

Synthesis of 1,2-annulated and 1,2-unsubstituted pyrrolo[2,1,5-*de*]quinolizin-5-ones (cyclo[3.3.2]azin-5-ones) via [3+2] cycloadditions of 1-oxoquinolizinium ylides with cyclic alkenes†

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1,2-Annulated pyrrolo[2,1,5-*de*]quinolizin-5-ones (cyclo[3.3.2]azin-5-ones) **6a–6k**, **8a–8b** and **9** have been synthesized by one pot tandem reactions of 2-acetyl-*N*-phenacylpyridinium bromides (**1a–1d**) with electron-deficient cyclic alkenes (*N*-alkyl(aryl)maleimides, benzoquinones and naphthoquinone) in the presence of sodium carbonate as a base and tetrakispyridinecobalt(II) dichromate (TPCD) as an oxidant. These products are formed by 1,3-dipolar cycloaddition of the 1-oxoquinolizinium ylides generated *in situ* from **1a–1d** with the alkene followed by dehydrogenation of the primary cycloadduct under the action of TPCD. Similar reactions of the ylides generated *in situ* from **1a–1f** with maleic anhydride gave the 1,2-unsubstituted pyrrolo[2,1,5-*de*]quinolizin-5-ones **7a–7f** via oxidative bisdecarboxylation and dehydrogenation of the primary cycloadducts under the action of TPCD.

Introduction

Polycyclic heterocycles with a bridgehead nitrogen atom, especially those with an indolizine core, constitute an important class of compounds that have drawn much recent research attention for both theoretical and practical reasons.¹ Their unique electronic structure and special chemical reactivity have long been of theoretical interest.² Many of these annulated indolizine derivatives possess a wide variety of biological activity and are now playing an increasingly important role in designing new antitumor,³ anti-HIV⁴ and cardiovascular drugs.⁵ Moreover, their strong absorption and fluorescence in the UV-visible region with the wavelength sensitively depending on the annulation and ring substitution pattern make them remarkable structural motif in designing novel classes of dyes, biomarkers⁶ and electroluminescent materials.⁷ As a class of annulated indolizines, pyrrolo[2,1,5-*de*]quinolizines (cyclo[3.3.2]azines) belong to the general family of cyclazines according to the naming system of Boekelheide⁸ and Leaver.⁹ Beside the general interest in their biological activity and optoelectric properties, their partly hydrogenated structures have been found in several naturally occurring coccinellid alkaloids¹⁰ such as exochomine¹¹ and chilocorine A,¹² B,¹³ C¹⁴ and D.¹⁵ They are also homologues of the myrmecarin alkaloids.¹⁶ Therefore, they are interesting synthetic target compounds. Also, the growing attention given to annulated indolizine derivatives and the resulting demand for systematic examination of the structure–activity relationship have raised the task of developing new synthetic approaches for

convenient access of this class of compounds with diversified structures. However, there have not been many reports on the synthesis of pyrrolo[2,1,5-*de*]quinolizines up to now, and with these syntheses, only a small number of pyrrolo[2,1,5-*de*]quinolizines have been prepared, none of which are with further annulation to the parent tricyclic core.^{17–20} We report here a general and regioselective synthesis of 1,2-annulated pyrrolo[2,1,5-*de*]quinolizine-5-ones and 1,2-unsubstituted pyrrolo[2,1,5-*de*]quinolizine-5-ones by tandem reactions of the 1-hydroxyquinolizinium ylide with cyclic alkenes in the presence of the mild oxidant tetrakispyridinecobalt(II) dichromate [Py₄Co(HCrO₄)₂] (TPCD)²¹ in generally high yield in an one pot procedure.²²

Results and discussion

The 1- and 3-oxoquinolizinium betaines (**I** and **II** in Chart 1) can be generated by deprotonation of the 1- and 3-hydroxyquinolizinium salt, which in turn can be prepared by intramolecular aldol condensation of the 2-acetyl-*N*-phenacyl pyridinium salt and 2-benzoyl-*N*-acetyl pyridinium salt, respectively.²³ The 3-oxo betaine **II** was used as a dipole to take part in [3+2] cycloadditions for the synthesis of pyrrolo[2,1,5-*de*]quinolizin-3-ones.^{17,20} On the other hand, the only report so far on the use of the 1-oxo betaine (**I**) in [3+2] cycloaddition for the synthesis of the corresponding pyrrolo[2,1,5-*de*]quinolizin-5-ones was about the reactions with electron deficient alkenes in the presence of chromium oxide as an oxidant to give the products in rather low yield.²⁰ We have found that, by using cyclic alkenes as dipolarophiles and TPCD as a dehydrogenative oxidant, the [3+2] cycloadditions with **I** afforded the 1,2-annulated pyrrolo[2,1,5-*de*]quinolizin-5-ones in satisfactory yield. The pyridinium salts used to prepare the quinolizinium ylides and the cyclic alkenes used as dipolarophiles are listed in Chart 1.

