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Metal/organo relay catalysis in a one-pot synthesis of methyl 4-aminopyrrole-2-carboxylates from 5-methoxyisoxazoles and pyridinium ylides

Ekaterina E. Galenko, Olesya A. Tomashenko, Alexander F. Khlebnikov, Mikhail S. Novikov

Methyl 4-aminopyrrole-2-carboxylates were synthesized in one-pot mode by the relay catalytic cascade reaction of 5-methoxyisoxazoles with pyridinium ylides by use of a FeCl2/Et3N binary catalytic system leading to 1-(5-methoxycarbonyl-1H-pyrrol-3-yl)pyridinium salts followed by hydrazinolysis. The approach permits the introduction of a substituent at the pyrrole nitrogen via a nucleophilic reaction of the pyrrolopyridinium ylide derived from the salt. Catalytic reduction of the ylides gives methyl 4-piperidinopyrrole-2-carboxylates.

Introduction

Derivatives of 4-aminopyrrole-2-carboxylic acid demonstrate various biological activities. We mention here only recently published works on the topic. 4-Aminopyrrole-2-carboxylates are particularly important building blocks for synthesis and biosynthesis of pyrrole-based polypeptides possessing antibiotic, antiviral and cytotoxic properties. The use of derivatives of 4-aminopyrrole-2-carboxylic acid in the synthesis of various heterocycles or ensembles with other heterocyclic systems, permits the preparation of such compounds as poly(ADP-ribosyl) polymerase-1 inhibitors, dual inhibitors of Aurora kinases and cyclin dependent kinase 1, androgen receptor antagonists, inhibitors of the phosphodiesterase 4 enzyme.

4-Aminopyrrole-2-carboxylates can be synthesized by reduction of the corresponding nitro-, nitroso-, azo-compounds and azides or by aminodecarboxylation of alkyl 4-carboxypyrrole-2-carboxylates via the Curtius rearrangement. A series of benzyl 4-(N-substituted-amino)-1H-pyrrole-2-carboxylates was synthesized by treatment of N-(9-phenylfluoren-9-yl)-4-oxoprolin benzyl ester with primary and secondary amines. Benzyl 4-aminopyrrole-2-carboxylate was prepared by Pd(PPh3)4/N,N-dimethylbarbituric acid induced deprotection of the corresponding N-allyl derivative.

An example of the formation of a 3-aminopyrrole derivative from a cyclic precursor is the cyclization of dimethyl 2-((cyano(phenyl)methyl)aminobutenedioate, providing dimethyl 4-amino-5-phenyl-1H-pyrrole-2,3-dicarboxylate.

Two approaches to 4-aminopyrrole-2-carboxylates involving the formation of two bonds of the pyrrole ring were also reported. In the first, the C2-C3 and C4-C5 bonds of the aminopyrrole system were formed via a two-step procedure. The EWG-substituted primary ketene N,O-acetals react with dimethyl tetrazene-3,6-dicarboxylate to furnish tetrafunctionalized pyridazines via [4+2] cycloaddition (Scheme 1, reaction 1).

The latter, possessing an EWG, primary amino- and two ester groups, undergoes reductive ring contraction to give the corresponding 4-aminopyrrole-2,5-dicarboxylates. In the second approach, the N-C2 and C3-C4 bonds of the pyrrole ring were formed by the reaction of 3-amino-2-phenylcarbamoyl-2H-azirine with dimethyl acetylenedicarboxylate, giving 3-amino-4,5-dimethoxycarbonyl-2-phenylcarbamoylpyrrole, albeit in low yield (Scheme 1, reaction 2). To expand the use of the valuable pyrrole derivatives discussed above for medicinal...
chemistry, there is still a need to develop new methods for the preparation of 4-aminopyrrole-2-carboxylates because the known methods often do not tolerate a wide range of functional groups and have limitations in changing the substituents at positions 1, 3 and 5.

We report here a new approach for the construction of the 4-aminopyrrole-2-carboxylate backbone via the formation of the C3-C4 and N-C5 pyrrole bonds from 5-methoxyisoxazoles and pyridinium salts, which can be performed as a one-pot procedure (Scheme 1, reaction 3).

