A Quick Synthesis of 1-Arylpyrrolopyrazinones from Linear Alkynylamide Derivatives

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Dedicated to Professor Josep Font on the occasion of his 70th birthday

Abstract: A rapid synthesis of pyrrolopyrazinone derivatives based on formal double addition across the triple bond of appropriately substituted substrates is presented. The key cyclization step features the formation, mediated by [bis(trifluoroacetoxy)iodo]benzene (PIFA), of a 5-aroylpyrrolidinone nucleus from appropriately functionalized N-protected *N*-(aminoethyl)amides. After removal of the protecting group, the free amino group is used to accomplish a second heterocyclization process onto the newly formed carbonyl group. By appropriate manipulation of these protecting groups and selection of reaction conditions, a series of pyrrolopyrazinones can be obtained in different stages of hydrogenation.

Key words: hypervalent iodine, alkynylamides, reductive aminations, pyrazinones, bicyclic compounds

The pharmacological and medical literature uses the term nootropic to refer to drugs that are used as memory enhancers. Since the first studies carried out with piracetam (**A**), and its hydroxylated analogue oxiracetam (**B**) (Figure 1), a number of structural modifications have been introduced to maximize the biological activity of this class of therapeutics and also to elucidate their mechanism of action.[1]

In addition to **A** and **B**, some of their derivatives, e.g. pramiracetam (**C**)[2] and nefiracetam (**D**),[3] have also been noted to be nootropic drugs (Figure 1). The vast majority of these derivatives are structurally characterized by a 2-pyrrolidinone nucleus substituted at the 1-position by an aminoethyl group and, in a few cases, this motif is conformationally constrained in a heterocycle fused to the pyrrolidinone skeleton. This is the case for both DM232 (unifiram, **E**), which has been reported to show cognition-enhancing properties with a potency four orders of magnitude greater than piracetam,[4] and dimiracetam (**F**), a pyrroloimidazole derivative 10–100 times more potent than piracetam (Figure 1).[5]

Recently, our group has discovered a straightforward cyclization of linear N-substituted alkynylamides to give 5-aroylpyrrolidinones, mediated by the hypervalent iodine reagent [bis(trifluoroacetoxy)iodo]benzene (PIFA) (Scheme 1). The extension of this preliminary study was very limited and only the behavior of substrates carrying

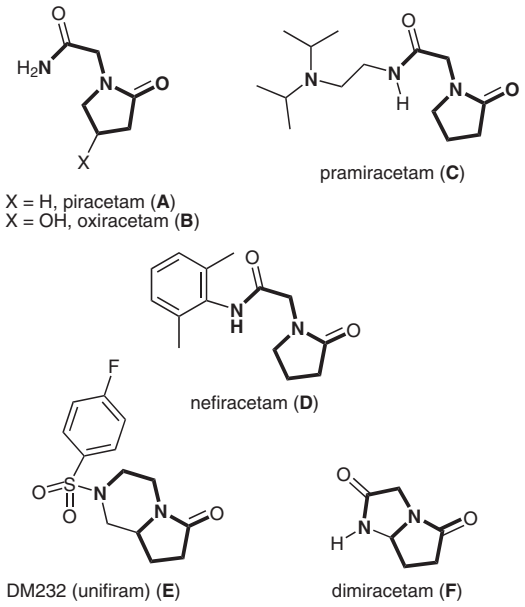
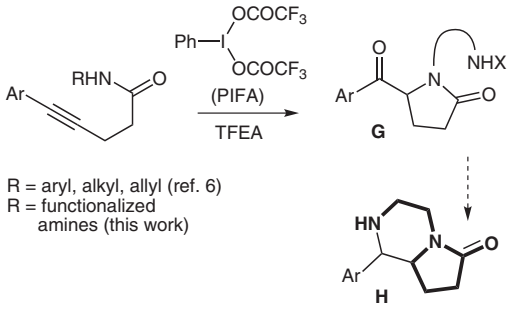


Figure 1 Selected representative and widely used examples of nootropic agents **A**–**F**

simple alkyl, aryl, and allyl groups as the amide substituents was tested.[6] Following on this, as the next stage of our research, we wished to evaluate the actual potential of this methodology by studying the behavior of more complex alkynylamides that include an additional amine group specifically located on the amide fragment of the substrate.



Scheme 1 Synthetic design for the preparation of pyrazinones of type **H**

Therefore, our synthetic design was conceived to allow a second intramolecular cyclization between the residual