Reaction of the 2-acetyl-*N*-phenacyl pyridinium salt (**1a**) with *N*-methylmaleimide (**2a**) under the typical reaction conditions for using TPCD in [3+2] cycloadditions of pyridinium ylide with alkene in DMF at 90 °C in the presence of sodium carbonate

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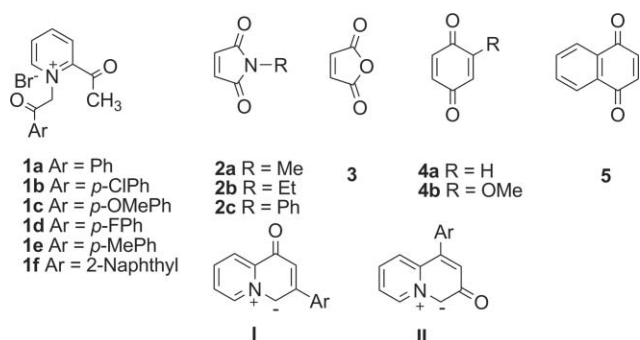
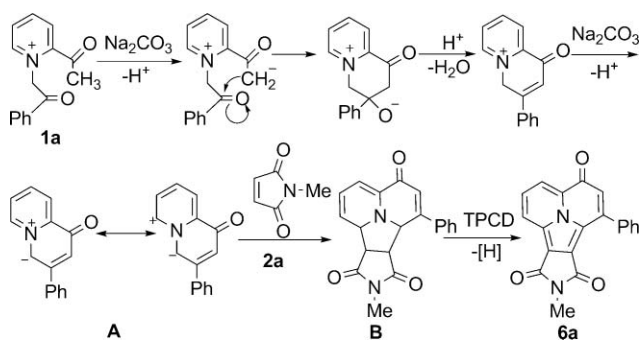


Chart 1

as a base and TPCD as the oxidant²¹ gave product **6a** in 80% yield. In this reaction, the 1-oxoquinolizinium ylide **A** generated *in situ* from **1a** took part in 1,3-dipolar cycloaddition with **2a** to give the primary cycloadduct **B**, which was dehydrogenated in the reaction mixture by TPCD to give the product **6a** (Scheme 1).



Scheme 1

Similar reactions of the ylides derived from **1a** with **2b** and **2c** and reactions of the ylides derived from **1b**, **1c** with **2a**, **2b** and **2c**, respectively, afforded the corresponding products **6b**, **6c** and **6d–6i**, respectively, in 65–88% yield. Reactions of the ylides from **1d** with **2a** and **2c**, respectively, afforded **6j** and **6k** in 91% and 80% yield (Chart 2).

Although an alternative mechanism as shown in Scheme 2 *via* an intramolecular aldol condensation of the indolizine product **10** could also be envisioned to rationalize the formation of product **6a**, we have not found even a trace amount of the indolizine product **10** in the reaction mixture after the completion of the reaction. Furthermore, it was found that when the quinolizinium ylide **A** was independently prepared and allowed to react with **2c** in DMF at 90 °C, the product **6c** was obtained in 65% yield. These facts suggest that the pyrrolo[2,1,5-*de*]quinolizin-5-ones **6a** is most likely formed by 1,3-dipolar cycloaddition of the ylide **A** with the maleimide **2a** as shown in Scheme 1.

We recently found that in the [3+2] cycloadditions of pyridinium ylides with maleic anhydride in the presence of the mild oxidant tetrakispyridinecobalt(II) dichromate (TPCD), TPCD caused the bisdecarboxylation of the primary cycloadduct to give 1,2-unsubstituted 3-acyl indolizines.²⁴ We have therefore further investigated the reactions of maleic anhydride with the pyridinium salts **1a–1f** respectively in the presence of sodium carbonate and TPCD and found that, these reactions gave the 1,2-unsubstituted 3-arylpyrrolo[2,1,5-*de*]quinolizin-5-ones **7a–7f**, respectively, in 62–

