}), 129.1 (CH_{arom}), 67.8 (Ph*C*H_2), 45.9 (CH_2), 44.5 (CH_2), 40.2 (CH_2), 35.6 (CH_2).

LC/MS (MeCN–H_2O–TFA, 0.5 mL/min, 60 °C, 20 V): t_R = 6.68 min; *m*/*z* = 328.1 $[M + H]^+$, 350.1 $[M + Na]^+$.

6-Benzoyl-3-nitro-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine (7)

^1H NMR (400.1 MHz, CD_3OD): δ = 9.18 (s, 1 H, CH_{arom}), 8.61 (s, 1 H, CH_{arom}), 7.49–7.40 (m, 3 H, CH_{arom}), 7.34 (m, 2 H, CH_{arom}), 4.91 (s, 1.4 H, CH_2, rotamer), 4.66 (s, 0.6 H, CH_2, rotamer), 4.10 (br, 0.6 H, CH_2, rotamer), 3.84 (br, 1.4 H, CH_2, rotamer), 3.42 (m, 2 H, CH_2), 2.01 (br, 0.6 H, CH_2, rotamer), 1.85 (br, 1.4 H, CH_2, rotamer).

^{13}C {^1H} NMR (125.8 MHz, CD_3OD): δ = 173.4 (C=O), 169.7 (C_{arom}), 144.4 (C_{arom}), 143.7 (CH_{arom}), 137.2 (C_{arom}), 136.7 (C_{arom}), 133.4 (CH_{arom}), 131.1 (CH_{arom}), 129.9 (CH_{arom}), 127.6 (CH_{arom}), 54.4 (CH_2), 49.7 (CH_2), 38.3 (CH_2), 28.6 (CH_2).

LC/MS (MeCN–H_2O–TFA, 0.5 mL/min, 60 °C, 20 V): t_R = 5.30 min; *m*/*z* = 298.1 $[M + H]^+$.

7-Benzoyl-3-nitro-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*d*]azepine (11)

^1H NMR (400.1 MHz, CD_3OD): δ = 9.15 (s, 1 H, CH_{arom}), 8.48 (s, 0.5 H, CH_{arom}, rotamer), 8.38 (s, 0.5 H, CH_{arom}, rotamer), 7.49–7.40 (m, 5 H, CH_{arom}), 3.97 (m, 2 H, CH_2), 3.67 (br, 2 H, CH_2), 3.64 (br, 1 H, CH_2), 3.27 (br, 2 H, CH_2), 3.27 (br, 1 H, CH_2).

LC/MS (MeCN–H_2O–TFA, 0.5 mL/min, 60 °C, 20 V): t_R = 5.30 min; *m*/*z* = 298.1 $[M + H]^+$.

6-Benzyl-3-nitro-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine (8)

^1H NMR (400.1 MHz, $CDCl_3$): δ = 9.18 (s, 1 H, CH_{arom}), 7.95 (s, 1 H, CH_{arom}), 7.33–7.22 (m, 5 H, CH_{arom}), 3.89 (s, 2 H, CH_2), 3.59 (s, 2 H, PhCH_2), 3.30 (m, 2 H, CH_2), 3.16 (m, 2 H, CH_2), 1.86 (m, 2 H, CH_2).

^{13}C {^1H} NMR (125.8 MHz, $CDCl_3$): δ = 169.9 (C_{arom}), 142.6 (CH_{arom}), 138.2, (C_{arom}), 137.9 (C_{arom}), 131.3 (CH_{arom}), 128.9 (CH_{arom}), 128.7 (CH_{arom}), 128.5 (CH_{arom}), 128.4 (CH_{arom}), 127.3 (CH_{arom}), 59.0 (Ph*C*H_2), 58.7 (CH_2), 57.2 (CH_2), 39.9 (CH_2), 23.6 (CH_2).

LC/MS (MeCN–H_2O–HCO_2H, 0.6 mL/min, 70 °C, 20 V): t_R = 1.46 min; *m*/*z* = 284.2 $[M + H]^+$.

7-Benzyl-3-nitro-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*d*]azepine (12)

^1H NMR (400.1 MHz, $CDCl_3$): δ = 9.14 (s, 1 H, CH_{arom}), 8.16 (s, 1 H, CH_{arom}), 7.33–7.22 (m, 5 H, CH_{arom}), 3.66 (s, 2 H, PhCH_2), 3.30 (m, 2 H, CH_2), 3.01 (m, 2 H, CH_2), 2.70 (m, 4 H, CH_2).

^{13}C {^1H} NMR (125.8 MHz, $CDCl_3$): δ = 169.0 (C_{arom}), 141.9 (CH_{arom}), 137.8 (C_{arom}), 130.7 (CH_{arom}), 128.9 (CH_{arom}), 128.7 (CH_{arom}), 128.5 (CH_{arom}), 128.4 (CH_{arom}), 127.5 (CH_{arom}), 63.4 (Ph*C*H_2), 54.3 (CH_2), 53.0 (CH_2), 38.9 (CH_2), 35.0 (CH_2).

LC/MS (MeCN–H_2O–HCO_2H, 0.6 mL/min, 70 °C, 20 V): t_R = 1.86 min; *m*/*z* = 284.2 $[M + H]^+$.

6-Methyl-3-nitro-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine (9)

^1H NMR (400.1 MHz, $CDCl_3$): δ = 9.15 (s, 1 H, CH_{arom}), 9.19 (s, 1 H, CH_{arom}), 3.86 (s, 2 H, CH_2), 3.24 (m, 2 H, CH_2), 3.05 (m, 2 H, CH_2), 2.37 (s, 3 H, CH_3), 1.86 (m, 2 H, CH_2).

^{13}C {^1H} NMR (125.8 MHz, $CDCl_3$): δ = 169.7 (C_{arom}), 142.7 (CH_{arom}), 142.7 (C_{arom}), 135.5 (C_{arom}), 131.3 (CH_{arom}), 60.9 (CH_2), 60.3 (CH_2), 44.1 (CH_3), 38.7 (CH_2), 23.8 (CH_2).

LC/MS (MeCN–H_2O–HCO_2H, 0.6 mL/min, 70 °C, 20 V): t_R = 0.27 min; *m*/*z* = 208.1 $[M + H]^+$.

7-Methyl-3-nitro-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*d*]azepine (13)

^1H NMR (400.1 MHz, $CDCl_3$): δ = 9.13 (s, 1 H, CH_{arom}), 8.16 (s, 1 H, CH_{arom}), 3.29 (m, 2 H, CH_2), 3.02 (m, 2 H, CH_2), 2.64 (m, 4 H, CH_2), 2.41 (s, 3 H, CH_3).

^{13}C {^1H} NMR (125.8 MHz, $CDCl_3$): δ = 168.8 (C_{arom}), 142.9 (C_{arom}), 142.0 (CH_{arom}), 137.7 (C_{arom}), 130.7 (CH_{arom}), 56.4 (CH_2), 55.0 (CH_2), 47.4 (CH_3), 39.7 (CH_2), 34.9 (CH_2).

LC/MS (MeCN–H_2O–HCO_2H, 0.6 mL/min, 70 °C, 20 V): t_R = 0.28 min; *m*/*z* = 208.1 $[M + H]^+$.

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