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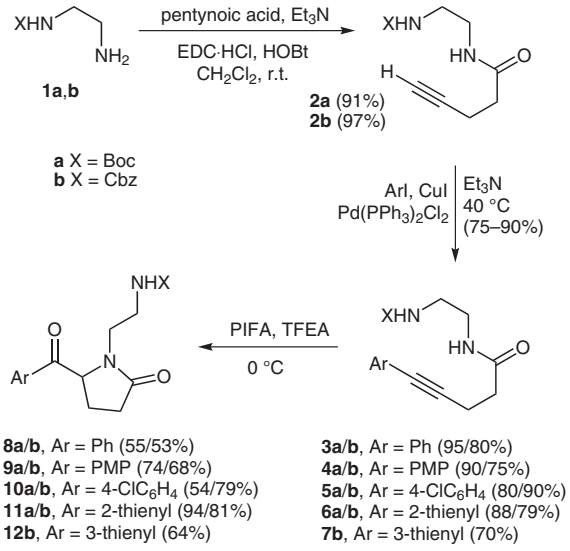
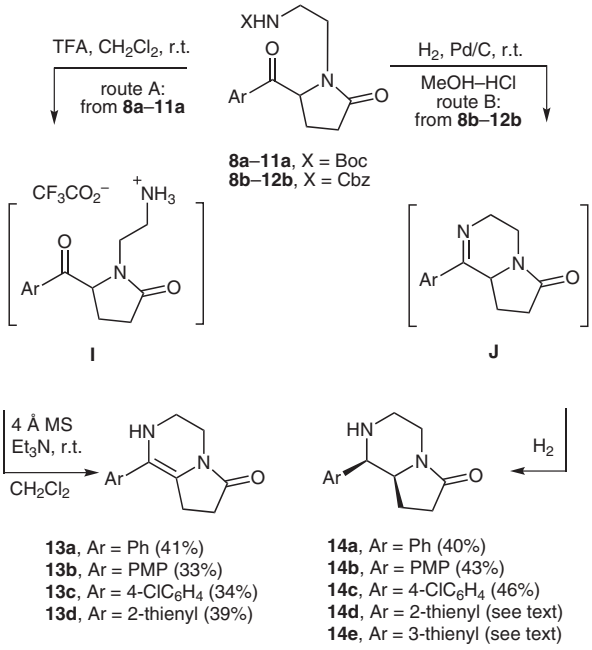
amine group and the keto carbonyl group of **G** to afford pyrrolopyrazinones of type **H** (Scheme 1). In this work, we present an original route to a series of derivatives with the pyrrolopyrazinone skeleton as model compounds that could potentially show biological activity.[7]

Two usual protecting groups (X = Boc, Cbz) for the terminal amino group were selected to evaluate their behavior under the PIFA-mediated cyclization conditions.[8] Thus, alkynylamides **3–6** were prepared in a two-step sequence as shown in Scheme 2. First, the amide linkages between the known monoprotected diamines **1a**,**b** and pentynoic acid were formed in almost quantitative yields for both cases with the aid of *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (BtOH) as activating agents.[9] The aryl groups were subsequently efficiently inserted (75–90% yield) at the terminal position of the triple bond by a Sonogashira coupling reaction in which copper(I) iodide and palladium(II) were used as catalysts.[10] The aryl fragments for this reaction were selected on the basis of our preliminary study,[6] in which it was found that alkynylamides substituted at the terminal position by deactivated aryl rings could not be transformed into the corresponding pyrrolidinone derivatives. Only activated (PMP, thienyl), nonactivated (Ph), and moderately deactivated (ClC_6H_4) aryl-substituted substrates (as in **3–6**) were expected to succeed in the desired heterocyclization step.[11,12] Thus, the key cyclization step took place by treatment of amides **3–6** with a slight excess (1.25 equiv) of PIFA in trifluoroethanol (TFEA) as solvent at room temperature; this afforded the desired pyrrolidinone series **8–11** in good to excellent yields (53–94%) in a transformation that proceeded to completion in less than two hours with no noticeable difference in the behavior of the two protecting groups.



Scheme 2 Preparation and reactivity of functionalized alkynylamides **3–7** and synthesis of 5-aroylpyrrolidinones **8–12**

At this point, we embarked on our next endeavor to prepare the bicyclic pyrazinones.[13] In the first stage, for both cases (the **a** and **b** series), the protecting groups had to be removed. Therefore, pyrrolidinones **8a–11a** were deprotected under acidic (TFA) conditions and, without any further purification, the resulting non-isolated intermediates **I** (resulting from release of the Boc group; confirmed by ^1H NMR, but not isolated) were submitted to a cyclization process under dehydration conditions (Scheme 3). This gave the unsaturated pyrrolopyrazinones **13a–d** in 33–41% yield, probably as a result of the isomerization of the imine intermediate. On the other hand, pyrrolidinones **8b–10b** were transformed directly (via putative intermediate **J**) into the reduced analogues **14a–c** in similar yields (40–46%) under palladium-catalyzed hydrogenation conditions by a one-pot sequence consisting of Cbz deprotection and intramolecular reductive amination.[14] Extensive NMR studies led us to conclude that the cyclization took place with complete *syn* diastereoselectivity.[15] As an exception, all attempts to transform the 5-(thienylcarbonyl)-substituted pyrrolidinones **11b** and **12b** into the desired bicyclic derivatives **14d** and **14e** resulted in the complete recovery of the unchanged starting material.[16]



Scheme 3 Synthesis of pyrrolopyrazinones **13** and **14**

In conclusion, this investigation showed that the intramolecular PIFA-mediated alkyne amidation reaction of relatively complex substrates can be an efficient alternative for the preparation of highly functionalized pyrrolidinones. A demonstration of its usefulness is that when this transformation is coupled with a second intramolecular amination step, the overall process results in a simple and rapid protocol for the synthesis of a series of pyrrolopyrazinone derivatives of different oxidation states.

All reagents were purchased and used as received. All solvents used in reactions were dried and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under

argon. The glassware was oven-dried (140 °C) overnight and purged with argon prior to use. Melting points were measured by using open glass capillaries and are uncorrected. IR spectra of samples prepared as thin films were recorded on a Perkin-Elmer 1600FT-IR instrument and only representative absorptions are given. Flash chromatography was carried out on silica gel 60 (230–400 mesh, ASTM). NMR spectra were recorded on a Bruker AC-300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75.4 MHz) at 20–25 °C unless otherwise indicated. Chemical shifts (δ) were measured relative to $CHCl_3$ (^{1}H: δ = 7.26, ^{13}C: δ = 77.0) as internal standard. DEPT and several two-dimensional NMR experiments (COSY, HSQC) were used to assist with the assignment of the signals and structural determinations. Mass spectra were recorded under EI (70 eV) or CI conditions.