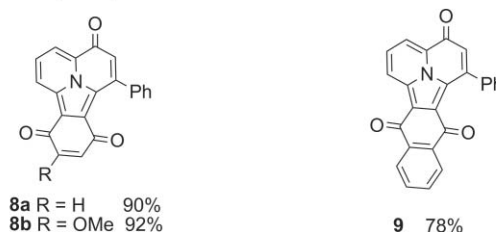
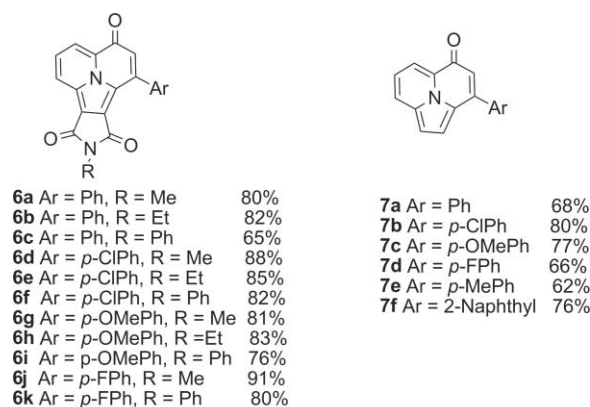
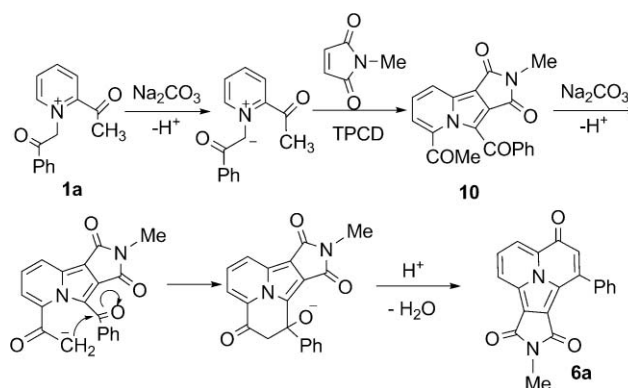


Chart 2



Scheme 2

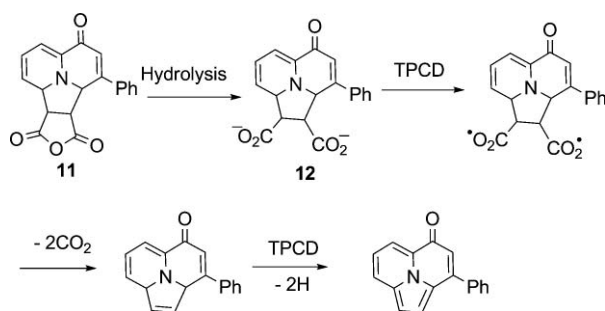
80% yield. These products are proposed to be formed by hydrolysis of the primary product **11** and the oxidative bisdecarboxylation of dicarboxylate (**12**) followed by dehydrogenation under the action of TPCD (Scheme 3). Therefore, these reactions provide a novel strategy to regioselectively synthesize the 1,2-unsubstituted cycl[3.3.2]azines which are otherwise difficult to access because in the [3+2] cycloaddition of the quinolizinium ylide (**I** or **II**) with electron-deficient alkynes or alkenes, the latter dipolarophiles have to bear at least one electron-withdrawing group(s). The smooth formation of the 1,2-unsubstituted **7a–7f** also indicated the generality of the application of TPCD as a promising new bisdecarboxylation reagent whose mild oxidizing ability can be well tolerated by such highly π -electron excessive substrates as the cyclazines and indolizines without strong electron withdrawing substituents, which are apt to be oxidized by strong oxidants.

Quinones can also serve as the dipolarophiles to take part in these cycloadditions. Therefore, reactions of the ylide derived from the pyridinium salt **1a** with benzoquinone (**4a**), 2-methoxybenzoquinone (**4b**) and 1,4-naphthoquinone (**5**), respectively, gave the corresponding 1,2-annulated pyrrolo[2,1,5-*de*]quinolizin-5-ones **8a**, **8b** and **9** in high yields.

Table 1 Fluorescence properties of a part of the products

Products	λ_F^a	Φ_F^b
6a	514	0.351461
6c	517	0.373289
7a	489	0.064314
9	573	0.030829

^a λ_F – Fluorescence wavelength. ^b Φ_F – Fluorescence quantum yield. The Φ_F values were measured by using perylene as a standard ($\Phi_F = 0.94$) in degassed cyclohexane.

**Scheme 3**

The UV-visible absorption and fluorescence spectra of a part of the products have been measured, which show that, some of these compounds have strong fluorescence in the blue region with high emission quantum yield (Table 1) and should be interesting target compounds for biological applications and as opto-electric materials.

