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Synthesis of pyrrolidine-substituted benzamides via iodocyclization of β-enaminoesters

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Abstract—Novel 2-, and N-substituted 5-methylene-pyrrolidine benzamides and 2-, 3-, and N-substituted 5-methylene-2-pyrroline benzamides were synthesized for the first time in a straightforward manner and in good yields via iodocyclization of γ- and α-alkenyl-β-enaminoesters, respectively. The key step in the process is the synthesis of the methylene-pyrrolidine iodide and methylene-2-pyrroline iodide intermediates. Functional group inter-conversion of these iodides to their amino analogs, and their subsequent coupling to benzoic acids via EDC, afforded the above pyrrolidine/2-pyrroline-substituted benzamides in yields of around 75%.

Heterocyclic benzamides represent an important class of therapeutic compounds with several agents showing activity in the central nervous system as antipsychotics, and as antiemetics and gastric motility stimulants.[1] The actions of these agents are primarily due to the blockade of dopamine (D_2) and/or serotonin (i.e., 5-HT_3) receptors. Structure–affinity relationship studies (SAFIR) of methylene-pyrrolidine benzamides were considered in order to address what role the heterocyclic substituents might play regarding their binding to D_2 and 5-HT_3 receptors. That is, although these benzamides have been shown to be therapeutically effective, the role of substituents at the pyrrolidine N-, 2-, and 3-positions (i.e., the equivalent N-, 4-, and 5-positions relative to the parent unsubstituted compound) has not been systematically investigated because an useful synthetic route to such analogs has not yet been developed. The purpose of this study was to identify a convenient method that would allow an entry to compounds bearing such substituents. To this end, we applied the method of iodocyclization of α- and γ-alkenyl-β-enaminoesters to the synthesis of the 2-pyrrolines and pyrrolidines substituted at positions C2, C3, and at the nitrogen atom.[2] This synthetic methodology was previously explored[2] and is presented here as an application to the synthesis of relevant, potentially biologically active benzamides currently under pharmacologic investigation (Fig. 1).

The synthesis of benzamides **1** and **2** started with the preparation of β-ketoesters **5** and **6** via appropriate alkylation of methyl acetoacetate enolates with allyl bromide. These enolates were generated in situ by treatment of the ester with NaH and/or *n*-BuLi in solution of THF (Scheme 1). The detailed procedures used for the synthesis of **5** and **6** are, respectively, noted by Refs. 4a and 4c. From the variety of methods available to prepare β-enaminoesters **3** and **4**,[3] we chose the condensation of ethylamine with β-ketoester **5** in a solution of toluene with azeotropic removal of water[4b] and the condensation of benzylamine to β-ketoester **6** in the presence of neutral Al_2O_3 at room temperature.[4d] Solvent removal followed by Kugelrohr distillation afforded the products **3** and **4** in good yields (Scheme 1). The iodocyclization of these β-enaminoesters is the key step for the synthesis of the desired benzamides. This reaction was performed under kinetically controlled conditions that afforded the substituted-pyrrolidine **7** and 2-pyrroline **8** derivatives under mild conditions and in good yields (Scheme 1). The mechanism proposed for this reaction is the attack of the nitrogen (internal nucleophile) to an iodonium ion intermediate (e.g., **9**) in an

