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Pd-catalyzed intramolecular cyclization of pyrrolo-2-carboxamides: regiodivergent routes to pyrrolo-pyrazines and pyrrolo-pyridines

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Abstract—Treatment of *N*-alkyl-*N*-allyl-pyrrolo-2-carboxamides with catalytic amounts of palladium derivatives gave regioselectively intramolecular cyclizations to generate bicyclic pyrrolo-fused structures. Pyrrolo[1,2-*a*]pyrazin-1-ones were achieved in high yields by an amination reaction, while pyrrolo[2,3-*c*]pyridin-7-ones and pyrrolo[3,2-*c*]pyridin-4-ones were obtained by an oxidative coupling process.

1. Introduction

Nitrogen-containing heterocycles have always constituted a subject of great interest due to their wide presence in biologically important compounds. Also in this field, the catalysis by palladium has become a powerful arm in the hands of the organic chemists.[1] All typologies of Pd-catalysis have been successfully employed: Heck[2] and Buchwald–Hartwig[3] protocols, cross coupling reactions,[4] alkene and alkyne amination,[5] oxidative coupling.[6]

As a part of an ongoing program directed to the development of palladium-catalyzed intramolecular cyclizations, we already reported efficient methods for the construction of β- and γ-carbolinones,[7–9] pyrazino[1,2-*a*]indoles,[9] quinazolinones and 1,4-benzodiazepin-5-ones,[10] dibenzodiazepinones and pyridobenzodiazepinones.[11]

In the wide range of Pd-catalyzed reactions known today, aryl- and vinyl-halides have been employed more than unhalogenated substrates despite them suffering from a general difficulty of synthesis. In an effort to expand the access to new nitrogenated heteropolycycles, we studied the behavior of *N*-alkyl-*N*-allyl-pyrrolo-2-carboxamides towards Pd-catalyzed intramolecular cyclizations. Particular interest came from the regioselective aspect of the process in the light of the possibility of reaction at the 1- and 3-positions of the pyrrole nucleus.

2. Results and discussion

As a model substrate, the unknown *N*-allyl-*N*-methyl-2-carboxamide **2a** was easily prepared starting from the pyrrole-2-carboxylic acid (Scheme 1). The first cyclization path, involving the pyrrolic nitrogen so giving the pyrrolo[1,2-*a*]pyrazine skeleton, was attained in 62% with 10 mol% of $Pd(OAc)_2$ as catalyst and DMSO as solvent at 100 °C, in presence of AcONa and tetrabutylammonium chloride. This latter, as well as a polar aprotic solvent, was essential to attain a satisfactory yield.

This amination process involves Pd(0) species as confirmed by its inhibition when operating in presence of *p*-benzoquinone as reoxidant agent. In this case, only unreacted starting material was recovered. However, the use of *p*-benzoquinone in different reaction conditions led to a new outcome involving the C-3 position of the pyrrolic ring to give a pyrrolo-pyridine skeleton by way of an oxidative coupling. More precisely, operating with $PdCl_2(CH_3CN)_2$ (10 mol%) as catalyst and a stoichiometric amount of *p*-benzoquinone in a mixture DMF/THF as solvent, the compound **2a** was totally converted in a 1:1 mixture of two products, isolated in 30 and 35% yields, respectively. The isomeric structures **4a** and **5a** were assigned on the base of the analytical and spectroscopic data. The diagnostic evidence to distinguish between the

