Res Chem Intermed (2010) 36:253–258
DOI 10.1007/s11164-010-0135-4

A rapid synthetic method of pyridobenzodiazepines

Fuqiang Shi · Xu Bai · Qun Dang · Long Zhang

Received: 20 November 2009 / Accepted: 27 January 2010 / Published online: 12 March 2010

Abstract A new one-pot Bischler–Napeiralski type cyclization reaction between pyridine-1,2-diamines and various carboxylic acids with PPA as catalyst to prepare pyridobenzodiazepines is proposed. In the new synthetic route, the reaction time is only one-third of the methods reported. The synthetic strategy provides an efficient way to prepare novel structurally diversified heterocyclic compounds of pyridobenzodiazepine family with potential pharmaceutical or biological activities.

Keywords Pyridobenzodiazepines · Cyclization · PPA · Catalyst · Bischler–Napeiralski reaction

Heterocyclic compounds are always considered privileged structures in medicinal chemistry due to their various biological effects. Pyridobenzodizepine derivatives, as the prototypical privileged substructures, possess high biological and pharmacological activities [1]. For example, 5,11-dihydro-benzo[*e*]pyrido[2,3-*b*][1,4]diazepin-6-ones has diverse therapeutic activities including inhibition of HIV-1 reverse transcriptase and muscarinic receptor inhibition. Pirenzepine (**1**, Fig. 1), prototypical the M_1 selective muscarinic antagonist, is currently marketed as an antiulcer drug providing safe and unproblematic treatment of duodenal ulcers and gastritis for

F. Shi (✉) · L. Zhang (✉)
Jilin Provincial Engineering Laboratory for the Complex Utilization of Petroresource and Biomass, 2055 Yanan St., Changchun, 130012 Jilin, People's Republic of China
e-mail: shifq@yahoo.com.cn

L. Zhang
e-mail: zhanglongzhl@163.com

X. Bai · Q. Dang
The Center for Combinatorial Chemistry and Drug Discovery, Jilin University, 75 Haiwai St., Changchun, 130012 Jilin, People's Republic of China

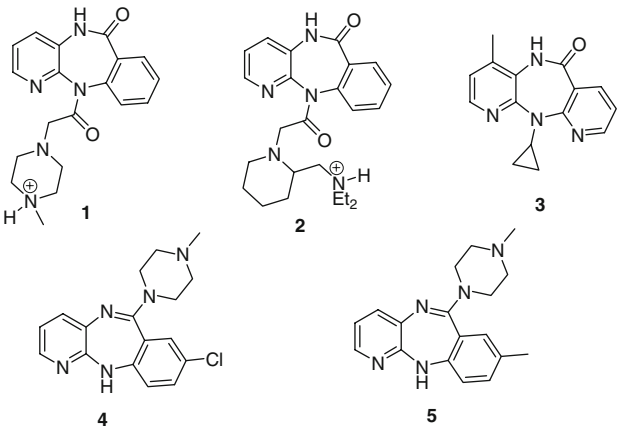
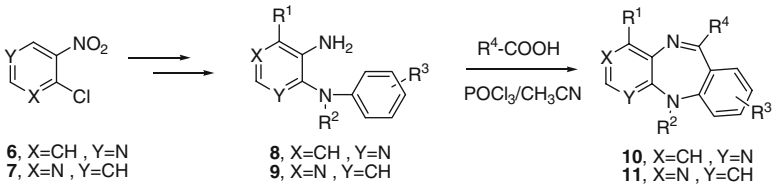