N-[2-(*tert*-Butoxycarbonylamino)ethyl]pent-4-ynamide (2a); Typical Procedure

A soln of pent-4-ynoic acid (740 mg, 7.2 mmol) in CH_2Cl_2 (5 mL) was added to a magnetically stirred soln of EDC·HCl (2.0 g, 10.8 mmol) and BtOH (1.5 g, 10.8 mmol) in the same solvent (20 mL); the addition of the monoprotected diamine **1a**[9a] (1.74 g, 10.8 mmol) dissolved in CH_2Cl_2 (5 mL) followed. The mixture was cooled to 0 °C, Et_3N (1.15 g, 10.8 mmol) was added dropwise, and then the mixture was left to react at r.t. overnight. Then the mixture was diluted with CH_2Cl_2 (25 mL), H_2O (25 mL) was added, the mixture was decanted, and the organic layer was consecutively washed with 5% aq HCl (20 mL), sat. aq $NaHCO_3$ (20 mL), and sat. aq NaCl (20 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed under vacuum. The resultant oil was crystallized from Et_2O; this afforded amide **2a**.

White solid; yield: 91%; mp 107–108 °C (Et_2O).

IR (film): 3284, 2978, 1655 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.24 (br s, 1 H), 4.88 (br s, 1 H), 3.41–3.27 (m, 4 H), 2.53–2.40 (m, 4 H), 2.00 (t, *J* = 2.6 Hz, 1 H), 1.44 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 156.9, 82.9, 79.8, 69.3, 40.7, 40.1, 35.3, 28.3, 14.9.

MS (CI): *m*/*z* [M + 1] (%) = 213 (21), 185 (32), 167 (42), 141 (100), 124 (72), 57 (24).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{21}N_2O_3$ [M + H]$^+$: 241.1552; found: 241.1877.

N-[2-(Benzyloxycarbonylamino)ethyl]pent-4-ynamide (2b)

According to the typical procedure, amide **2b** was obtained from monoprotected amine **1b**[9b] after purification by crystallization from hexanes.

White solid; yield: 97%; mp 108–110 °C (hexanes).

IR (film): 3307, 1690, 1643 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 5 H), 6.14 (br s, 1 H), 5.18 (s, 1 H), 5.10 (s, 2 H), 3.39–3.35 (m, 4 H), 2.33–2.49 (m, 4 H), 1.98 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 157.2, 136.3, 128.3, 128.2, 128.1, 83.9, 69.3, 66.7, 40.8, 40.2, 35.2, 14.9.

MS (CI): *m*/*z* [M + 1] (%) = 167 (48), 107 (18), 91 (100), 87 (17), 79 (28).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{19}N_2O_3$ [M + H]$^+$: 275.1396; found: 275.1399.

N-[2-(*tert*-Butoxycarbonylamino)ethyl]-5-phenylpent-4-ynamide (3a); Typical Procedure

A soln of iodobenzene (550 mg, 2.7 mmol), $PdCl_2(PPh_3)_2$ (15 mg, 0.02 mmol), PPh_3 (12 mg, 0.04 mmol), and amide **2a** (939 mg, 4.0 mmol) in Et_3N (15 mL) was stirred at 40 °C for 15 min. Then CuI (8 mg, 0.04 mmol) was added and the mixture was heated at 80 °C for 2 d. The whole crude was purified by column chromatography (silica gel, EtOAc); this afforded amide **3a** as a white solid, which was triturated in hexanes.

Yield: 95%; mp 118–120 °C (hexanes).

IR (film): 3284, 2967, 1649, 1549 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 2 H), 7.28–7.25 (m, 3 H), 6.36 (br s, 1 H), 4.93 (br s, 1 H), 3.41–3.26 (m, 4 H), 2.74 (t, *J* = 7.3 Hz, 2 H), 2.46 (t, *J* = 7.3 Hz, 2 H), 1.42 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 156.9, 131.6, 127.8, 123.4, 88.4, 81.4, 79.7, 40.8, 40.3, 35.6, 28.3, 15.9.

MS (CI): *m*/*z* [M + 1] (%) = 289 (26), 261 (100), 243 (13), 217 (56), 57 (39).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{25}N_2O_3$ [M + H]$^+$: 317.1865; found: 317.1860.

N-[2-(*tert*-Butoxycarbonylamino)ethyl]-5-(*p*-methoxyphenyl)pent-4-ynamide (4a)

According to the typical procedure, amide **4a** was obtained from amide **2a** after purification by column chromatography (silica gel, EtOAc) followed by crystallization from hexanes.

White solid; yield: 90%; mp 109–111 °C (hexanes).

IR (film): 3296, 2967, 1689, 1643 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.30 (d, *J* = 8.8 Hz, 2 H), 6.82–6.79 (d, *J* = 8.8 Hz, 2 H), 6.28 (br s, 1 H), 4.88 (br s, 1 H), 3.80 (s, 3 H), 3.43–3.23 (m, 4 H), 2.72 (t, *J* = 7.3 Hz, 2 H), 2.48 (t, *J* = 7.3 Hz, 2 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 159.2, 156.9, 132.9, 115.6, 113.8, 86.8, 81.5, 79.5, 56.2, 40.5, 40.3, 35.6, 26.3, 15.9.

MS (CI): *m*/*z* [M + 1] (%) = 291 (100), 290 (28), 273 (27), 247 (44), 231 (45), 230 (65).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{27}N_2O_4$ [M + H]$^+$: 347.1971; found: 347.1972.

N-[2-(*tert*-Butoxycarbonylamino)ethyl]-5-(*p*-chlorophenyl)pent-4-ynamide (5a)

According to the typical procedure, amide **5a** was obtained from amide **2a** after purification by column chromatography (silica gel, EtOAc) followed by crystallization from hexanes.