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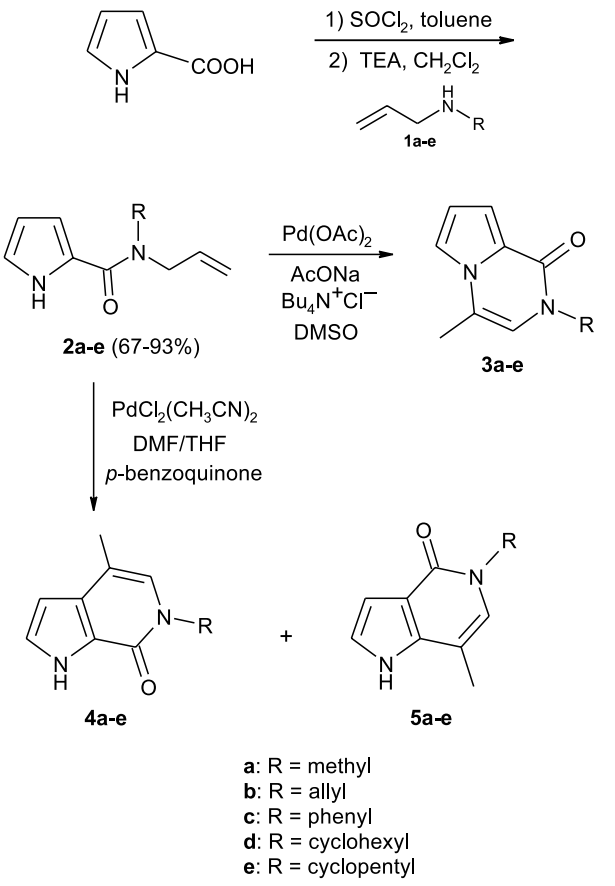
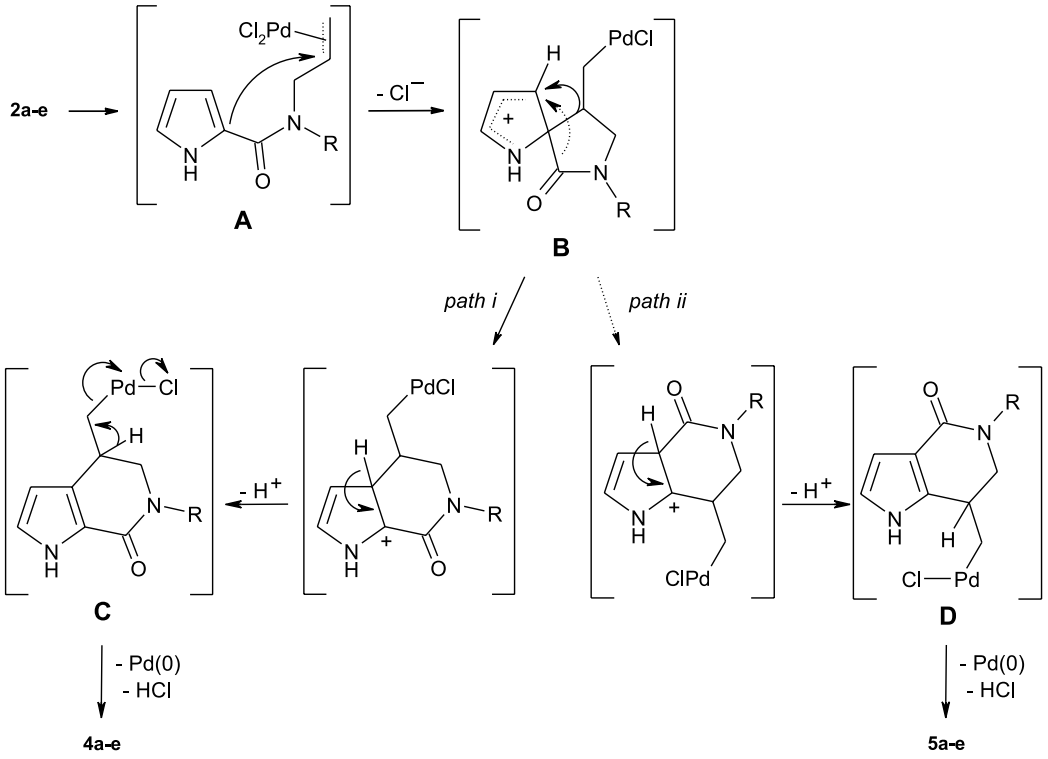


Scheme 1.