Fig. 1 Some pyridobenzodizepine derivatives with biological and pharmacological activities

many years; AF-DX 116 (**2**) is the inhibitor of cardio (M_2) selective muscarinic receptor, which shows in vitro a 10-fold higher affinity for receptors of heart than for those of the cortex (M_1); [2–4] Nevirapine (**3**), the first non-nucleoside inhibitors of HIV-1 RT, is employed in the treatment of AIDS and AIDS-related complex (ARC) [5–9]. Moreover, as clozapine-like analogs, 8-chloro-6-(4′-methyl-l-piperazinyl)-11*H*-pyrido[2,3-*b*] [1,4] benzodiazepine (**4**) and 8-methyl-6-(4′-methyl-1-piperaziny1)-11*H*-pyrido[2,3-*b*][1,4] benzodiazepine (**5**) showed the behavioral features for neuroleptics [10, 11]. Pyridobenzodizepine derivatives have been extensively studied as potential agents to modulate activities of the central nervous system and vasopressin V_2 receptor [12, 13].

Recently, we reported the synthesis of C6-aryl and alkyl substituted pyridobenzodiazepines, which relied on Bischler–Napeiralski-type cyclization reactions as the key transformation step, and the reaction conditions of four equivalents of $POCl_3$ in refluxing acetonitrile were identified for the conversion of pyridines **8** (or **9**) to pyridobenzodiazepines **10** (or **11**), However, this method requires a long reaction time [14]. The reaction scheme (1) is shown below.

Here, we report a more effective method of ready access to pyridobenzodiazepines with various carbon-derived substituents at the 6-position of the central heterocycle core.



Scheme 1 Efficient alternative route to pyridobenzodiazepine

Experimental section

General considerations

All commercial reagents were used as received without additional purification. Melting points were uncorrected. Mass spectra and HPLC (ELSD) data were recorded on an Agilent 1100 LC/MS-ELSD (Altech) system using a 4.6 × 50 mm column (5 μm) with a linear gradient of 30–90% (v/v) acetonitrile–water with 0.035% trifluoroacetic acid (TFA) over 5 min with a flow rate of 3.5 mL/min. Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25-mm thickness of silica gel GF_{254}. Column chromatography was performed using silica gel G (200–300 mesh). All ^{1}H NMR spectra (300 or 500 MHz) are reported as follows: chemical shifts in ppm downfield from TMS as internal standard (δ scale) and $CDCl_3$ as the solvent. Multiplicities are indicated as the following: multiplicity [br = broad, *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, and coupling constant (Hz)]. All ^{13}C NMR spectra (75 or 125 MHz) were determined with complete proton decoupling and reported in ppm.

New synthetic route of pyridobenzodiazepine (**10**)

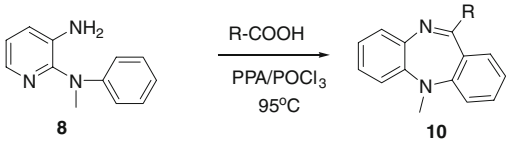
The synthetic scheme (2) of pyridobenzodiazepine (**10**) proposed is shown below.

In the new synthetic route, PPA is exployed as the catalyst to speed the reaction. The preparation of 2-substituted pyridines **8** which is starting material for the proposed synthetic route to pyridobenzodiazepines, is prepared from 2-chloro-3-nitropyridine (**6**) as depicted in [14].

PPA (0.75 mmol, 254 mg), precursors **8** (0.5 mmol) and acid (0.75 mmol) were dissolved in $POCl_3$ (5 mL). After heated at 95 °C in an oil bath for due time, the mixture was poured into ice-water (20 mL) and treated with 5 N aqueous NaOH to pH 9–10, then extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with saturated $NaHCO_3$ and brine, dried with anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography with petroleum ether/EtOAc (10:1, v/v) as eluent to afford products **10**. Various pyridobenzodiazepines prepared are shown below.

11-Methyl-6-phenylpyrido[2,3-*b*][1,4]benzodiazepine (**10a**). Yellow solid, yield: 88%, mp 109.0–110.7 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09 (d, J = 3.0 Hz, 1H), 7.77 (d, J = 7.2 Hz, 2H), 7.57 (d, J = 7.2 Hz, 1H), 7.42–7.47 (m, 4H), 7.15 (d, J = 8.1 Hz, 1H), 7.01–7.06 (m, 3H), 3.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 156.0, 155.0, 144.5, 140.2, 137.0, 135.1, 131.8, 131.0, 130.3, 129.5, 128.6, 127.9, 122.6, 119.6, 118.4, 35.5. ES-MS: 286.1 [$(M + H^+)$].