Results and discussion

Earlier we disclosed the reaction of 2-aryl-substituted 2H-azirines with pyridinium ylides leading to 1-(1H-pyrrolo-3-yl)pyridinium salts. It is also known, that FeCl2·4H2O effectively catalyzes the isomerization of 3-aryl-5-methoxyisoxazoles to methyl 3-aryl-2H-azirine-2-carboxylates. Recently this transformation was used to prepare 4-acylpyrrole-2-carboxylic acid derivatives by the domino reaction of 3-aryl-5-methoxyisoxazoles with 1,3-dicarbonyl compounds under relay catalysis.

Taking into account all these facts, we envisioned that the synthesis of alkyl 3-alkyl/aryl-4-amino-5-arylpentra-2-carboxylates could be carried out starting from easily available 3-alkyl/aryl-5-alkoxyisoxazoles and N-phenacylpyridinium salts according to Scheme 2. This synthetic scheme implies the possibility of an implementation of parallel and sequential stages (a: the generation of azirine from isoxazole under FeCl2·4H2O catalysis; b: the formation of phenacylpyridinium ylides catalyzed by Et3N; c: activation of azirine with Et3HN+Br−; d: reaction of the activated azirine with the pyridinium ylide, leading to 1-(1H-pyrrolo-3-yl)pyridinium salt) as a domino process under relay catalysis, which does not involve isolation of the often unstable 2H-azirines. The last stage on the way to aminopyrroles, a Zincke cleavage of the pyridinium salts, can hardly be coupled with the previously mentioned domino process, because there is a possibility that a Zincke ring opening reaction of salt will occur, but the implementation of Scheme 2 as a one-pot procedure is not excluded.

Scheme 2. The mechanistic representation of the synthetic route to methyl 4-aminopyrrole-2-carboxylates.

The reaction of aryl-substituted 2H-azirines with pyridinium ylides leading to 1-(1H-pyrrolo-3-yl)pyridinium salts is usually performed in CH2Cl2 at room temperature. Since acetonitrile is the solvent of choice for the transformation of 3-aryl-5-methoxyisoxazoles to alkyl 3-aryl-2H-azirine-2-carboxylates under FeCl2·4H2O catalysis, the test reaction of methyl 3-phenyl-2H-azirine-2-carboxylate was carried out in MeCN at 20 °C. The 1-(1H-pyrrolo-3-yl)pyridinium bromide was obtained in 40% yield after stirring for 36 h. It was decided to be performed the reaction of the isoxazoles with the pyridinium salts at a slightly higher temperature (45 °C) to accelerate the reaction of the pyridinium ylide with transient azirine and thus prevent its decomposition. A very simple procedure, consisting of stirring a mixture of isoxazole 1, pyridinium salt 2, FeCl2·4H2O and Et3N in MeCN at 45 °C gave compounds 5 in reasonable yields, except for the isoquinolinium derivative 6 (Table 1). All new compounds were characterized by 1H and 13C NMR, IR spectroscopy, and mass-spectrometry.

According to a recent paper, 2H-chromen-3-pyridinium chlorides can be efficiently transformed via the Zincke ring opening reaction into the corresponding amino-substituted heterocycles using N-methylpiperazine. The reaction of pyridinium salt 5b with N-methylpiperazine led, however, to the tarring of the reaction mixture and only traces of the corresponding amine were detected. We tested, therefore, the traditional reagent, hydrazine hydrate, to induce Zincke cleavage of the N-heterocycl-pyridinium salts, affording the corresponding heterocyclylamines. The reaction of hydrazine hydrate with pyridinium salt 5b led cleanly to the corresponding amine and consequently this reagent was used in the developed one-pot transformation of 5-
methoxyisoxazoles 1 and N-(2-aryl-2-oxoethyl)pyridinium bromides 2 to methyl 4-aminopyrrole-2-carboxylates 6.

Table 1 Synthesis of 1-(1H-pyrrolo-3-yl)pyridinium bromides 5 by the reaction of 5-methoxyisoxazoles 1 and N-(2-aryl-2-oxoethyl)pyridinium bromides 2

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<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
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The alkylation provides a good yield of the N-alkylation product being produced prior to the deprotection of the amino group by hydrazinolysis. Thus, pyridinium ylide 7a was converted into N-benzyl derivative with benzyl bromide in the presence of potassium carbonate. The deprotection of the N-benzylpyridinium salt 8 gave aminopyrrole 9 in high yield.