Conclusions

In summary, 1,2-annulated pyrrolo[2,1,5-de]quinolizine-5-one derivatives (cyclo[3.3.2]azine-5-ones) have been prepared by one pot tandem reactions of 2-acetyl-*N*-phenacyl pyridinium salts **1a–1d** with cyclic alkenes (maleimides, benzoquinones and naphthoquinone) in the presence of sodium carbonate as a base and TPCD as an oxidant by 1,3-dipolar cycloadditions of the *in situ* generated 1-oxoquinolizinium ylide with the cyclic alkene and subsequent oxidative dehydrogenation of the primary cycloadduct. Similar reactions of the quinolizinium ylides generated *in situ* from **1a–1f** with maleic anhydride, on the other hand, provided a regioselective synthesis to the otherwise hardly accessible 1,2-unsubstituted cyclo[3.3.2]azine-5-ones by oxidative bisdecarboxylation and dehydrogenation of the primary products under the action of TPCD. This array of compounds has substantially expanded the library of the cyclo[3.3.2]azine class and may serve as target compounds for biological and optoelectric properties investigation.

Experimental

General

Melting points are uncorrected. ¹H NMR spectra were measured on a Bruker DPX 300 spectrometer at 300 MHz with CDCl₃ as solvent. The chemical shifts (δ) are reported in parts per million relative to the residual deuterated solvent signal, and coupling constants (*J*) are given in Hz. ¹³C NMR spectra were measured

on a Bruker Avance 300 spectrometer at 75 MHz with CDCl₃ or DMSO as solvent. IR spectra were recorded with a Shimadzu IR 440 spectrometer as KBr pellets. Mass spectra were taken on a VG ZAB-HS spectrometer in the electron impact ionization mode. Elemental analyses were performed with a Perkin-Elmer 240 C analyzer.

General procedure for the preparation of 1,2-annulated pyrrolo[2,1,5-de]quinolizine-5-ones (**6**, **8** and **9**)

A mixture of 2-acetyl-*N*-phenacyl pyridinium salt **1** (1 mmol), the cyclic alkene (*N*-alkyl or arylmaleimides **2a–2c**, benzoquinones **4a**, **4b** and 1,4-naphthoquinone **5**, respectively) (2 mmol), TPCD (1 g) and sodium carbonate (0.371 g) in DMF (15 ml) was heated at 90 °C for 16 h with magnetic stirring. The reaction course was monitored by TLC. The solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with petroleum ether (bp 60–90 °C)/ethyl acetate as an eluent to give the products **6**, **8** and **9**, respectively.

General procedure for the preparation of 1,2-unsubstituted pyrrolo[2,1,5-de]quinolizine-5-ones (**7**)

A mixture of 2-acetyl-*N*-phenacyl pyridinium salt **1** (1 mmol), maleic anhydride **3** (2 mmol, 0.196 g), TPCD (1 g) and sodium carbonate (3.5 mmol, 0.371 g) in DMF (15 ml) was heated at 90 °C for 16 h with magnetic stirring. The reaction course was monitored by TLC. The solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with petroleum ether (bp 60–90 °C)/ethyl acetate as an eluent to give the products **7**.

1-Phenyl-8-methyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-de]quinolizine-3,7,9-trione (6a**).** Yield: 80%; red solid; mp 229–231 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.11 (s, 3H), 7.18 (s, 1 H), 7.60 (s, 5H), 8.02 (t, *J* = 8.1 Hz, 1H), 8.55 (d, *J* = 8.4 Hz, 1H), 8.63 (dd, *J* = 7.5, 0.9 Hz, 1H). IR (KBr): 1762, 1731, 1712, 1614, 1434, 1359, 1315, 1248, 1137, 809, 768, 736. MS (EI): *m/z* (%) 328 (100) [M⁺], 283 (23), 269 (25), 241 (5), 214 (10), 108 (8). Anal. Calcd for C₂₀H₁₂N₂O₃: C, 73.17; H, 3.66; N, 8.54. Found: C, 73.13; H, 3.67; N, 8.54%.

1-Phenyl-8-ethyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-de]quinolizine-3,7,9-trione (6b**).** Yield: 82%; red solid; mp 216–218 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.21 (t, *J* = 7.2 Hz, 3H), 3.65 (q, *J* = 7.2 Hz, 2H), 7.16 (s, 1 H), 7.60 (s, 5H), 8.00 (t, *J* = 8.1 Hz, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.60 (d, *J* = 7.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 175.4, 163.6, 162.4, 145.7, 135.4, 134.3, 130.2, 130.1, 129.2, 129.1, 128.6, 127.8, 127.1, 123.1, 119.8, 118.3, 115.8, 33.3, 14.1. IR (KBr): 1756, 1721, 1706, 1610, 1444, 1344, 1315, 1245, 1138, 894, 810, 743. MS (EI): *m/z* (%) 342 (100) [M⁺], 298 (14), 269 (15), 241 (5), 215 (10), 149 (18), 105 (17). Anal. Calcd for C₂₁H₁₄N₂O₃: C, 73.68; H, 4.09; N, 8.19. Found: C, 73.62; H, 4.07; N, 8.17%.