Scheme 2 The synthetic scheme of pyridobenzodiazepine



11-Methyl-6-(4′-methoxyphenyl)pyrido[2,3-*b*][1,4]benzodiazepine (**10b**). Yellow solid, yield: 92%, mp 152.0–154.3 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (dd, $J = 4.8$ Hz, 1.8 Hz, 1H), 7.72–7.77 (m, 2H), 7.54 (dd, $J = 7.5$ Hz, 1.8 Hz, 1H), 7.44 (td, $J = 7.2$ Hz, 1.8 Hz, 1H), 7.10–7.16 (m, 2H), 6.99–7.04 (m, 2H), 6.90–6.95 (m, 2H), 3.87 (s, 3H), 3.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1, 161.6, 156.0, 155.1, 144.2, 137.3, 134.9, 132.8, 131.8, 131.3, 131.1, 128.6, 122.6, 119.7, 118.4, 113.3, 55.3, 35.5. ES-MS: 316.1 [$(M + H^+)$].

11-Methyl-6-(3′-methyl-phenyl)pyrido[2,3-*b*][1,4]benzodiazepine (**10c**). Yellow solid, yield: 96%, mp 110.7–111.4 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (dd, $J = 4.8$ Hz, 1.8 Hz, 1H), 7.63 (s, 1H), 7.59 (dd, $J = 7.8$ Hz, 1.8 Hz, 1H), 7.42–7.51 (m, 2H), 7.29–7.33 (m, 2H), 7.15 (d, $J = 8.1$ Hz, 1H), 6.99–7.09 (m, 3H), 3.37 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.0, 156.0, 155.1, 144.5, 140.4, 137.7, 137.1, 135.2, 131.9, 131.1, 130.0, 128.8, 127.9, 127.0, 122.7, 119.7, 118.4, 35.6, 21.4. ES-MS: 300.1 [$(M + H^+)$].

11-Methyl-6-(4′-methyl-phenyl)pyrido[2,3-*b*][1,4]benzodiazepine (**10d**). Yellow solid, yield: 86%, mp 170.5–171.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (dd, $J = 4.8$ Hz, 1.8 Hz, 1H), 7.66 (d, $J = 8.1$ Hz, 2H), 7.55 (dd, $J = 7.5$ Hz, 1.8 Hz, 1H), 7.44 (td, $J = 8.1$ Hz, 1.8 Hz, 1H), 7.22 (d, $J = 8.1$ Hz, 2H), 7.14 (d, $J = 8.1$ Hz, 1H), 7.08 (dd, $J = 7.5$ Hz, 1.5 Hz, 1H), 6.98–7.03 (m, 2H), 3.34 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, 155.8, 155.0, 143.9, 141.6, 136.5, 136.4, 135.9, 132.6, 131.8, 130.0, 128.9, 128.2, 123.1, 119.8, 118.9, 35.9, 21.5. ES-MS: 300.0 [$(M + H^+)$].

11-Methyl-6-(2′-methyl-phenyl)pyrido[2,3-*b*][1,4]benzodiazepine (**10e**). Yellow solid, yield: 91%, mp 138.8–141.2 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.12 (dd, $J = 4.8$ Hz, 1.8 Hz, 1H), 7.57 (dd, $J = 7.8$ Hz, 1.8 Hz, 1H), 7.51 (dd, $J = 7.5$ Hz, 1.8 Hz, 1H), 7.35–7.42 (m, 1H), 7.28–7.33 (m, 2H), 7.19–7.22 (m, 1H), 7.09 (d, $J = 7.8$ Hz, 1H), 7.00–7.04 (m, 1H), 6.91 (td, $J = 7.5$ Hz, 0.9 Hz, 1H), 6.82 (dd, $J = 7.8$ Hz, 1.8 Hz, 1H), 3.38 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.8, 155.1, 155.0, 145.0, 141.3, 136.9, 136.2, 135.6, 132.0, 130.6, 130.3, 129.3, 129.1, 125.7, 123.1, 119.7, 118.2, 35.8, 19.8. ES-MS: 300.1 [$(M + H^+)$].