pyrrolo[2,3-*c*]pyridin-7-one (**4a**) and the pyrrolo[3,2-*c*]-pyridine-4-one (**5a**) resulted from the ^{1}H NMR and IR spectra. The chemical shift of the NH proton resonates at 10.21 δ in the former suffering of the deshielding effect of the carbonyl group, in comparison with the NH signal at 9.08 δ in the latter. On the other hand, the infrared frequency of the carbonyl group stretch is greater in compound **4a** with respect to **5a** according to analogue structures reported in the literature.[12]

A plausible mechanism, although highly speculative, is shown in Scheme 2. The olefin–palladium complex **A** would undergo the nucleophilic attack by the 2-carbon of the electron-rich pyrrole nucleus to give the transient spiro-derivative **B**. The latter would rearomatize through an anionotropic shift and subsequent loss of a proton. However, both σ bonds at the spiranic center are able to migrate so that two different skeleton types are formed, namely the Pd-σ-complexes **C** (path (i)) and **D** (path (ii)). The subsequent β-elimination afforded unisolable exo-methylenic compounds by loss of hydrochloride acid and Pd(0). Double bond migration inside the six-membered ring originated the thermodynamically more stable structures **4a** or **5a**. Finally, it must be underlined as the palladium can go back to the catalytic cycle after reoxidation due to the presence of the *p*-benzoquinone. The alternative pathway assuming a Heck type mechanism with aromatic palladation,[6j] though consistent with compound **4a**, does not justify the isomeric compound **5a**. In any case, we do not rule out both the mechanisms may be operating.

Given these results, both the reactions of amination and oxidative coupling were carried out with various substrates accessible from commercial alkyl–allyl-amines **1b–e**. The



Scheme 2.

Table 1. Yields (%) of the intramolecular cyclization products **3–5a–e**

Entry	R	**3**[a]	**4**[b]	**5**[b]
a	Methyl	62	30	35
b	Allyl	85	33	31
c	Phenyl	57	27	41
d	Cyclohexyl	89	38	45
e	Cyclopentyl	82	29	48

[a] Reaction conditions: $Pd(OAc)_2$, AcONa, Bu_4NCl, DMSO.
[b] Reaction conditions: $PdCl_2(CH_3CN)_2$, *p*-benzoquinone, DMF/THF.

latter gave the amides **2b–e** in 67–93% yields, the behavior of which resulted analogue to the model **2a**. The cyclization yields (collected in Table 1) were not significantly affected by the *N*-substituents.

In summary, using catalytic amount of palladium, we have developed regioselective cyclization conditions of *N*-allyl-pyrrolo-2-carboxamides to access to different pyrrolo-fused heterocycles. Pyrrolo[1,2-*a*]pyrazin-1-ones were generated in very high yields by an amination process when the Pd(0) species is at work. Conversely, pyrrolo[2,3-*c*]pyridin-7-ones and pyrrolo[3,2-*c*]pyridin-4-ones were formed by an oxidative coupling when using Pd(II) in the presence of an oxidant.

3. Experimental

3.1. General

Preparative column chromatography was carried out on silica gel 60 (Merck) (mesh size 63–200 μm). Melting points were measured on a Büchi B-540 heating unit and are not corrected. NMR spectra were recorded on an AVANCE 400 Bruker. IR spectra were taken on a Jasco FT/IR 5300 spectrophotometer.

3.2. General procedure for the preparation of allylamides 2a–e

A solution of 2-pyrrole-carboxylic acid (1.07 g, 9.6 mmol) and $SOCl_2$ (3.49 ml, 48 mmol) in toluene (30 ml) was refluxed for 4 h. After evaporation of the solvent, the crude mixture was taken up with CH_2Cl_2 (10 ml), then a solution of **1a–e** (14.4 mmol) and TEA (1.35 ml, 9.6 mmol) in CH_2Cl_2 (6 ml) was dropped at 0 °C. The resultant solution was stirred at room temperature for 2 h, then washed with 5% HCl (2×25 ml) and 5% aqueous NaOH (2×25 ml). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was chromatographed on a silica gel column to give compounds **2a–e**.