1,8-Diphenyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-de]quinolizine-3,7,9-trione (6c**).** Yield: 65%; red solid; mp 246–248 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.21 (s, 1H), 7.35–7.40 (m, 3H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.56–7.66 (m, 5H), 8.09 (t, *J* = 7.5 Hz, 1H), 8.65 (d, *J* = 8.5 Hz, 1H), 8.69 (d, *J* = 7.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 175.5, 162.7, 161.6, 145.9, 135.3,

134.4, 132.0, 130.5, 130.2, 129.1, 129.0, 128.8, 128.7, 128.4, 128.1, 127.4, 127.2, 123.4, 120.2, 117.8, 116.2. IR (KBr): 1761, 1720, 1648, 1616, 1598, 1501, 1445, 1343, 1137, 870, 746. MS (EI): m/z (%) 390 (100) [M⁺], 345 (68), 306 (15), 269 (20), 214 (29), 133 (24), 105 (34), 77 (31), 55 (16), 44 (71). Anal. Calcd for C₂₅H₁₄N₂O₃: C, 76.92; H, 3.59; N, 7.18. Found: C, 76.88; H, 3.62; N, 7.16%.

1-(4-Chlorophenyl)-8-methyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-*de*]quinolizine-3,7,9-trione (6d). Yield: 88%; red solid; mp 252–253 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.14 (s, 3H), 7.14 (s, 1H), 7.57 (s, 4H), 8.03 (t, J = 8.1 Hz, 1H), 8.56 (d, J = 8.4 Hz, 1H), 8.62 (d, J = 7.5 Hz, 1H). IR (KBr): 1756, 1753, 1709, 1619, 1488, 1375, 1363, 1249, 1093, 808, 738. MS (EI): m/z (%) 362 (100) [M⁺], 317 (10), 303 (17), 268 (3), 214 (5). Anal. Calcd for C₂₀H₁₁N₂O₃Cl: C, 66.30; H, 3.04; N, 7.73. Found: C, 66.35; H, 3.06; N, 7.70%.

1-(4-Chlorophenyl)-8-ethyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-*de*]quinolizine-3,7,9-trione (6e). Yield: 85%; red solid; mp 260–262 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.25 (t, J = 7.2 Hz, 3H), 3.69 (q, J = 7.2 Hz, 2H), 7.13 (s, 1H), 7.57 (s, 4H), 8.03 (td, J = 7.6, 0.9 Hz, 1H), 8.56 (dd, J = 8.5, 1.2 Hz, 1H), 8.62 (dd, J = 7.5, 1.1 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 175.3, 163.5, 162.5, 144.4, 136.6, 134.3, 133.8, 130.6, 130.2, 129.1, 128.9, 127.9, 127.1, 123.2, 129.9, 118.4, 115.4, 33.3, 14.1. IR (KBr): 1749, 1698, 1606, 1488, 1340, 1314, 1263, 1136, 1085, 894, 745. MS (EI): m/z (%) 376 (100) [M⁺], 361 (20), 332 (37), 304 (12), 214 (5). Anal. Calcd for C₂₁H₁₃N₂O₃Cl: C, 67.02; H, 3.46; N, 7.45. Found: C, 67.08; H, 3.48; N, 7.43%.

1-(4-Chlorophenyl)-8-phenyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-*de*]quinolizine-3,7,9-trione (6f). Yield: 82%; red solid; mp 258–260 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.17 (s, 1H), 7.36–7.43 (m, 3H), 7.47–7.60 (m, 6H), 8.08 (t, J = 8.1 Hz, 1H), 8.65 (t, J = 7.5 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 175.4, 162.6, 161.8, 144.6, 136.6, 134.4, 133.7, 131.9, 130.6, 130.5, 129.2, 129.0, 128.4, 128.2, 127.4, 127.1, 123.5, 120.3, 117.9, 115.8. IR (KBr): 1760, 1720, 1618, 1597, 1503, 1489, 1350, 1319, 1138, 1097, 812, 744. MS (EI): m/z (%) 424 (100) [M⁺], 379 (50), 345 (8), 303 (6), 268 (3), 214 (12). Anal. Calcd for C₂₅H₁₃N₂O₃Cl: C, 70.75; H, 3.07; N, 6.60. Found: C, 70.71; H, 3.08; N, 6.58%.