11-Methyl-6-(4′-nitrophenyl)pyrido[2,3-*b*][1,4]benzodiazepine (**10f**). Yellow solid, yield: 40%, mp 195.0–195.4 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.27 (d, $J = 9.0$ Hz, 2H), 8.15 (dd, $J = 4.8$ Hz, 1.8 Hz, 1H), 7.96 (d, $J = 8.7$ Hz, 2H), 7.60 (dd, $J = 7.5$ Hz, 1.5 Hz, 1H), 7.49 (td, $J = 7.5$ Hz, 1.5 Hz, 1H), 7.17 (d, $J = 8.1$ Hz, 1H), 7.02–7.08 (m, 2H), 6.96 (dd, $J = 7.8$ Hz, 1.5 Hz, 1H), 3.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.6, 156.4, 154.8, 148.8, 146.1, 145.6, 136.6, 135.8, 132.5, 130.5, 127.8, 123.2, 123.1, 119.9, 119.0, 35.7. ES-MS: 331.0 [$(M + H^+)$].

11-Methyl-6-(4′-fluorophenyl)pyrido[2,3-*b*][1,4]benzodiazepine (**10g**). Yellow solid, yield: 75%, mp 155.0–155.8 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (dd, $J = 4.8$ Hz, 1.8 Hz, 1H), 7.78 (dd, $J = 8.7$ Hz, 5.4 Hz, 2H), 7.55 (dd, $J = 7.8$ Hz, 1.5 Hz, 1H), 7.43 (t, $J = 6.6$ Hz,), 7.00–7.17 (m, 6H), 3.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.6, 164.3 (d, $J = 249.53$ Hz), 156.1, 155.1, 144.7, 137.0, 136.5, 135.2, 132.1 (d, $J = 24.08$ Hz), 131.7 (d, $J = 9.15$ Hz), 131.0, 128.4, 122.8, 119.8, 118.6, 115.1 (d, $J = 21.75$ Hz), 35.6. ES-MS: 304.0 [$(M + H^+)$].

6,11-Dimethylpyrido[4,5-*b*][1,4]benzodiazepine (**10h**). Yellow solid, yield: 72%, mp 119.3–119.7 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, $J = 3.6$ Hz, 1H),

7.32–7.42 (m, 3H), 6.95–7.08 (m, 3H), 3.30 (s, 3H), 2.59 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.4, 155.2, 154.6, 144.3, 136.7, 134.6, 131.6, 130.4, 128.2, 123.0, 119.6, 118.1, 35.6, 28.0. ES-MS: 224.2 [(M + H^+)].

11-Methyl-6-(pyridin-3′-yl)pyrido[2,3-*b*][1,4]benzodiazepine (**10i**). Yellow solid, yield: 84%, mp 119.2–120.8 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.95 (s, 1H), 8.70 (d, J = 3.9 Hz, 1H), 8.12 (d, J = 6.3 Hz, 2H), 7.57 (dd, J = 7.8 Hz, 1.5 Hz, 1H), 7.47 (dd, J = 8.4 Hz, 4.5 Hz, 1H), 7.37 (dd, J = 8.1 Hz, 4.8 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.03–7.07 (m, 3H), 3.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.4, 155.3, 154.1, 145.0, 149.7, 144.2, 135.9, 135.9, 135.0, 134.5, 131.5, 129.7, 126.9, 122.1, 118.9, 117.9, 34.7, 28.7. ES-MS: 287.1 [(M + H^+)].