Pale yellow solid; yield: 80%; mp 131–132 °C (hexanes).

IR (film): 3296, 2967, 1684, 1637 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 9.2 Hz, 2 H), 7.23 (d, *J* = 9.2 Hz, 2 H), 6.37 (br s, 1 H), 4.90 (br s, 1 H), 3.39–3.25 (m, 4 H), 2.73 (t, *J* = 7.3 Hz, 2 H), 2.46 (t, *J* = 7.3 Hz, 2 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 157.0, 133.7, 132.8, 128.5, 122.0, 89.5, 80.3, 79.7, 40.8, 40.3, 35.4, 28.3, 15.9.

MS (CI): *m*/*z* [M + 1] (%) = 323 (17), 295 (91), 277 (50), 251 (100), 234 (57), 192 (30).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{24}ClN_2O_3$ [M + H]$^+$: 351.1475; found: 351.1465.

N-[2-(*tert*-Butoxycarbonylamino)ethyl]-5-(2-thienyl)pent-4-ynamide (6a)

According to the typical procedure, amide **6a** was obtained from amide **2a** after purification by column chromatography (silica gel, EtOAc) followed by crystallization from hexanes.

White solid; yield: 88%; mp 128–130 °C (hexanes).

IR (film): 3284, 2967, 1690, 1649 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18–7.12 (m, 2 H), 6.99–6.91 (m, 1 H), 6.34 (br s, 1 H), 4.93 (br s, 1 H), 3.39–3.27 (m, 4 H), 2.76 (t, *J* = 7.3 Hz, 2 H), 2.64 (t, *J* = 7.3 Hz, 2 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 156.9, 131.3, 126.8, 126.3, 123.5, 92.5, 79.6, 74.5, 40.7, 40.3, 35.3, 28.3, 16.1.

MS (CI): *m*/*z* [M + 1] (%) = 267 (100), 249 (23), 223 (44), 206 (50), 180 (26).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{23}N_2O_3S$ [M + H]$^+$: 323.1429; found: 323.1440.

_N_-[2-(Benzyloxycarbonylamino)ethyl]-5-phenylpent-4-ynamide (3b)

According to the typical procedure, amide **3b** was obtained from amide **2b** after purification by column chromatography followed by crystallization of the resultant oil in hexanes.

White solid; yield: 80%; mp 151–152 °C (hexanes).

IR (film): 3296, 3070, 1690, 1637 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 10 H), 6.17 (br s, 1 H), 5.17–5.07 (m, 3 H), 3.38 (m, 4 H), 2.72 (t, *J* = 7.2 Hz, 2 H), 2.44 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 157.2, 136.3, 131.5, 128.5, 128.3, 128.1, 127.9, 123.4, 88.3, 81.5, 66.9, 41.0, 40.9, 40.3, 35.6, 15.9.

MS (CI): *m*/*z* [M + 1] (%) = 351 (20), 286 (100), 266 (18), 243 (23), 91 (61), 79 (19).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{23}N_2O_3$ [M + H]$^+$: 351.1709; found: 351.1708.

_N_-[2-(Benzyloxycarbonylamino)ethyl]-5-(*p*-methoxyphenyl)pent-4-ynamide (4b)

According to the typical procedure, amide **4b** was obtained from amide **2b** after purification by column chromatography (silica gel, EtOAc) followed by crystallization from hexanes.

White solid; yield: 75%; mp 124–125 °C (hexanes).

IR (film): 3296, 1684, 1637 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.29 (m, 7 H), 6.80–6.77 (d, *J* = 8.8 Hz, 2 H), 6.17 (br s, 1 H), 5.13–5.07 (m, 3 H), 3.78 (s, 3 H), 3.41–3.34 (m, 4 H), 2.70 (t, *J* = 7.1 Hz, 2 H), 2.43 (t, *J* = 7.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 159.3, 157.0, 136.4, 132.9, 128.5, 128.2, 128.1, 115.5, 113.9, 86.7, 81.3, 66.8, 56.2, 41.0, 40.3, 35.7, 15.9.

MS (CI): *m*/*z* [M + 1] (%) = 381 (22), 273 (65), 272 (44), 231 (100), 91 (78), 79 (29).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{25}N_2O_4$ [M + H]$^+$: 381.1814; found: 381.1818.

_N_-[2-(Benzyloxycarbonylamino)ethyl]-5-(*p*-chlorophenyl)pent-4-ynamide (5b)

According to the typical procedure, amide **5b** was obtained from amide **2b** after purification by column chromatography (silica gel, EtOAc) followed by crystallization from hexanes.

Pale yellow solid; yield: 90%; mp 169–170 °C (hexanes).

IR (film): 3284, 1684, 1637 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 9 H), 6.22 (br s, 1 H), 5.18 (br s, 1 H), 5.07 (s, 2 H), 3.40–3.34 (m, 4 H), 2.70 (t, *J* = 7.2 Hz, 2 H), 2.43 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 157.2, 136.3, 133.8, 132.8, 128.5, 128.2, 126.9, 126.3, 121.9, 89.4, 80.4, 66.9, 40.9, 40.5, 35.4, 15.9.

MS (CI): *m*/*z* [M + 1] (%) = 385 (11), 324 (10), 279 (40), 277 (100), 237 (23), 235 (73), 193 (11).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{22}ClN_2O_3$ [M + H]$^+$: 385.1319; found: 385.1315.

_N_-[2-(Benzyloxycarbonylamino)ethyl]-5-(2-thienyl)pent-4-ynamide (6b)

According to the typical procedure, amide **6b** was obtained from amide **2b** after purification by column chromatography (silica gel, EtOAc) followed by crystallization from hexanes.

White solid; yield: 79%; mp 127–128 °C (hexanes).