3.2.1. *N*-Allyl-*N*-methyl-pyrrolo-2-carboxamide (2a). Eluent: Et_2O/light petroleum 1:4. Yield: 93%. Mp 55–56 °C (from diisopropyl ether). IR (nujol): 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=3.20$ (3H, s), 4.23 (2H, d, $J=4.4$ Hz), 5.24 (1H, d, $J=10.5$ Hz), 5.26 (1H, d, $J=17.1$ Hz), 5.91 (1H, tdd, $J=4.4$, 10.5, 17.1 Hz), 6.24–6.29 (1H, m), 6.61 (1H, br.s), 6.95 (1H, br.s), 9.57 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=34.6$ (q), 46.2 (t), 109.9 (d), 113.0 (d), 117.5 (t), 121.8 (d), 125.1 (s), 133.4 (d), 160.3 (s). Anal. calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found C, 65.92; H, 7.25; N, 16.87.

3.2.2. *N*,*N*-Diallyl-pyrrolo-2-carboxamide (2b). Eluent: AcOEt/light petroleum 1:4. Yield: 69%. Mp 63–64 °C (from diisopropyl ether). IR (nujol): 1649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=4.19$ (4H, br.s), 5.16–5.24 (4H, overlapping), 5.86–5.95 (2H, overlapping), 6.24 (1H, dd, $J=2.3$, 2.6 Hz), 6.60 (1H, d, $J=2.3$ Hz), 6.93 (1H, d, $J=2.6$ Hz), 9.80 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=50.0$ (t), 109.6 (d), 112.9 (d), 117.5 (t), 122.5 (d), 124.6 (s), 133.7 (d), 163.6 (s). Anal. calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found C, 69.56; H, 7.25; N, 14.80.

3.2.3. *N*-Allyl-*N*-phenyl-pyrrolo-2-carboxamide (2c). Eluent: AcOEt/light petroleum 4:1. Yield: 81%. Mp 117–118 °C (from diisopropyl ether). IR (nujol): 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=4.45$ (2H, d, $J=6.2$ Hz), 4.90 (1H, br.s), 5.15 (1H, d, $J=16.9$ Hz), 5.18 (1H, d, $J=10.3$ Hz), 5.90–6.12 (2H, overlapping), 6.83 (1H, br.s), 7.25–7.31 (2H, overlapping), 7.43–7.53 (3H, overlapping), 9.75 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=53.8$ (t), 110.0 (d), 114.3 (d), 118.3 (t), 121.5 (d), 125.4 (s), 128.7 (d), 129.5 (d), 130.0 (d), 133.6 (d), 143.2 (s), 161.5 (s). Anal. calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found C, 74.22; H, 6.43; N, 12.29.

3.2.4. *N*-Allyl-*N*-cyclohexyl-pyrrolo-2-carboxamide (2d). Eluent: AcOEt/light petroleum 1:5. Yield: 68%. Mp 109–110 °C (from diisopropyl ether). IR (nujol): 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.09$–1.20 (1H, m), 1.27–1.48 (2H, overlapping), 1.50–1.62 (2H, overlapping), 1.65–1.75 (1H, m), 1.78–1.85 (4H, overlapping), 4.18 (2H, d, $J=5.2$ Hz), 4.43 (1H, tt, $J=3.1$, 11.9 Hz), 5.19 (1H, d, $J=10.0$ Hz) 5.26 (1H, d, $J=17.4$ Hz), 5.92 (1H, tdd, $J=5.2$, 10.0, 17.4 Hz), 6.24 (1H, d, $J=2.9$ Hz), 6.56 (1H, br.s), 6.93 (1H br.s), 10.34 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=26.0$ (t), 26.4 (t), 31.5 (t), 46.7 (d), 56.8 (t), 109.6 (d), 112.3 (d), 116.3 (t), 121.7 (d), 125.5 (s), 136.6 (d), 163.1 (s). Anal. calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found C, 74.41; H, 8.52; N, 12.12.