11-Methyl-6-(thiophen-3′-yl)pyrido[4,5-*b*][1,4]benzodiazepine (**10j**). Yellow solid, yield: 58%, mp 154.2–155.4 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.08 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 7.66 (dd, J = 5.5 Hz, 1.5 Hz, 1H), 7.60 (dd, J = 3.0 Hz, 1.0 Hz, 1H), 7.53 (dd, J = 7.5 Hz, 1.5 Hz, 1H), 7.45 (td, J = 7.0 Hz, 1.5 Hz, 1H), 7.35 (dd, J = 5.5 Hz, 3.5 Hz, 1H), 7.31 (dd, J = 7.5 Hz, 1.5 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H,), 7.06 (td, J = 7.0 Hz, 1.0 Hz, 1H), 7.01 (dd, J = 8.0 Hz, 5.0 Hz, 1H), 3.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.9, 156.2, 155.3, 144.6, 143.5, 137.5, 135.4, 132.2, 130.8, 130.0, 129.1, 128.7, 125.8, 123.0, 120.1, 118.8, 35.8. ES-MS: 292.0 [(M + H^+)].

11-Methyl-6-(furan-2′-yl)pyrido[2,3-*b*][1,4]benzodiazepine (**10k**). Yellow solid, yield: 53%, mp 191.4–193.3 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09 (d, J = 3.6 Hz, 1H), 7.67 (s, 1H), 7.62 (d, J = 6.6 Hz, 1H), 7.41–7.49 (m, 2H), 7.07–7.16 (m, 2H), 7.02 (dd, J = 7.8 Hz, 5.1 Hz, 1H), 6.77 (d, J = 3.3 Hz, 1H), 6.54 (d, J = 1.5 Hz, 1H), 3.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.9, 156.2, 154.9, 152.8, 145.7, 144.6, 137.0, 135.4, 132.2, 130.1, 127.1, 122.9, 119.9, 118.5, 117.3, 111.9, 35.5. ES-MS: 276.1 [(M + H^+)].

Results and discussions

To test the universality of the new preparation method under this condition, a small pyridobenzodiazepine library was prepared by reaction of 11 carboxylic acids with pyridine **8** and the results are summarized in Table 1. In general, various carboxylic acids such as aromatic, aliphatic, and heterocyclic acids reacted well with precursors **8** to give 6,11-disubstituted pyridobenzodiazepines **10a**–**10k** in moderate to high yields. The outcome and rule of reaction are similar under the existence of $POCl_3$ and acetonitrile, but the reaction time is only one-third of the previous procedure. Especially, 2*H*-pyrrole-3-carboxylic acid and furan-2-carboxylic acid do not perform by previous procedure, while giving higher yields by employing the new route.

Conclusion

A rapid route to synthesize pyridobenzodizepines in one-pot Bischler–Napeiralski-type cyclization reaction between pyridine-1,2-diamines and various carboxylic

Table 1 The comparison of preparation conditions of the proposed route with that in [14]

Entry	Pdt	R	Reference [14]		New route	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	**10a**	Ph	30	91	12	88
2	**10b**	*p*-MeO–C_6H_4	33	96	12	92
3	**10c**	*m*-Me–C_6H_4	26	90	12	96
4	**10d**	*p*-Me–C_6H_4	28	82	12	86
5	**10e**	*o*-Me–C_6H_4	85	93	12	91
6	**10f**	*p*-NO_2–C_6H_4	85	74	40	40
7	**10g**	*p*-F–C_6H_4	36	63	12	75
8	**10h**	CH_3	7	72	2.5	72
9	**10i**	Pyridin-3-yl	–	–	84	84
10	**10j**	Thiophen-3-yl	24	62	10	58
11	**10k**	Furan-2-yl	–	–	14	53

acids was developed. The current strategy provides new methodologies to enable the exploration of biological activities for this class of heterocycles.

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