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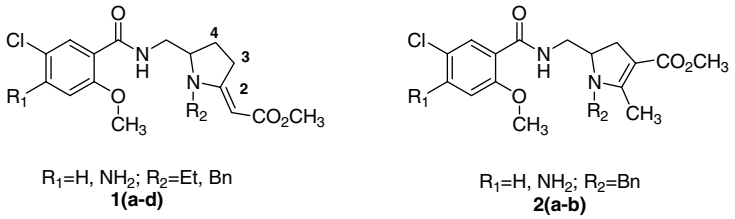
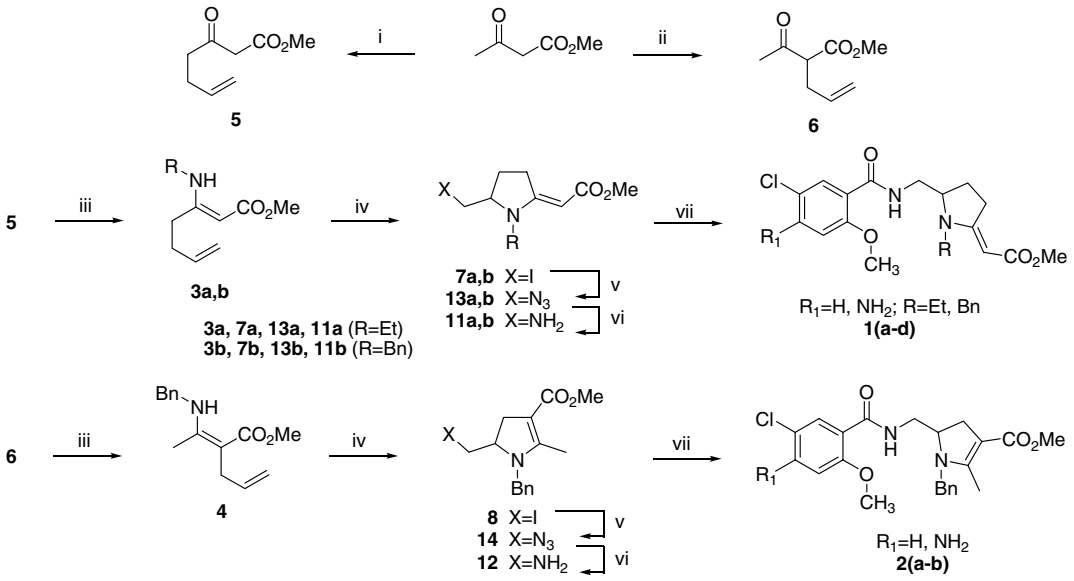


Figure 1. Novel pyrrolidine- and 2-pyrroline-substituted benzamides synthesized via iodocyclization of β-enaminoesters and selected for SAFIR at D_2 and 5-HT_3 receptors.



Scheme 1. Reagents and conditions: (i) NaH, THF, 0 °C, N_2, 10 min, then *n*-BuLi, 10 min, allylbromide, 15 min, 0 °C to rt, then HCl, 74%;[4a] (ii) NaH, THF, 0 °C, N_2, then allylbromide, 0 °C to rt, 24 h, 49%;[4c] (iii) 70% $EtNH_2$, AcOH, toluene, reflux, Dean–Stark, 18 h, 95% or $BnNH_2$, Al_2O_3 neutral, rt, 12 h, 96–98%;[16] (iv) I_2, $NaHCO_3$, CH_2Cl_2, rt, 24 h, 49–53%;[15] (v) NaN_3, $(Et)_4NBr$, DMF, reflux, 4 h, 52–64%;[14] (vi) H_2 Parr hydrogenator, 50 psi, Lindlar®, rt, EtOH abs., 2–4 days, 70–90%;[13] (vii) 5-chloro-2-methoxybenzoic acid (**15**) or 4-amino-5-chloro-2-methoxybenzoic acid (**16**), EDC, CH_2Cl_2, rt, 6 h, 74–76%.[12]

antiperiplanar orientation[5] (Fig. 2). Alternatively, an alkene-iodine π-complex has also been proposed for this type of reaction.[6] The ring-closure process follows classical Baldwin's rule and occurs in a 5-*exo*-trig manner.[7] In order for α-allyl-β-enaminoesters **4** to achieve the proper geometry for nitrogen attack for ring formation, the tautomeric imine-enamine equilibrium might be shifted to a less stable enamine tautomer **4a**. This is not required for the cyclization of γ-allyl-β-enaminoesters **3** due to the high flexibility of the iodine-acceptor carbon chain bearing the double bond. In situ deprotonation of putative intermediate (e.g., **10**) by $NaHCO_3$ affords heterocyclic iodides **7** and **8** (Fig. 2).