3.2.5. *N*-Allyl-*N*-cyclopenthyl-pyrrolo-2-carboxamide (2e). Eluent: AcOEt/light petroleum 1:6. Yield: 67%. Mp 94–95 °C (from diisopropyl ether). IR (nujol): 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.53$–1.82 (6H, overlapping), 1.85–2.09 (2H, overlapping), 4.16 (2H, d, $J=4.5$ Hz), 4.78–4.89 (1H, m), 5.23 (1H, d, $J=12.3$ Hz), 5.27 (1H, d, $J=18.4$ Hz), 5.94 (1H, tdd, $J=4.5$, 12.3, 18.4 Hz), 6.22 (1H, ddd, $J=2.6$, 2.7, 2.9 Hz), 6.60 (1H, br.s), 6.92 (1H, br.s), 10.50 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=24.2$ (t), 24.3 (t), 47.2 (d), 58.8 (t), 109.6 (d), 112.3 (d), 116.3 (t), 121.7 (d), 125.5 (s), 136.1 (d), 163.6 (s). Anal.

calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found C, 71.39; H, 8.51; N, 12.92.

3.3. General procedure for the cyclization to give pyrrolo[1,2-*a*]pyrazin-1-ones 3a–e

To a solution of **2a–e** (1 mmol) in DMSO (5 ml), AcONa (82 mg, 1 mmol), Bu_4NCl (277 mg, 1 mmol) and $Pd(OAc)_2$ (22.4 mg, 0.1 mmol) were added. The mixture was stirred for 72 h at 120 °C. The solution was washed with brine (50 ml) and extracted with Et_2O (2×50 ml). The organic layer was dried over Na_2SO_4 and taken to dryness under reduced pressure. The residue was chromatographed on a silica gel column to give **3a–e**.

3.3.1. 2,4-Dimethyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (3a). Eluent: Et_2O/light petroleum 1:4. Yield: 62%. Oil. IR (nujol): 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 2.31 (3H, s), 3.46 (3H, s), 6.20 (1H, s), 6.62 (1H, dd, J=2.7, 3.9 Hz), 7.08 (1H, dd, J=1.6, 2.7 Hz), 7.18 (1H, dd, J=1.6, 3.9 Hz). ^{13}C NMR (100 MHz, $CHCl_3$): δ=14.9 (q), 41.2 (q), 110.6 (d), 112.8 (d), 115.8 (s), 115.9 (d), 116.1 (d), 124.7 (s), 156.4 (s). Anal. calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found C, 66.60; H, 6.45; N, 17.32.

3.3.2. 2-Allyl-4-methyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (3b). Eluent: Et_2O/light petroleum 1:4. Yield: 85%. Oil. IR (nujol): 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 2.30 (3H, s), 4.49 (2H, d, J=5.8 Hz), 5.21 (1H, d, J= 16.5 Hz), 5.25 (1H, d, J=11.3 Hz), 5.93 (1H, tdd, J=5.8, 11.3, 16.5 Hz), 6.17 (1H, s), 6.61 (1H, dd, J=2.4, 2.9 Hz), 7.08 (1H, dd, J=1.8, 2.4 Hz) 7.18 (1H, dd, J=1.8, 2.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.1 (q), 48.9 (t), 111.7 (d), 112.9 (d), 114.4 (d), 116.3 (d), 116.1 (s), 118.4 (t), 124.6 (s), 133.4 (d), 155.9 (s). Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found C, 70.29; H, 6.25; N, 14.97.

3.3.3. 4-Methyl-2-phenyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (3c). Eluent: AcOEt/light petroleum 1:4. Yield: 57%. Oil. IR (nujol): 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=2.36 (3H, s), 6.42 (1H, s), 6.68 (1H, dd, J=3.6, 2.8 Hz), 7.16 (1H, d, J=2.8 Hz), 7.28 (1H, d, J=3.6 Hz), 7.33–7.55 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.1 (q), 112.4 (d), 113.2 (d), 116.0 (d), 116.1 (s), 116.7 (d), 124.7 (s), 127.1 (d), 128.1 (d), 129.7 (d), 140.6 (s), 155.6 (s). Anal. calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found C, 74.87; H, 5.59; N, 12.57.