IR (film): 3296, 3070, 1690, 1637 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 5 H), 7.17–7.11 (m, 2 H), 6.93–6.90 (m, 1 H), 6.17 (br s, 1 H), 5.13–5.07 (m, 3 H), 3.41–3.34 (m, 4 H), 2.70 (t, *J* = 7.1 Hz, 2 H), 2.43 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 157.2, 136.3, 131.4, 128.5, 128.2, 128.1, 126.9, 126.3, 123.4, 92.4, 74.7, 66.9, 40.9, 40.4, 35.3, 16.1.

MS (CI): *m*/*z* [M + 1] (%) = 296 (11), 249 (39), 248 (30), 208 (14), 207 (100), 164 (16), 108 (22).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{21}N_2O_3S$ [M + H]$^+$: 357.1273; found: 357.1289.

_N_-[2-(Benzyloxycarbonylamino)ethyl]-5-(3-thienyl)pent-4-ynamide (7b)

According to the typical procedure, amide **7b** was obtained from amide **2b** after purification by column chromatography (silica gel, EtOAc) followed by crystallization from hexanes.

White solid; yield: 70%; mp 150–151 °C (hexanes).

IR (film): 3300, 3078, 1685, 1641 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 6 H), 7.21–7.19 (m, 1 H), 7.06–7.02 (m, 1 H), 6.34 (br s, 1 H), 5.30 (br s, 1 H), 5.07 (s, 2 H), 3.42–3.30 (m, 4 H), 2.69 (t, *J* = 7.2 Hz, 2 H), 2.33 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 157.2, 136.4, 125.2, 129.9, 128.6, 128.1, 123.4, 122.3, 87.9, 66.9, 40.9, 40.3, 35.5, 15.9.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{21}N_2O_3S$ [M + H]$^+$: 357.1273; found: 357.1289.

5-Benzoyl-_N_-[2-(*tert*-butoxycarbonylamino)ethyl]pyrrolidin-2-one (8a); Typical Procedure

A soln of alkynylamide **3a** (250 mg, 0.8 mmol) in CF_3CH_2OH (TFEA; 12 mL) was stirred and cooled to 0 °C, and then a soln of PIFA (526.8 mg, 1.2 mmol) in the same solvent (6 mL) was added dropwise. The reaction mixture was stirred at that temperature for 2 h. For the workup, 10% aq Na_2CO_3 (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL) and dried (Na_2SO_4), and the solvent was evaporated. Purification of the crude by flash chromatography (silica gel, EtOAc) gave the desired product **8a**.

Yellowish oil; yield: 55%.

IR (film): 3331, 2967, 1690, 1519 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.1 Hz, 2 H), 7.64–7.63 (m, 1 H), 7.55–7.50 (m, 2 H), 5.39–5.35 (m, 1 H), 4.90 (br s, 1 H), 3.80–3.77 (m, 1 H), 3.49–3.40 (m, 1 H), 3.11–3.02 (m, 2 H), 2.44–2.30 (m, 3 H), 2.11–2.01 (m, 1 H), 1.41 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.1, 176.3, 156.3, 134.0, 129.0, 128.4, 79.2, 61.8, 42.2, 33.2, 29.3, 28.3, 23.5.

MS (EI): *m*/*z* (%) = 332 (36), 317 (31), 305 (100), 287 (26), 277 (16).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{24}N_2O_4$ 332.1736; found: 332.1731.

N-[2-(*tert*-Butoxycarbonylamino)ethyl]-5-(*p*-methoxybenzoyl)pyrrolidin-2-one (9a)

According to the typical procedure, pyrrolidinone **9a** was obtained from amide **4a** after purification by column chromatography (silica gel, EtOAc) followed by crystallization from EtOAc.

White solid; yield: 74%; mp 111–113 °C (EtOAc).

IR (film): 3331, 2967, 1684, 1596, 1508 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.7 Hz, 2 H), 6.99 (d, *J* = 8.7 Hz, 2 H), 5.34–5.30 (m, 1 H), 4.92 (br s, 1 H), 3.89 (s, 3 H), 3.80–3.76 (m, 1 H), 3.51–3.33 (m, 1 H), 3.11–3.06 (m, 2 H), 2.50–1.97 (m, 4 H), 1.41 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.7, 176.4, 164.2, 156.3, 130.8, 127.1, 114.2, 79.1, 61.5, 55.5, 42.2, 38.2, 29.4, 28.3, 23.7.

MS (CI): *m*/*z* [M + 1] (%) = 246 (15), 245 (83), 244 (100), 215 (5).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{27}N_2O_5$ $[M + H]^+$: 363.1920; found: 363.1877.

N-[2-(*tert*-Butoxycarbonylamino)ethyl]-5-(*p*-chlorobenzoyl)pyrrolidin-2-one (10a)

According to the typical procedure, pyrrolidinone **10a** was obtained from amide **5a** after purification by column chromatography (silica gel, EtOAc).

Yellowish oil; yield: 54%.

IR (film): 3343, 2967, 1690, 1588, 1519 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 5.35–5.28 (m, 1 H), 5.00 (br s, 1 H), 3.87–3.75 (m, 1 H), 3.50–3.27 (m, 1 H), 3.12–2.94 (m, 2 H), 2.49–2.32 (m, 3 H), 2.02–1.86 (m, 1 H), 1.39 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.0, 176.1, 156.4, 140.6, 132.4, 129.9, 129.4, 79.3, 61.6, 42.1, 30.0, 28.3, 28.2, 23.4.

MS (CI): *m*/*z* [M + 1] (%) = 294 (20), 280 (15), 267 (21), 266 (91), 238 (100), 194 (17), 180 (19).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{24}ClN_2O_4$ $[M + H]^+$: 367.1425; found: 367.1317.