The functional group inter-conversion of intermediate iodides **7** and **8** to amines **11** and **12**, respectively, was achieved by nucleophilic displacement of the iodine atom by an azide anion with further selective reduction of compounds **13** and **14** (Scheme 1). Azide formation was performed in a solid–liquid phase transfer catalysis fashion.[8] The iodide substrates were mixed with NaN_3 and $(Et)_4NBr$ in anhydrous DMF[17] and allowed to stir for 4 h at reflux. Under these conditions, no product of dehydrohalogenation was detected which would have led to double bond migration and formation of the aromatic pyrrole derivatives, which is observed with reagents of strong basicity but weak nucleophilicity (i.e., DBU,[17] phenoxide anion).[2,9] The isolated azides were then subjected to hydrogenation in the presence of Lindlar® catalyst in EtOH as solvent[10] to give the amines in a fairly good yield (Scheme 1).

Finally, representative benzamides **1** and **2** were synthesized in good yields by coupling amines **11** and **12** with benzoic acids **15** and **16**, respectively, in the presence of EDC[17] at room temperature in CH_2Cl_2 (Scheme 1, Table 1).

In conclusion, we have provided for the first time, a synthetic application of iodocyclization of β-enaminoesters to the synthesis of potentially interesting N-, C2-, and/or C3-substituted 5-methylene-pyrrolidine and 5-methylene-2-pyrroline benzamides. Though not stereoselective, the method proved to be robust by affording the key, highly functionalized iodide intermediates in three synthetic steps. Also, their functional group inter-conversion to amines and subsequent coupling with the benzoic acids via EDC was achieved in a straightforward manner and in good yields. Although the scope of the reaction remains to be fully explored, it provides

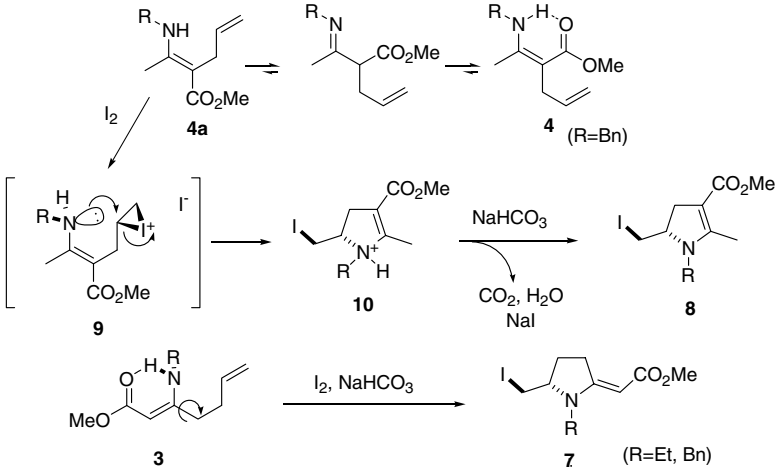
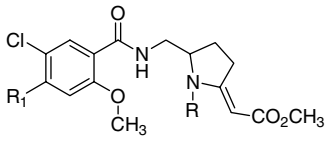
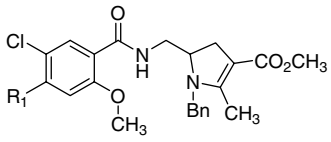


Figure 2. Proposed mechanism for the iodocyclization of β-enaminoesters.

Table 1. Novel representative pyrrolidine- and 2-pyrroline-substituted benzamides synthesized via iodocyclization of β-enaminoesters[a]

Compound		R_1	R	Yield[b] (%)	Mp[c] (°C)
	**1a**	H	Et	74	105–106
	1b	NH_2	Et	75	159–160
	1c	H	Bn	76	120–121
	1d	NH_2	Bn	75	146–148
	**2a**	H	—	75	136–137
	2b	NH_2	—	74	145–146

[a] See Refs. 11 and 12.
[b] Isolated yield for the last synthetic step after SiO_2 flash chromatography.
[c] Determined in a Thomas–Hoover apparatus. Uncorrected.

entry to analogs that have not been previously readily available for pharmacological evaluation.