3.3.4. 2-Cyclohexyl-4-methyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (3d). Eluent: AcOEt/light petroleum 1:4. Yield: 89%. Oil. IR (nujol): 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.10–1.35 (1H, m), 1.42–1.65 (4H, overlapping), 1.67–1.79 (1H, m), 1.83–1.95 (4H, overlapping), 2.32 (3H, s), 4.76–4.85 (1H, m), 6.26 (1H, s), 6.61 (1H, dd, J=2.8, 3.7 Hz), 7.07 (1H, dd, J=1.1, 2.8 Hz), 7.17 (1H, dd, J=1.1, 3.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.4 (q), 25.7 (t), 26.1 (t), 32.4 (t), 52.1 (d), 110.7 (d), 110.9 (d), 112.8 (d), 115.6 (d), 115.7 (s) 124.8 (s) 155.7 (s). Anal. calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found C, 72.93; H, 8.02; N, 12.12.

3.3.5. 2-Cyclopenthyl-4-methyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (3e). Eluent: AcOEt/light petroleum 1:7. Yield: 82%. Oil. IR (nujol): 1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.55–1.94 (6H, overlapping), 2.03–2.19 (2H, overlapping), 2.34 (3H, s), 5.37 (1H, dddd, J=8.2, 8.2, 8.2, 8.2 Hz), 6.21 (1H, s), 6.61 (1H, dd, J=3.2, 3.8 Hz), 7.07 (1H, br.s), 7.16 (1H, d, J=3.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.5 (q), 25.0 (t), 31.8 (t), 54.0 (d), 110.7 (d), 111.0 (d), 112.9 (d), 115.7 (d), 116.3 (s), 124.7 (s), 156.2 (s). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found C, 72.11; H, 7.53; N, 12.83.

3.4. General procedure for the cyclization to give pyrrolo[2,3-*c*]pyridin-7-ones (4a–e) and pyrrolo[3,2-*c*]-pyridin-4-ones (5a–e)

To a solution of **2a–e** (1 mmol) in DMF (6 ml) and THF (12 ml), $PdCl_2(CH_3CN)_2$ (389 mg, 0.15 mmol) and *p*-benzoquinone (108, 1 mmol) were added under N_2. The mixture was stirred for 18 h at 100 °C, then poured into brine (30 ml) and extracted with Et_2O (2×25 ml). The solvent evaporated to give a residue that was chromatographed on silica gel column to give the compounds **4a–e** and **5a–e**.

Entry a. Elution with CH_2Cl_2/MeOH 10:1 gave **4a** (30%) and **5a** (35%).

3.4.1. 4,6-Dimethyl-1,6-dihydro-pyrrolo[2,3-*c*]pyridin-7-ones (4a). Mp 238–239 °C (from diisopropyl ether). IR (nujol): 3394, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=2.26 (3H, s), 3.67 (3H, s), 6.41 (1H, dd, J=2.3, 2.5 Hz), 6.74 (1H, s), 7.31 (1H, d, J=2.3 Hz), 10.21 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.6 (q), 36.4 (q), 102.0 (d), 112.0 (s), 123.8 (s), 126.3 (d), 127.5 (d), 132.5 (s), 155.6 (s). Anal. calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found C, 66.49; H, 6.35; N, 17.13.

3.4.2. 5,7-Dimethyl-1,5-dihydro-pyrrolo[3,2-*c*]pyridin-4-ones (5a). Mp 243–245 °C (from diisopropyl ether). IR (nujol): 3260, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=2.27 (3H, s), 3.62 (3H, s), 6.85 (1H, s), 6.88 (1H, dd, J= 2.5, 2.6 Hz), 7.03 (1H, dd, J=2.6, 2.6 Hz), 9.08 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7 (q), 36.9 (q), 105.3 (s), 106.1 (d), 115.3 (s), 122.2 (d), 129.7 (d), 139.7 (s), 160.0 (s). Anal. calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found C, 66.47; H, 6.38; N, 17.12.