N-[2-(*tert*-Butoxycarbonylamino)ethyl]-5-(2-thienylcarbonyl)pyrrolidin-2-one (11a)

According to the typical procedure, pyrrolidinone **11a** was obtained from amide **6a** after purification by column chromatography (silica gel, EtOAc).

Yellowish oil; yield: 94%.

IR (film): 3331, 2967, 1684, 1514 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.70 (m, 2 H), 7.19–7.14 (m, 1 H), 5.18–5.09 (m, 2 H), 3.75–3.72 (m, 1 H), 3.41–3.37 (m, 1 H), 3.11–2.88 (m, 2 H), 2.44–2.27 (m, 3 H), 2.12–2.10 (m, 1 H), 1.35 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.8, 176.3, 156.2, 141.1, 135.2, 132.9, 128.6, 79.1, 62.3, 42.2, 38.2, 29.4, 28.3, 24.0.

MS (CI): *m*/*z* [M + 1] (%) = 265 (4), 222 (20), 221 (93), 220 (100), 191 (11).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{23}N_2O_4S$ $[M + H]^+$: 339.1379; found: 339.1334.

5-Benzoyl-N-[2-(benzyloxycarbonylamino)ethyl]pyrrolidin-2-one (8b)

According to the typical procedure, pyrrolidinone **8b** was obtained from amide **3b** after purification by column chromatography (silica gel, EtOAc).

Yellowish oil; yield: 53%.

IR (film): 3331, 2931, 1690, 1525, 1449 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.80 (m, 2 H), 7.60–7.55 (m, 1 H), 7.48–7.43 (m, 1 H), 7.26–7.23 (m, 5 H), 5.83–5.76 (m, 1 H), 5.35–5.29 (m, 1 H), 5.06 (d, *J* = 12.3 Hz, 1 H), 4.94 (d, *J* = 12.3 Hz, 1 H), 2.97–2.74 (m, 4 H), 2.40–2.19 (m, 3 H), 1.89–1.83 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2, 176.5, 156.9, 136.8, 134.1, 132.1, 129.0, 128.4, 128.0, 127.9, 66.4, 62.0, 42.1, 38.9, 29.3, 23.5.

MS (CI): *m*/*z* [M + 1] (%) = 259 (75), 216 (40), 215 (100), 214 (75), 153 (29), 108 (35).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{23}N_2O_4$ $[M + H]^+$: 367.1658; found: 367.1653.

N-[2-(Benzyloxycarbonylamino)ethyl]-5-(*p*-methoxybenzoyl)pyrrolidin-2-one (9b)

According to the typical procedure, pyrrolidinone **9b** was obtained from amide **4b** after purification by column chromatography (silica gel, EtOAc).

Yellowish oil; yield: 68%.

IR (film): 3331, 2943, 1684, 1596, 1514 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.6 Hz, 2 H), 7.33–7.30 (m, 5 H), 6.97 (d, *J* = 8.6 Hz, 2 H), 5.31–5.24 (m, 2 H), 5.10 (d, *J* = 12.2 Hz, 1 H), 5.03 (d, *J* = 12.2 Hz, 1 H), 3.89 (s, 3 H), 3.80–3.75 (m, 1 H), 3.60–3.49 (m, 1 H), 3.24–3.09 (m, 2 H), 2.43–2.25 (m, 3 H), 1.95–1.74 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.6, 176.5, 164.3, 156.8, 136.7, 128.1, 128.0, 127.9, 127.0, 114.2, 66.6, 61.7, 56.6, 42.2, 39.1, 29.4, 23.9.

MS (CI): *m*/*z* [M + 1] (%) = 290 (14), 289 (100), 246 (26), 245 (13), 153 (13).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{25}N_2O_5$ $[M + H]^+$: 397.1763; found: 397.1767.

N-[2-(Benzyloxycarbonylamino)ethyl]-5-(*p*-chlorobenzoyl)pyrrolidin-2-one (10b)

According to the typical procedure, pyrrolidinone **10b** was obtained from amide **5b** after purification by column chromatography (silica gel, EtOAc).

Yellowish oil; yield: 79%.

IR (film): 3319, 2943, 1690, 1590, 1525 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.32–7.25 (m, 5 H), 5.42–5.36 (m, 1 H), 5.30–5.28 (m, 1 H), 5.09 (d, *J* = 12.2 Hz, 1 H), 5.02 (d, *J* = 12.2 Hz, 1 H), 3.86–3.77 (m, 1 H), 3.49–3.30 (m, 1 H), 3.20–2.96 (m, 2 H), 2.32–2.20 (m, 2 H), 1.87–1.80 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.0, 176.3, 156.8, 140.7, 136.6, 132.3, 129.8, 129.4, 128.5, 128.1, 127.9, 66.6, 61.8, 42.1, 38.7, 29.2, 23.4.

MS (CI): *m*/*z* [M + 1] (%) = 295 (33), 293 (100), 252 (10), 250 (84), 289 (77), 153 (95), 108 (26).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{22}ClN_2O_4$ $[M + H]^+$: 401.1268; found: 401.1261.

N-[2-(Benzyloxycarbonylamino)ethyl]-5-(2-thienylcarbonyl)pyrrolidin-2-one (11b)

According to the typical procedure, pyrrolidinone **11b** was obtained from amide **6b** after purification by column chromatography (silica gel, EtOAc).

Yellowish oil; yield: 81%.