Table 2 Synthesis of 4-aminopyrrole-2-carboxylates 6 via the one-pot procedure

<table>
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<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>1+2</th>
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<td>1d+2c</td>
<td>6i, 38</td>
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<sup>a</sup> Step wise procedure.

This approach has an important advantage over the above mentioned methodologies 1 and 2 (Scheme 1) since only here is it possible to make the simple introduction of a substituent at the pyrrole nitrogen of compounds 6 via nucleophilic reaction of the corresponding pyridinium ylide. Pyridinium salts 5 were converted in high yield into the corresponding stable pyridinium ylides 7 by the action of potassium hydroxide under very mild conditions (Scheme 3). The ester group remains intact under this procedure.

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Conclusions

A convenient and efficient approach was developed for the synthesis of methyl 4-aminopyrrole-2-carboxylates from easily available compounds, 5-methoxyisoxazoles and phenacylpyridinium salts. The innovation of this synthetic route consists in an implementation of parallel and sequential reaction stages (the generation of an azirine from isoxazoles, the formation of phenacylpyridinium ylide, the activation of azirine, the reaction of the activated azirine with pyridinium ylide) as a domino process under relay catalysis, followed by a one-pot Zincke cleavage of the resulting pyridinium salts. The approach permits the introduction of a substituent at the pyrrole nitrogen via a nucleophilic reaction of the corresponding pyrrolylpyridinium ylide under very mild conditions.
conditions. Catalytic hydrogenation of the pyrrolypyridinium ylides gave 4-piperidino-substituted methyl 1H-pyrrole-2-carboxylates.

Experimental

General

Melting points were determined on a capillary melting point apparatus Stuart® SMP30. 1H (400 MHz) and 13C (100 MHz) NMR spectra were determined in CDCl3 or DMSO-d6 with Bruker AVANCE III 400. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane (TMS δ = 0.00); 1H NMR spectra were calibrated according to the residual peak of CDCl3 (7.26 ppm) or DMSO-d6 (2.50 ppm). For all new compounds 13C(1H) and 13C DEPT135 were recorded and calibrated according to the peak of CDCl3 (77.00 ppm) or DMSO-d6 (39.51 ppm). Mass spectra were recorded on a Bruker maXis HRMS-QTOF, electrospray ionization, positive mode. IR-spectra were recorded on a Bruker FT-IR spectrometer Tensor 27 for tablets in KBr, only characteristic absorption is indicated. Thin-layer chromatography (TLC) was conducted on aluminium sheets with 0.2 mm silica gel (fluorescent indicator, Macherey-Nagel). The pyridinium salts25 and isoxazoles26 were synthesized by known literature procedures.

Synthesis of N-pyrrolypyridinium salts 5

General procedure for the synthesis of N-pyrrolypyridinium salts 5 from isoxazoles 1 and N-phenacylpyridinium bromides 2.

Isoxazole 1 (1.2–1.5 mmol) and pyridinium salt 2 (1.0 mmol) were suspended in MeCN (4 mL), FeCl3-4H2O (0.06–0.08 mmol, 5 mol% calc'd on isoxazole) and Et3N (3.0 mmol) were added, and the mixture was stirred at 45 °C (6–7 h, monitored by TLC). Reaction mixture was evaporated to dryness, ethyl acetate was added and the precipitate formed was filtered off and the mixture was stirred at 45 °C (6–7 h, monitored by TLC). Light rose solid, mp 245–246 °C (dec.) (ethyl acetate/CH2Cl2).