1-(4-Methoxyphenyl)-8-methyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-*de*]quinolizine-3,7,9-trione (6g). Yield: 81%; red solid; mp 281–283 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.13 (s, 3H), 3.93 (s, 3H), 7.08 (d, J = 8.4 Hz, 2H), 7.13 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.98 (t, J = 8.0 Hz, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 7.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 175.4, 163.8, 163.0, 161.5, 145.5, 134.4, 130.8, 130.1, 128.9, 127.7, 126.8, 122.9, 119.7, 118.1, 116.1, 114.1, 55.4, 24.4. IR (KBr): 1763, 1727, 1712, 1617, 1601, 1496, 1284, 1185, 809, 738. MS (EI): m/z (%) 358 (100) [M⁺], 313 (5), 299 (13), 283 (1). Anal. Calcd for C₂₁H₁₄N₂O₄: C, 70.39; H, 3.91; N, 7.82. Found: C, 70.43; H, 3.88; N, 7.81%.

1-(4-Methoxyphenyl)-8-ethyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-*de*]quinolizine-3,7,9-trione (6h). Yield: 83%; red solid; mp 228–230 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.23 (t, J = 7.2 Hz, 3H), 3.68 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 7.08 (d, J = 8.4 Hz, 2H), 7.15 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.99 (t, J = 7.8 Hz, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 7.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 175.3, 163.6, 162.6, 161.5, 145.5, 134.3,

130.9, 130.1, 129.1, 127.8, 127.7, 126.7, 122.9, 119.7, 118.3, 116.0, 114.1, 55.4, 33.3, 14.1. IR (KBr): 1753, 1702, 1602, 1494, 1346, 1246, 1178, 896, 808. MS (EI): m/z (%) 372 (100) [M⁺], 328 (19), 299 (5), 241 (5), 230 (1). Anal. Calcd for C₂₂H₁₆N₂O₄: C, 70.97; H, 4.30; N, 7.53. Found: C, 70.91; H, 4.28; N, 7.55%.

1-(4-Methoxyphenyl)-8-phenyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-*de*]quinolizine-3,7,9-trione (6i). Yield: 76%; red solid; mp 245–247 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.88 (s, 3H), 7.05 (d, J = 8.7 Hz, 2H), 7.15 (s, 1H), 7.35–7.38 (m, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 8.03 (t, J = 7.5 Hz, 2H), 8.61 (t, J = 7.5 Hz, 2H). IR (KBr): 1762, 1718, 1620, 1602, 1492, 1354, 1276, 1246, 1186, 846, 808, 743. MS (EI): m/z (%) 420 (100) [M⁺], 375 (24), 345 (2), 299 (8), 230 (2), 202 (2), 149 (7). Anal. Calcd for C₂₆H₁₆N₂O₄: C, 74.29; H, 3.81; N, 6.67. Found: C, 74.35; H, 3.83; N, 6.66%.

1-(4-Fluorophenyl)-8-methyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-*de*]quinolizine-3,7,9-trione (6j). Yield: 91%; red solid; mp 285–287 °C. ¹H NMR (300 MHz, CDCl₃): δ 3.14 (s, 3H), 7.19 (s, 1H), 7.28 (t, J = 8.4 Hz, 2H), 7.59–7.64 (m, 2H), 8.05 (t, J = 7.8 Hz, 1H), 8.57 (d, J = 8.4 Hz, 1H), 8.65 (dd, J = 8.4, 0.8 Hz, 1H). IR (KBr): 1760, 1728, 1709, 1621, 1600, 1500, 1236, 1160, 809, 738. MS (EI): m/z (%) 346 (100) [M⁺], 301 (6), 387 (12), 214 (5). Anal. Calcd for C₂₀H₁₁N₂O₃F: C, 69.36; H, 3.18; N, 8.09. Found: C, 69.31; H, 3.19; N, 8.10%.

1-(4-Fluorophenyl)-8-phenyl-3*H*,7*H*,9*H*,10*H*-pyrrolo[3',4'-3,4]pyrrolo[2,1,5-*de*]quinolizine-3,7,9-trione (6k). Yield: 80%; red solid; mp 272–274 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.23 (s, 1H), 7.24–7.29 (m, 2H), 7.35–7.43 (m, 3H), 7.49 (t, J = 7.5 Hz, 2H), 7.64 (dd, J = 8.9, 5.2 Hz, 2H), 8.10 (t, J = 8.1 Hz, 1H), 8.67 (t, J = 8.6 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 175.3, 165.1, 163.1, 162.6, 161.8, 144.8, 134.4, 131.9, 131.4, 131.3, 131.2, 131.1, 130.5, 129.1, 128.4, 128.2, 128.1, 127.4, 127.1, 123.5, 120.3, 117.9, 116.1, 116.0, 115.8. IR (KBr): 1760, 1720, 1618, 1602, 1499, 1348, 1240, 1163, 811, 744. MS (EI): m/z (%) 408 (100) [M⁺], 363 (86), 232 (13), 104 (17), 76 (11). Anal. Calcd for C₂₅H₁₃N₂O₃F: C, 73.53; H, 3.19; N, 6.86. Found: C, 73.58; H, 3.17; N, 6.86%.