IR (film): 3319, 3072, 1678, 1590 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.67 (m, 2 H), 7.27–7.22 (m, 5 H), 7.14–7.11 (m, 1 H), 5.79–5.73 (m, 1 H), 5.13–5.10 (m, 1 H),

5.03 (d, *J* = 12.2 Hz, 1 H), 4.96 (d, *J* = 12.2 Hz, 1 H), 3.76–3.68 (m, 1 H), 3.49–3.30 (m, 1 H), 3.20–2.96 (m, 2 H), 2.30–2.14 (m, 3 H), 1.97–1.90 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.8, 176.5, 156.8, 141.0, 135.3, 128.7, 128.4, 128.0, 127.9, 66.4, 62.7, 42.0, 38.7, 29.4, 24.0.

MS (CI): *m*/*z* [M + 1] (%) = 329 (8), 256 (34), 222 (38), 221 (100), 220 (69), 108 (34).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{21}N_2O_4S$ $[M + H]^+$: 373.1222; found: 373.1224.

N-[2-(Benzyloxycarbonylamino)ethyl]-5-(3-thienylcarbonyl)pyrrolidin-2-one (12b)

According to the typical procedure, pyrrolidinone **12b** was obtained from amide **7b** after purification by column chromatography (silica gel, EtOAc).

Yellowish oil; yield: 64%.

IR (film): 3315, 3088, 1685, 1528 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (br s, 1 H), 7.56–7.54 (m, 1 H), 7.39–7.33 (m, 1 H), 5.39 (br s, 1 H), 5.12–5.00 (m, 3 H), 3.85–3.76 (m, 1 H), 3.52–3.45 (m, 1 H), 3.19–3.04 (m, 2 H), 2.42–2.22 (m, 3 H), 2.00–1.93 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.8, 176.5, 156.8, 139.1, 136.5, 133.3, 128.5, 128.1, 128.0, 127.2, 127.0, 66.6, 62.9, 42.0, 38.8, 29.3, 23.7.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{21}N_2O_4S$ $[M + H]^+$: 373.1222; found: 373.1224.

1-Phenyl-3,4,7,8-tetrahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (13a); Typical Procedure

A soln of pyrrolidinone **8a** (170 mg, 0.5 mmol) in TFA–CH_2Cl_2 (1:1, 20 mL) was stirred for 30 min. An aliquot was taken to confirm (by ^{1}H NMR) that the protecting group was completely released. Then both solvents were removed under vacuum, and the residue was taken up in CH_2Cl_2 (50 mL); the mixture was cooled to 0 °C and treated with Et_3N (0.7 mL, 5 mmol). After stirring for 20 min, 4 Å MS were added and the stirring was continued for an additional 15 min. The mixture was then filtered through Celite, washed with sat. aq $NaHCO_3$ (20 mL), and finally extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure, and the resulting residue was purified by column chromatography (silica gel, EtOAc–MeOH, 95:5); this afforded pyrazinone **13a** as a yellowish oil, which was finally crystallized from MeOH.

Yield: 41%; mp 127–128 °C (MeOH).

IR (film): 3236, 1667 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.0 Hz, 2 H), 7.43–7.36 (m, 3 H), 5.14 (br s, 1 H), 4.05–3.95 (m, 2 H), 3.68–3.57 (m, 1 H), 3.23–3.16 (m, 1 H), 2.71–2.59 (m, 1 H), 2.37–2.25 (m, 2 H), 2.09–1.96 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 165.2, 135.9, 130.2, 128.3, 128.1, 83.9, 48.1, 32.6, 32.5, 29.4.

MS (CI): *m*/*z* [M + 1] (%) = 231 (12), 215 (72), 214 (100), 213 (14), 185 (10).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{15}N_2O$ $[M + H]^+$: 215.1184; found: 215.1191.

1-(*p*-Methoxyphenyl)-3,4,7,8-tetrahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (13b)

According to the typical procedure, pyrrolidinone **13b** was obtained from amide **9a** after purification by column chromatography (silica gel, EtOAc–MeOH, 70:30) followed by crystallization from MeOH.

Yellowish solid; yield: 33%; mp 131–132 °C (MeOH).

IR (film): 3355, 1696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 9.0 Hz, 2 H), 6.93 (d, *J* = 9.0 Hz, 2 H), 4.14–4.02 (m, 2 H), 3.87 (s, 3 H), 3.70–3.58 (m, 1 H), 3.22–3.12 (m, 1 H), 2.75–2.66 (m, 1 H), 2.48–2.34 (m, 2 H), 2.14–2.04 (m, 1 H), 1.64 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 163.9, 161.2, 129.7, 128.3, 113.6, 84.0, 55.3, 48.0, 32.8, 32.7, 29.3.

MS (CI): *m*/*z* [M + 1] (%) = 261 (43), 245 (71), 244 (100), 243 (53), 242 (42).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}N_2O_2$ $[M + H]^+$: 245.1290; found: 245.1288.

1-(*p*-Chlorophenyl)-3,4,7,8-tetrahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (13c)

According to the typical procedure, pyrrolidinone **13c** was obtained from amide **10a** after purification by column chromatography (silica gel, EtOAc–MeOH, 95:5).

Yellowish oil; yield: 34%.

IR (film): 3302, 1678 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.7 Hz, 2 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 4.10–3.99 (m, 2 H), 3.70–3.57 (m, 1 H), 3.48 (s, 1 H), 3.25–3.14 (m, 1 H), 2.74–2.62 (m, 1 H), 2.38–2.27 (m, 2 H), 2.05–1.98 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 163.9, 136.4, 134.2, 129.5, 128.6, 83.8, 48.2, 32.7, 32.6, 29.3.

MS (CI): *m*/*z* [M + 1] (%) = 265 (16), 250 (36), 249 (58), 248 (100), 213 (11).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{14}{}^{35}ClN_2O$ $[M + H]^+$: 249.0795; found: 249.0783.