1H NMR (DMSO-d6): δ = 3.70 (s, 3H), 7.22–7.24 (m, 2H), 7.27–7.30 (m, 5H), 7.38–7.41 (m, 3H), 8.15–8.19 (m, 2H), 8.69–8.73 (m, 1H), 9.10–9.12 (m, 2H), 13.18 (br s, 1H). 13C NMR (DMSO-d6): δ = 51.6, 118.0, 124.8, 126.7, 127.1, 127.9, 129.7, 129.8, 128.4, 128.9, 129.3, 129.7, 130.9, 134.7, 147.7, 160.2. ESI/HRMS (m/z): 355.1441 calcd for C23H19N2O2 [M – Br]+, found 355.1438. IR (KBr, cm−1): v = 3397, 2986, 1707, 1626.

1-(2-(4-Chlorophenyl)-5-(methoxyacrylic)-4-phenyl-1H-pyrrol-3-y1)pyridine-1-ium bromide (5c). Compound 5c (280 mg, 75%) was obtained from 5-methoxy-3-phenylisoxazole (1a) (175 mg, 1.00 mmol), 1-(2-(4-chlorophenyl)-2-oxoethyl)pyridin-1-ium bromide (2c) (248 mg, 0.793 mmol), FeCl3-4H2O (10 mg, 0.05 mmol, 5% mol) and Et3N (245 mg, 2.42 mmol) according to the general procedure. Light rose solid, mp 245–246 °C (dec.) (ethyl acetate/CH2Cl2).

1H NMR (DMSO-d6): δ = 3.71 (s, 3H), 7.20–7.23 (m, 2H), 7.29–7.32 (m, 5H), 7.46–7.49 (m, 2H), 8.69–8.73 (m, 1H), 9.07–9.08 (m, 2H), 13.27 (br s, 1H). 13C NMR (DMSO-d6): δ = 51.6, 116.2, 124.9, 126.0, 126.7, 128.1, 128.1, 128.5, 129.0, 129.6, 129.7, 129.78, 129.83, 134.1, 147.5, 147.8, 160.2. ESI/HRMS (m/z): 389.1051 calcd for C23H18ClN2O2 [M – Br]+, found 389.1052. IR (KBr, cm−1): v = 3398, 3000, 1703, 1626.

1-(5-Methoxyacrylicyl)-2-(4-methylphenyl)-4-phenyl-1H-pyrrol-3-yl)pyridine-1-ium bromide (5d). Compound 5d (247 mg, 64%) was obtained from 5-methoxy-3-phenylisoxazole (1a) (175 mg, 1.00 mmol), 1-(2-(4-methylphenyl)-2-oxoethyl)pyridin-1-ium bromide (2d) (259 mg, 0.802 mmol), FeCl3-4H2O (10 mg, 0.05 mmol) and Et3N (245 mg, 2.42 mmol) according to the general procedure. Light rose solid, mp 249–250 °C (dec.) (ethyl acetate/CH2Cl2).

1H NMR (DMSO-d6): δ = 3.73 (s, 3H), 7.21–7.24 (m, 2H), 7.29–7.31 (m, 3H), 7.54–7.56 (m, 2H), 8.18–8.21 (m, 2H), 8.22–8.24 (m, 2H), 8.72–8.76 (m, 1H), 9.12–9.13 (m, 2H), 13.53 (br s, 1H). 13C NMR (DMSO-d6): δ = 51.8, 119.3, 124.0, 125.7, 127.0, 128.1, 128.5, 128.7, 129.1, 129.6, 129.7, 133.4, 147.3, 147.4, 148.0, 160.1. ESI/HRMS (m/z): 400.1292 calcd for C23H18ClN2O2 [M – Br]+, found 400.1293. IR (KBr, cm−1): v = 3439, 2997, 1724.

1-(2-(2-Bromophenyl)-5-(methoxycarbonyl)-4-phenyl-1H-pyrrol-3-yl)pyridine-1-ium bromide (5a). Compound 5a (292 mg, 71%) was obtained from 5-methoxy-3-phenylisoxazole (1a) (175 mg, 1.00 mmol), 1-(2-(2-bromophenyl)-2-oxoethyl)pyridin-1-ium bromide (2a) (286 mg, 0.801 mmol), FeCl3-4H2O (10 mg, 0.05 mmol) and Et3N (245 mg, 2.42 mmol) according to the general procedure. Light rose solid, mp 185–187 °C (ethyl acetate).