Entry b. Elution with CH_2Cl_2/MeOH 10:1 gave **4b** (33%) and **5b** (31%).

3.4.3. 6-Allyl-4-methyl-1,6-dihydro-pyrrolo[2,3-*c*]pyridin-7-ones (4b). Mp 211–212 °C (from diisopropyl ether). IR (nujol): 3389, 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=2.27 (3H, s), 4.72 (2H, d, J=5.6 Hz), 5.17 (1H, d, J= 17.1 Hz), 5.24 (1H, d, J=10.2 Hz), 6.02 (1H, ddd, J=5.6, 10.2, 17.1 Hz), 6.37 (1H, br.s), 6.70 (1H, s), 7.30 (1H, br.s), 10.48 (1H, br.s). ^{13}C NMR (100 MHz, $CHCl_3$): δ=15.7 (q), 50.3 (t), 102.1 (d), 112.3 (s), 117.6 (t), 123.8 (s), 125.1 (d), 127.5 (d), 132.5 (s), 134.1 (d), 155.0 (s). Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found C, 70.24; H, 6.33; N, 15.00.

3.4.4. 5-Allyl-7-methyl-1,5-dihydro-pyrrolo[3,2-*c*]pyridin-4-ones (5b). Mp 86–87 °C (from diisopropyl ether).

IR (nujol): 3270, 1649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.26$ (3H, s), 4.67 (2H, d, $J=5.6$ Hz), 5.16 (1H, d, $J=17.1$ Hz), 5.21 (1H, d, $J=10.3$ Hz), 5.99 (1H, ddd, $J=5.6$, 10.3, 17.1 Hz), 6.81 (1H, s), 6.88 (1H, dd, $J=2.6$, 2.6 Hz), 7.01 (1H, dd, $J=2.6$, 2.7 Hz), 8.80 (1H, br.s); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.7$ (q), 50.4 (t), 105.1 (s), 106.5 (d), 115.7 (s), 117.7 (t), 121.9 (d), 128.5 (d), 134.3 (d), 139.4 (s), 159.7 (s). MS: *m/z* 188 (M^+). Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found C, 70.16; H, 6.55; N, 14.73.

Entry c. Elution with CH_2Cl_2/MeOH 15:1 gave **4c** (27%) and **5c** (41%).

3.4.5. 4-Methyl-6-phenyl-1,6-dihydro-pyrrolo[2,3-*c*]-pyridin-7-ones (4c). Mp 128–129 °C (from diisopropyl ether). IR (nujol): 3385, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.30$ (3H, s), 6.43 (1H, br.s), 6.84 (1H, s), 7.28 (1H, br.s), 7.35–7.55 (5H, overlapping), 10.75 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=15.5$ (q), 102.7 (d), 107.9 (s), 123.6 (s), 126.6 (d), 127.6 (d), 127.7 (d), 128.3 (d), 129.5 (d), 132.7 (s), 141.7 (s), 155.1 (s). Anal. calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found C, 74.89; H, 5.43; N, 12.52.

3.4.6. 7-Methyl-5-phenyl-1,5-dihydro-pyrrolo[3,2-*c*]-pyridin-4-ones (5c). Mp 83–84 °C (from diisopropyl ether). IR (nujol): 3268, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.23$ (3H, s), 6.87 (1H, dd, $J=2.6$, 2.6 Hz), 6.90 (1H, br.s), 6.97 (1H, dd, $J=2.6$, 2.8 Hz), 7.32–7.54 (5H, overlapping), 9.27 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.7$ (q), 106.1 (d), 106.3 (s), 115.3 (s), 123.0 (d), 127.8 (d), 128.2 (d), 129.3 (d), 129.4 (d), 140.0 (s), 142.2 (s), 160.1 (s). Anal. calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found C, 75.03; H, 5.25; N, 12.52.