Acknowledgment

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra (300 MHz and 75 MHz, respectively) for compounds **1a**–**d** and **2a**,**b** in $CDCl_3$) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.166.

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11. *Data for compound* **1a**: Yield 74%. Mp 105–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, $J = 6.96$ Hz, 3H), 1.78–1.86 (m, 1H), 2.11–2.21 (m, 1H), 3.10–3.42 (m, 5H), 3.64 (s, 3H), 3.88–3.97 (m, 2H), 3.91 (s, 3H), 4.64 (s, 1H); 6.92 (d, $J = 8.8$ Hz, 1H), 7.41 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.9$ Hz, 1H), 7.91 (br s, 1H), 8.17 (d, $J = 2.94$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.4, 24.8, 31.2, 39.1, 41.3, 50.1, 56.3, 62.1, 78.1, 112.9, 122.2, 126.8, 131.9, 132.6, 155.9, 164.5, 164.9, 169.6.
12. *General procedure for the synthesis of benzamides* **1** *and* **2**: A mixture of benzoic acid (**15** or **16**) (10 mmol), amine **11** or **12** (10 mmol), and EDC (12 mmol) in CH_2Cl_2 (80 mL), was allowed to stir at rt for 24 h. The mixture was successively washed with H_2O (20 mL), 10% NaOH (10 mL), H_2O (20 mL), brine (20 mL), and dried (Na_2SO_4). The solvent was removed and the product purified by flash chromatography (CH_2Cl_2–MeOH 19:1). See Ref. 11 and Supplementary data for complete ^{1}H and ^{13}C NMR data. See Table 1 for yields and melting points.
13. *General procedure for the synthesis of amines* **11** *and* **12**: The azide (**13** or **14**) (6 mmol) was added to a proper flask for hydrogenation containing Lindlar® catalyst (372 mg) dispersed in absolute EtOH (100 mL). The mixture was shaken in a Parr hydrogenator for 2–4 days at rt and at 50 psi (reaction followed by TLC). The catalyst was removed by filtration through Celite® and the product was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give a light yellow oil. **11a** (R = Et): yield 88%; **11b** (R = Bn): yield 90%; **12**: yield 70%.
14. *General procedure for the synthesis of azides* **13** *and* **14**: A mixture of iodide (**7** or **8**) (6 mmol), NaN_3 (24 mmol), and $(Et)_4NBr$ (10% w/w over iodide) in DMF (120 mL) was stirred at reflux for 4 h. The mixture was poured into H_2O (100 mL), extracted with benzene (3×50 mL) and dried (Na_2SO_4). The solvent was removed and the product purified by flash chromatography (hexanes–AcOEt 4:1). **13a** (R = Et): yield 52%, brownish oil, R_f 0.25; **13b** (R = Bn): yield 64%, brownish oil, R_f 0.15; **14**: yield 61%, brownish oil, R_f 0.30. All R_f's in hexanes–AcOEt 4:1.
15. *General procedure for the synthesis of iodides* **7** *and* **8**: See Ref. 2. Compound **7a** (R = Et): yield 49% (rec. EtOH), beige solid, R_f 0.35; **7b** (R = Bn): yield 53% (rec. EtOH), beige solid, R_f 0.25; **8**: yield 53% (rec. EtOH), beige solid, R_f 0.41. All R_f's in hexanes–AcOEt 4:1.
16. *General procedure for the synthesis of* β*-enaminoesters*: **3** (See Ref. 4b and 4d); **4** (see Ref. 4d). Compound **3a** (R = Et): yield 95%, light yellow oil, R_f 0.60; **3b** (R = Bn): yield 98%, light yellow oil, R_f 0.53; **4**: yield 96%, light yellow oil, R_f 0.74. All R_f's in hexanes–AcOEt 4:1.
17. EDC: *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene; DMF: *N*,*N*-Dimethylformamide.