1H NMR (DMSO-d6): δ = 3.72 (s, 3H), 7.25–7.29 (m, 2H), 7.30 (m, 3H), 7.40–7.44 (m, 1H), 7.50–7.54 (m, 1H), 7.65–7.69 (m, 2H), 8.07–8.11 (m, 2H), 8.60–8.65 (m, 1H), 8.85–8.87 (m, 2H), 13.31 (br s, 1H). 13C NMR (DMSO-d6): δ = 51.6, 118.1, 123.3, 125.0, 125.7, 128.0, 128.1, 128.15, 128.22, 128.3, 129.6, 129.7, 129.9, 132.0, 132.7, 133.5, 147.0, 147.5, 160.0. ESI/HRMS (m/z): 433.0546 calcd for C23H18BrN2O2+ [M – Br]+, found 433.0563. IR (KBr, cm−1): v = 3403, 2998, 1714, 1625.

1-(5-(Methoxycarbonyl)-2,4-diphenyl-1H-pyrrol-3-yl)pyridine-1-ium bromide (5b). Compound 5b (294 mg, 84%) was obtained from 5-methoxy-3-phenylisoxazole (1a) (175 mg, 1.00 mmol), 1-(2-(2-phenethyl)pyridin-1-ium bromide (2b) (223 mg, 0.802 mmol), FeCl3-4H2O (10 mg, 0.05 mmol) and Et3N (245 mg, 2.42 mmol) according to the general procedure. Light rose solid, mp 240–243 °C (dec.) (ethyl acetate/CH2Cl2).
Compound 5f (306 mg, 70%) was obtained from 5-methoxy-3-(4-methyl-2-phenyl-1H-pyrryl-3-yl)pyridin-1-ium bromide (5h). ESI/HRMS (m/z): 465.0633 calcd for C24H20BrN2O3 [M – Br]+, found 510.9675. IR (KBr, cm⁻¹): v 3404, 2947, 1699, 1626.

FeCl₂∙4H₂O (15 mg, 0.08 mmol) and Et₃N (300 mg, 3.0 mmol) were added, and the mixture obtained was stirred at 45°C till the completion of the reaction (6–7 h, monitored by TLC). Then the reaction mixture was evaporated to dryness. The residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH 40:1), additionally washed with Et₂O or water and dried to give analytically pure compound 6a.

Methyl 4-amino-5-(2-bromophenyl)-3-phenyl-1H-pyrryl-2-carboxylate (6a). Compound 6a (341 mg, 64%) was obtained from 5-methoxy-3-phenylisoxazole (1a) (304 mg, 1.74 mmol), FeCl₂∙4H₂O (0.06–0.08 mmol, 5% mol) and Et₂N (3.0 mmol) were added, and the mixture obtained was stirred at 45°C till the completion of the reaction (6–7 h, monitored by TLC). Hydrazine hydrate (10.0 mmol, 10 equiv) was added and the mixture was stirred at 45°C (6–7 h, monitored by TLC). Then the reaction mixture was evaporated to dryness. The residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH 40:1), additionally washed with Et₂O or water and dried to give analytically pure compound 6.
Methyl 4-amino-3,5-diphenyl-1H-pyrrole-2-carboxylate (6b). Compound 6b (183 mg, 63%) was obtained from 5-methoxy-3-phenylisoxazole (1a) (210 mg, 1.20 mmol), 1-(2-oxo-2-phenylethyl)pyridin-1-ium iodide (2b) (278 mg, 1.00 mmol), FeCl2·4H2O (12 mg, 0.06 mmol), Et3N (300 mg, 3.0 mmol) and hydrazine hydrate (500 mg, 10.0 mmol) according to the general procedure. Before chromatography the crude residue was washed with EtOH. Yellow solid, mp 160–162 °C (ether).

Methyl 4-amino-5-(2-chlorophenyl)-3-phenyl-1H-pyrrole-2-carboxylate (6c). Compound 6c (156 mg, 52%) was obtained from 5-methoxy-3-phenylisoxazole (1a) (194 mg, 1.11 mmol), 1-(2-(2,4-dichlorophenyl)-2-oxoethyl)pyridin-1-ium iodide (2c) (288 mg, 0.921 mmol), FeCl2·4H2O (11 mg, 0.06 mmol, 5% mol), Et3N (300 mg, 3.0 mmol) and hydrazine hydrate (500 mg, 10.0 mmol) according to the general procedure. Before chromatography the crude residue was washed with EtOH. Light yellow solid, mp 160–162 °C (ether).