3-Phenyl-5*H*-pyrrolo[2,1,5-*de*]quinolizin-5-one (7a). Yield: 68%; yellow solid; mp 124–126 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.29 (s, 1H), 7.35 (d, J = 4.8 Hz, 1H), 7.57–7.62 (m, 3H), 7.66 (d, J = 4.8 Hz, 1H), 7.73 (dd, J = 7.8, 2.3 Hz, 2H), 7.87 (t, J = 7.8 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.69 (d, J = 7.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 174.4, 144.1, 138.7, 137.0, 133.5, 129.5, 129.3, 129.0, 124.1, 122.9, 122.4, 121.9, 121.5, 118.3, 110.5. IR (KBr): 1590, 1529, 1473, 1396, 1293, 1269, 1087, 809, 771, 696. MS (EI): m/z (%) 245 (100) [M⁺], 217 (29), 216 (5), 189 (2), 108 (3), 96 (3). Anal. Calcd for C₁₇H₁₁NO: C, 83.27; H, 4.49; N, 5.71. Found: C, 83.22; H, 4.51; N, 5.72%.

3-(4-Chlorophenyl)-5*H*-pyrrolo[2,1,5-*de*]quinolizin-5-one (7b). Yield: 80%; yellow solid; mp 181–183 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.21 (s, 1H), 7.36 (d, J = 4.5 Hz, 1H), 7.55–7.61 (m, 3H), 7.67 (d, J = 8.1 Hz, 2H), 7.86 (t, J = 7.5 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.68 (d, J = 7.2 Hz, 1H). ¹³C NMR (75 MHz, DMSO): δ 173.9, 142.3, 139.0, 135.7, 134.9, 133.4, 131.5, 129.6, 125.2, 123.8, 122.2, 121.5, 120.6, 117.9, 111.2. IR (KBr): 1584, 1531, 1478, 1394, 1294, 1274, 1089, 806, 737. MS (EI): m/z (%) 279 (100) [M⁺], 251 (33), 215 (18), 108 (18), 57 (10). Anal. Calcd

for $C_{17}H_{10}NOCl$: C, 73.12; H, 3.58; N, 5.02. Found: C, 73.05; H, 3.61; N, 5.00%.

3-(4-Methoxyphenyl)-5H-pyrrolo[2,1,5-de]quinolizin-5-one (7c). Yield: 77%; yellow solid; mp 178–180 °C. 1H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H), 7.12 (d, J = 8.7 Hz, 2H), 7.30 (s, 1H), 7.35 (d, J = 4.8 Hz, 1H), 7.67–7.71 (m, 3H), 7.85 (t, J = 7.9 Hz, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.68 (d, J = 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 160.8, 143.9, 138.5, 133.5, 130.6, 129.3, 123.8, 122.4, 122.2, 121.7, 121.3, 118.0, 114.5, 110.1, 55.5. IR (KBr): 1561, 1522, 1471, 1389, 1274, 1262, 1082, 817, 746. MS (EI): m/z (%) 275 (100) [M^+], 247 (1), 232 (12), 204 (6). Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.55; H, 4.73; N, 5.09. Found: C, 78.53; H, 4.75; N, 5.10%.

3-(4-Fluorophenyl)-5H-pyrrolo[2,1,5-de]quinolizin-5-one (7d). Yield: 66%; yellow solid; mp 186–188 °C. 1H NMR (300 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.27 (t, J = 8.7 Hz, 2H), 7.35 (d, J = 4.8 Hz, 1H), 7.61 (d, J = 4.8 Hz, 1H), 7.69–7.74 (m, 2H), 7.86 (t, J = 8.0 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.68 (d, J = 7.7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO): δ 173.9, 164.4, 162.4, 142.6, 138.9, 133.4, 133.3, 133.2, 131.9, 131.8, 125.1, 123.7, 122.2, 121.5, 120.7, 117.9, 116.7, 116.5, 111.1. IR (KBr): 1590, 1536, 1493, 1480, 1294, 1224, 1084, 805, 737, 728. MS (EI): m/z (%) 263 (100) [M^+], 235 (24), 234 (2), 132 (1), 118 (1). Anal. Calcd for $C_{17}H_{10}NOF$: C, 77.57; H, 3.80; N, 5.32. Found: C, 77.50; H, 3.83; N, 5.34%.