Entry d. Elution with CH_2Cl_2/MeOH 20:1 gave **4d** (38%) and **5d** (45%).

3.4.7. 6-Cyclohexyl-4-methyl-1,6-dihydro-pyrrolo[2,3-*c*]pyridin-7-ones (4d). Mp 120–121 °C (from diisopropyl ether). IR (nujol): 3396, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.15$–1.40 (1H, m), 1.42–1.67 (4H, overlapping), 1.74–1.83 (1H, m), 1.91–2.01 (4H, overlapping), 2.30 (3H, s), 5.03 (1H, tt, $J=3.2$, 11.6 Hz), 6.39 (1H, dd $J=2.4$, 2.7 Hz,), 6.82 (1H, s), 7.29 (1H, dd $J=2.7$, 2.7 Hz), 10.35 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.0$ (q), 25.9 (t), 30.1 (t), 33.3 (t), 53.9 (d), 102.3 (d), 112.3 (s), 121.4 (d), 127.4 (s), 127.6 (d), 130.7 (s), 150.5 (s). Anal. calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found C, 73.13; H, 7.72; N, 12.25.

3.4.8. 5-Cyclohexyl-7-methyl-1,5-dihydro-pyrrolo[3,2-*c*]pyridin-4-ones (5d). Mp 251–255 °C (from diisopropyl ether). IR (nujol): 3261, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.15$–1.42 (1H, m), 1.44–1.63 (4H, overlapping), 1.70–1.78 (1H, m), 1.84–2.01 (4H, overlapping), 2.27 (3H, s), 5.01–5.15 (1H, m), 6.88 (1H, dd, $J=2.5$, 2.7 Hz), 6.90 (1H, s), 7.00 (1H, dd, $J=2.7$, 2.6 Hz), 8.85 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.0$ (q), 25.9 (t), 26.4 (t), 33.3 (t), 53.2 (d), 102.3 (d), 111.6 (s), 121.4 (d), 123.8 (s), 126.7 (d), 131.4 (s), 154.6 (s). Anal. calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found C, 72.98; H, 7.95; N, 12.13.

Entry e. Elution with CH_2Cl_2/MeOH 27:1 gave **4e** (29%) and **5e** (48%).

3.4.9. 6-Cyclopentyl-4-methyl-1,6-dihydro-pyrrolo[2,3-*c*]pyridin-7-ones (4e). Mp 119–120 °C (from diisopropyl ether). IR (nujol): 3385, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.66$–1.82 (4H, overlapping), 1.83–2.00 (2H, overlapping), 2.14–2.28 (2H, overlapping), 2.29 (3H, s), 5.53 (1H, dddd, $J=8.1$ Hz), 6.37 (1H, br.s), 6.77 (1H, s), 7.27 (1H, br.s), 10.66 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.0$ (q), 25.1 (t), 32.8 (t), 55.2 (d), 102.2 (d), 112.2 (s), 121.4 (d), 123.7 (s), 127.0 (d), 131.5 (s), 155.2 (s). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found C, 72.02; H, 7.53; N, 12.99.

3.4.10. 5-Cyclopentyl-7-methyl-1,5-dihydro-pyrrolo[3,2-*c*]pyridin-4-ones (5e). Mp 135–136 °C (from diisopropyl ether). IR (nujol): 3256, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.52$–1.83 (4H, overlapping), 1.84–2.01 (2H, overlapping), 2.10–2.28 (2H, overlapping), 2.29 (3H, s), 5.53 (1H, dddd, $J=8.0$ Hz), 6.88 (1H, dd, $J=2.3$, 2.6 Hz), 6.90 (1H, s), 7.01 (1H, dd, $J=2.6$, 2.7 Hz), 9.22 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.2$ (q), 25.0 (t), 32.9 (t), 55.4 (d), 106.5 (d), 115.1 (s), 116.6 (d), 124.9 (d), 139.1 (s), 150.1 (s), 159.9 (s). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found C, 72.05; H, 7.56; N, 12.97.

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