Methyl 4-amino-5-(4-nitrophenyl)-3-phenyl-1H-pyrrole-2-carboxylate (6d). Compound 6d (90 mg, 42%) was obtained from 5-methoxy-3-phenylisoxazole (1a) (135 mg, 0.771 mmol), 1-(2-(4-chlorophenyl)-2-oxoethyl)pyridin-1-ium iodide (2d) (205 mg, 0.634 mmol), FeCl2·4H2O (8 mg, 0.04 mmol), Et3N (180 mg, 1.8 mmol) and hydrazine hydrate (300 mg, 6.0 mmol) according to the general procedure. Before chromatography the crude residue was washed with EtOH. Bright red solid, mp 211–216 °C (ether).

Methyl 4-amino-5-(3-bromophenyl)-3-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (6e). Compound 6e (203 mg, 53%) was obtained from 5-methoxy-3-phenylisoxazole (1a) (247 mg, 1.41 mmol), 1-(2-(2,4-dichlorophenyl)-2-oxoethyl)pyridin-1-ium iodide (2g) (368 mg, 1.20 mmol), FeCl2·4H2O (14 mg, 0.07 mmol), Et3N (300 mg, 3.0 mmol) and hydrazine hydrate (600 mg, 12.0 mmol) according to the general procedure. Colorless solid, mp 164–165 °C (ether/hexane).

Methyl 4-amino-5-(2,4-dimethylphenyl)-3-phenyl-1H-pyrrole-2-carboxylate (6f). Compound 6f (368 mg, 1.20 mmol), FeCl2·4H2O (14 mg, 0.07 mmol), Et3N (300 mg, 3.0 mmol) and hydrazine hydrate (500 mg, 10.0 mmol) according to the general procedure. Before chromatography the crude residue was washed with EtOH. Light grey solid, mp 169–170 °C (ether).

Methyl 4-amino-5-(3-bromophenyl)-3-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (6g). Compound 6g (17 mg, 63%) was obtained from 1-(2-(bromophenyl)-5-(methoxybenzoyl)-4-(4-methoxyphenyl)-1H-pyrrole-2-yl)pyridin-1-ium iodide (5f) (36 mg, 0.0661 mmol) and hydrazine hydrate (66 mg, 1.322 mmol). Colorless solid, mp 138–140 °C (ether/hexane).

1H NMR (CDCl3): δ = 3.24 (br s, 2H), 3.72 (s, 3H), 3.86 (s, 3H), 6.98 (d, J = 7.7 Hz, 2H), 7.26-7.30 (m, 1H), 7.32-7.39 (m, 3H), 7.54 (d, J = 8.7 Hz, 1H), 7.78 (s, 1H), 8.87 (br s, 1H). 13C NMR (CDCl3): δ = 51.3, 55.2, 113.7, 117.3, 119.1, 121.9, 123.4, 123.9, 124.8, 128.2, 126.9, 126.9, 129.7, 129.9, 130.1, 130.3, 130.7, 133.5, 160.7. ESI/HRMS (m/z): 403.0520 calcd for C18H15BrN2O2 [M + H]+, found 403.0476. IR (KBr, cm⁻¹): v 3314, 1662, 1450.

Methyl 4-amino-3-methyl-5-phenyl-1H-pyrrole-2-carboxylate (6h). Compound 6h (149 mg, 43%) was obtained from 5-methoxy-3-methylisoxazole (1c) (230 mg, 2.03 mmol), 1-(2-oxo-2-phenylethyl)pyridin-1-ium iodide (2b) (415 mg, 1.49 mmol), FeCl2·4H2O (20 mg, 0.10 mmol), Et3N (450 mg, 4.5 mmol) and hydrazine hydrate (750 mg, 15.0 mmol) according to the general procedure. Colorless solid, mp 119–120 °C (ether/hexane).