1-(2-Thienyl)-3,4,7,8-tetrahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (13d)

According to the typical procedure, pyrrolidinone **13d** was obtained from amide **11a** after purification by column chromatography (silica gel, EtOAc–MeOH, 95:5) followed by crystallization from MeOH.

Yellowish solid; yield: 39%; mp 131–132 °C (MeOH).

IR (film): 3296, 1690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.39 (m, 2 H), 7.08–7.06 (m, 1 H), 4.12–3.93 (m, 2 H), 3.91–3.79 (m, 1 H), 3.66–3.58 (m, 1 H), 3.18–2.80 (m, 1 H), 2.79–2.56 (m, 2 H), 2.42–2.22 (m, 1 H), 1.68 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 160.3, 141.4, 129.2, 129.1, 127.7, 83.9, 48.1, 33.6, 32.9, 29.3.

MS (CI): *m*/*z* [M + 1] (%) = 237 (99), 221 (67), 220 (100), 153 (13), 127 (14).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{13}N_2OS$ $[M + H]^+$: 221.0749; found: 221.0739.

(1*R*,8a*S*)-1-Phenylhexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (14a); Typical Procedure

A soln of pyrrolidinone **8b** (209.5 mg, 0.6 mmol) in MeOH (6 mL) and 1 M aq HCl (0.5 mL) was hydrogenated (70 psi) overnight in the presence of Pd/C (21 mg). The catalyst was removed by filtration through Celite and the soln was treated with 20% aq Na_2CO_3 (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated under vacuum. The resulting oil was purified by column chromatography (silica gel, MeOH); this afforded pyrazine **14a**.

Yellowish oil; yield: 40%.

IR (film): 3350, 1655 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.61 (d, *J* = 8.0 Hz, 1 H), 3.79–3.77 (m, 1 H), 3.71–3.68 (m, 1 H), 3.47–3.44 (m, 1 H), 3.38–3.36 (m, 1 H), 2.93–2.90 (m, 1 H), 2.45–2.38 (m, 1 H), 2.26–2.19 (m, 1 H), 1.90–1.83 (m, 1 H), 1.72–1.68 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.5, 141.4, 128.5, 127.9, 127.0, 77.1, 66.6, 46.8, 39.2, 30.1, 22.6.

MS (CI): *m*/*z* [M + 1] (%) = 259 (74), 216 (39), 215 (100), 214 (76), 153 (29), 108 (35).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{17}N_2O$ $[M + H]^+$: 217.1341; found: 217.1348.

(1*R*,8a*S*)-1-(*p*-Methoxyphenyl)hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (14b)

According to the typical procedure, pyrrolidinone **14b** was obtained from amide **9b** after purification by column chromatography (silica gel, EtOAc).

Yellowish oil; yield: 43%.

IR (film): 3425, 1667 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.7 Hz, 2 H), 6.85 (d. *J* = 8.7, 2 H), 4.09–4.04 (m, 1 H), 3.76 (s, 3 H), 3.48–3.43 (m, 1 H), 3.22 (d, *J* = 9.3 Hz, 1 H), 3.13–3.10 (m, 1 H), 2.97–2.91 (m, 1 H), 2.82–2.76 (m, 1 H), 2.46–2.26 (m, 3 H), 1.84–1.77 (m, 1 H), 1.64–1.56 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 159.5, 131.6, 128.8, 114.0, 79.7, 61.9, 55.2, 45.4, 40.2, 30.1, 21.6.

MS (CI): *m*/*z* [M + 1] (%) = 275 (15), 258 (15), 247 (100), 246 (66), 230 (28), 161 (13).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{19}N_2O_2$ $[M + H]^+$: 247.1447; found: 247.1440.

(1*R*,8a*S*)-1-(*p*-Chlorophenyl)hexahydropyrrolo[1,2-*a*]-pyrazin-6(2*H*)-one (14c)

According to the typical procedure, pyrrolidinone **14c** was obtained from amide **10b** after purification by column chromatography (silica gel, MeOH).

Yellowish oil; yield: 46%.

IR (film): 3387, 1667.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.33 (m, 4 H), 4.12–4.09 (m, 1 H), 3.54–3.49 (m, 1 H), 3.30 (d, *J* = 9.2 Hz, 1 H), 3.17–3.14 (m, 1 H), 3.00–2.96 (m, 1 H), 2.86–2.80 (m, 1 H), 2.42–2.29 (m, 2 H), 1.98 (br s, 1 H), 1.84–1.80 (m, 1 H), 1.66–1.62 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 139.6, 128.7, 128.5, 127.7, 68.3, 61.9, 45.4, 40.3, 30.1, 21.6.

MS (CI): *m*/*z* [M + 1] (%) = 245 (10), 218 (14), 217 (100), 216 (60), 200 (23).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}ClN_2O$ $[M + H]^+$: 251.0951; found: 251.0953.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(11) These results led us to propose a mechanism in which the activated triple bond easily coordinates with the iodine(III) reagent and, hence, assisting the nucleophilic attack of the amidic nitrogen. In addition, alkyl-substituted alkynes also failed in the PIFA-mediated cyclization step.

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(14) Additional attempts to hydrogenate unsaturated pyrrolopyrazinone **13a** to afford **14a** resulted in the recovery of the unchanged starting material. Hydrogenation of the imine intermediate **J** appears to proceed much faster than the isomerization process that would lead to its enamine tautomer.

(15) Diastereomers **14** showed a significant NOE between the H1 and H8a protons, indicating that they are located on the same face of the heterocyclic ring.

(16) It is known that, in some cases, thiophene-containing olefins can be unreactive under palladium-catalyzed hydrogenation conditions.