1H NMR (CDCl3): δ = 2.28 (s, 3H), 3.13 (br s, 2H), 3.85 (s, 3H), 7.25-7.29 (m, 1H), 7.41-7.44 (m, 2H), 7.53-7.55 (m, 2H), 8.67 (br s, 1H). 13C NMR (CDCl3): δ = 9.1, 51.1, 117.3, 117.7, 121.4, 125.6, 126.8, 129.2, 131.9, 162.1. ESI/HRMS (m/z): 231.1128 calcd for C18H12N2O2 [M + H]+, found 231.1134. IR (KBr, cm⁻¹): v 3344, 1673.

Methyl 4-amino-5-(4-chlorophenyl)-3-methyl-1H-pyrrole-2-carboxylate (6i). Compound 6i (149 mg, 38%) was obtained from 5-methoxy-3-methylisoxazole (1c) (230 mg, 2.03 mmol), 1-(2-(4-chlorophenyl)-2-oxoethyl)pyridin-1-ium iodide (2e) (469 mg, 1.50 mmol), FeCl2·4H2O (20 mg, 0.10 mmol), Et3N (450 mg, 4.5 mmol) and hydrazine hydrate (750 mg, 15.0 mmol) according to the general procedure. Colorless solid, mp 148–151 °C (ether/hexane).

1H NMR (CDCl3): δ = 2.17 (s, 3H), 3.76 (s, 3H), 3.92 (s, 2H), 7.39-7.42 (m, 2H), 7.74-7.76 (m, 2H), 10.97 (br s, 1H). 13C NMR (CDCl3): δ = 9.2, 50.6, 116.9, 117.0, 121.3, 126.8, 126.9, 127.6, 128.0, 128.7, 130.0, 130.2, 131.5, 133.4, 137.2, 138.3, 161.6. ESI/HRMS (m/z): 321.1598 calcd for C18H12N2O2 [M + H]+, found 321.1657. IR (KBr, cm⁻¹): v 3310, 1670, 1452.
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General procedure for the synthesis of pyrrolylpyridinium ylides 7 from N-pyrrolylpyridinium salts 5

N-pyrrolylpyridinium salt 5 (1 mmol) was suspended in water (2 mL) and the excess of 2-5% aq KOH (2-4 mmol) was added. The suspension was stirred for 15 min, the solid was filtered off, washed with water and dried to give analytically pure compound.

5-(2-Bromophenyl)-2-(methoxycarbonyl)-3-phenyl-4-(pyridine-1-ium-1-yl)pyrrol-1-ide (7a). Compound 7 (324 mg, 96%) was obtained from 1-(2-(bromomethyl)-5-(methoxycarbonyl)-4-phenyl-1H-pyrrol-3-yl)pyridine-1-ium bromide (5a) (400 mg, 0.78 mmol) and aq solution of KOH (84 mg, 1.50 mmol, 4 mL H2O). Bright orange solid, mp >300 °C without melting. 1H NMR (CDCl3): δ = 3.78 (s, 3H), 7.10-7.14 (m, 1H), 7.20-7.26 (m, 2H), 8.47-8.51 (m, 1H), 8.95-8.96 (m, 2H). 13C NMR (CDCl3): δ = 50.5, 125.1, 125.2, 125.6, 126.9, 128.1, 128.3, 128.4, 129.0, 130.3, 132.2, 134.1, 134.3, 136.4, 140.9, 144.3, 165.1. ESI/HRMS (m/z): 433.0546 calcd for C23H19N2O2 [M + H]+, found 433.0543. IR (KBr, cm⁻¹): v 3430, 3033, 2929, 1618, 1576, 1500. 2H, 8.11-8.14 (m, 2H), 8.57-8.61 (m, 1H), 8.87-8.89 (m, 2H). 13C NMR (DMSO-d6): δ = 10.2, 49.5, 54.9, 113.7, 121.1, 125.5, 125.7, 126.8, 128.1, 128.9, 134.4, 144.2, 146.5, 157.1, 165.4. ESI/HRMS (m/z): 323.1390 calcd for C14H17NO4 [M + H]+, found 323.1401. IR (KBr, cm⁻¹): v 3528, 3393, 1670

Introduction of a substituent at the pyrrole nitrogen

1-(1-Benzyl-2-(2-bromophenyl)-5-(methoxycarbonyl)-4-phenyl-1H-pyrrol-3-yl)pyridine-1-ium bromide (8). A mixture of 5-(2-bromophenyl)-2-(methoxycarbonyl)-3-phenyl-4-(pyridine-1-ium-1-yl)pyrrol-1-ide (7a) (324 mg, 0.748 mmol), benzyl bromide (256 mg, 1.50 mmol) and K2CO3 (207 mg, 1.50 mmol) was stirred in MeCN (15 mL) for 3 h at room temperature. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography (CH2Cl2/MeOH 15:1) to give analytically pure compound as bright orange solid, 320 mg (71%), mp 188-189 °C. 1H NMR (CDCl3): δ = 3.54 (s, 3H), 5.31 (d, J = 15.6 Hz, 1H), 5.72 (d, J = 15.6 Hz, 1H), 6.99-7.01 (m, 2H), 7.22-7.32 (m, 9H), 7.40-7.44 (m, 1H), 7.50-7.52 (m, 1H), 7.84-8.06 (m, 1H), 8.06-8.09 (m, 2H), 8.47-8.51 (m, 1H), 8.95-8.96 (m, 2H). 13C NMR (CDCl3): δ = 50.5, 51.0, 150.0, 124.7, 124.8, 125.6, 126.6, 126.8, 127.7, 128.4, 128.5, 128.6, 128.7, 128.8, 129.9, 130.0, 132.6, 132.9, 133.2, 134.1, 135.1, 146.5, 146.6, 160.8. ESI/HRMS (m/z): 523.1016 calcd for C25H20BrN2O2 [M – Br]+, found 523.1033. IR (KBr, cm⁻¹): v 3028, 1709, 1626.

Methyl 4-amino-1-benzyl-5-(2-bromophenyl)-3-phenyl-1H-pyrrolyl-2-carboxylate (9). A solution of 1-(1-benzyl-2-(2-bromophenyl)-5-(methoxycarbonyl)-4-phenyl-1H-pyrrol-3-yl)pyridine-1-ium bromide (8) (300, 0.496 mmol) and hydrazine hydrate (250 mg, 5.00 mmol) in MeCN (10 mL) was stirred at 45 °C for 7 h. Then the reaction mixture was evaporated to dryness. The residue was purified by column chromatography on silica gel (CH2Cl2/MeOH 40:1), additionally washed with hexane and dried to give analytically pure compound as light yellow oil, 196 mg (86%). 1H NMR (CDCl3): δ = 2.90 (br s, 2H), 3.49 (s, 3H), 5.15 (d, J = 15.9 Hz, 1H), 5.63 (d, J = 15.9 Hz, 1H), 6.85-6.87 (m, 2H), 7.13-7.34 (m, 7H), 7.39-7.43 (m, 4H), 7.66-7.68 (m, 1H). 13C NMR (CDCl3): δ = 49.4, 50.7, 117.6, 122.5, 124.9, 125.0, 126.1, 126.7, 127.5, 127.8, 128.0, 128.2, 129.6, 131.8, 133.9, 141.2, 144.2, 145.9, 147.2, 164.3. ESI/HRMS (m/z): 400.1292 calcd for C23H19BrN2O2 [M + H]+, found 400.1306. IR (KBr, cm⁻¹): v 3319, 3065. 1695.

General procedure for the preparation of methyl 4-(piperidin-1-yl)-1H-pyrrolyl-2-carboxylates 10 by hydrogenation of pyrrolylpyridinium ylides 7

Hydrogen was passed through a suspension of ylide (100 mg) and Adams’ catalyst (10 mg, 10% w/w) in MeOH (2 mL) till the completion of the reaction (0.5-1.5 h, monitored by TLC). Then the reaction mixture was evaporated to dryness. The residue was purified by column chromatography on silica gel (CH2Cl2/MeOH 40:1), additionally washed with hexane and dried to give analytically pure compound 10.

Methyl 3,5-diphenyl-4-(piperidine-1-yl)-1H-pyrrolyl-2-carboxylate (10a). Compound 10a (107 mg, 88%) was obtained...
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Notes and references