3-(4-Methylphenyl)-5H-pyrrolo[2,1,5-de]quinolizin-5-one (7e). Yield: 62%; yellow solid; mp 183–185 °C. 1H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H), 7.27 (s, 1H), 7.33 (d, J = 4.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 4.8 Hz, 1H), 7.84 (t, J = 8.0 Hz, 1H), 8.26 (d, J = 8.2 Hz, 1H), 8.68 (d, J = 7.6 Hz, 1H). IR (KBr): 1579, 1526, 1474, 1390, 1288, 1268, 1083, 806, 723. MS (EI): m/z (%) 259 (100) [M^+], 231 (11), 230 (7), 129 (1), 84 (1). Anal. Calcd for $C_{18}H_{13}NO$: C, 83.40; H, 5.02; N, 5.41. Found: C, 83.33; H, 5.05; N, 5.43%.

3-(2-Naphthyl)-5H-pyrrolo[2,1,5-de]quinolizin-5-one (7f). Yield: 76%; yellow solid; mp 108–110 °C. 1H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, J = 4.8 Hz, 1H), 7.42 (s, 1H), 7.60–7.63 (m, 2H), 7.72 (d, J = 4.8 Hz, 1H), 7.83–7.92 (m, 2H), 7.95–8.01 (m, 2H), 8.05 (d, J = 8.5 Hz, 1H), 8.23 (s, 1H), 8.30 (d, J = 8.1 Hz, 1H), 8.73 (d, J = 7.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO): δ 173.3, 143.6, 139.0, 134.2, 133.6, 133.4, 133.3, 129.4, 129.2, 129.1, 128.1, 127.7, 127.3, 127.1, 125.4, 123.8, 122.3, 122.0, 121.3, 118.1, 111.6. IR (KBr): 1569, 1525, 1474, 1389, 1272, 1080, 810, 757, 738. MS (EI): m/z (%) 295 (100) [M^+], 267 (14), 266 (7), 148 (2), 133 (5), 84 (2). Anal. Calcd for $C_{21}H_{13}NO$: C, 85.42; H, 4.41; N, 4.75. Found: C, 85.46; H, 4.38; N, 4.76%.

3-Phenyl-3H,7H,10H-isoindolo[1,2,3-de]quinolizine-3,7,10-trione (8a). Yield: 90%; red solid; mp 210–212 °C. 1H NMR (300 MHz, $CDCl_3$): δ 6.65 (d, J = 10.2 Hz, 1H), 6.83 (d, J = 10.2 Hz, 1H), 7.13 (s, 1H), 7.40 (d, J = 6.9 Hz, 2H), 7.50–7.59 (m, 3H), 8.08 (t, J = 7.8 Hz, 1H), 8.66 (d, J = 7.5 Hz, 1H), 9.05 (d, J = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.3, 181.6, 175.3, 147.0, 139.2, 138.3, 137.8, 134.9, 133.4, 129.2, 129.1, 129.0, 128.5, 128.2, 125.5, 125.2, 120.9, 118.9, 117.0. IR (KBr): 1663, 1646, 1640, 1588, 1456, 1265, 1110, 1019, 847, 760. MS (EI): m/z (%) 325 (100) [M^+], 308 (1), 297(1), 268 (2), 239 (1), 214 (4). Anal.

Calcd for $C_{21}H_{11}NO_3$: C, 77.54; H, 3.38; N, 4.31. Found: C, 77.61; H, 3.42; N, 4.29%.

3-Phenyl-8-methoxy-3H,7H,10H-isoindolo[1,2,3-de]quinolizine-3,7,10-trione (8b). Yield: 92%; red solid; mp 275–277 °C. 1H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H), 5.84 (s, 1H), 7.11 (s, 1H), 7.40 (d, J = 9.6 Hz, 2H), 7.52–7.58 (m, 3H), 8.09 (t, J = 8.1 Hz, 1H), 8.63 (d, J = 7.2 Hz, 1H), 9.05 (d, J = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.1, 176.6, 175.1, 160.8, 147.4, 137.9, 135.2, 133.4, 129.6, 129.1, 129.0, 128.4, 128.2, 126.2, 125.3, 120.7, 118.9, 116.2, 110.2, 56.6. IR (KBr): 1660, 1640, 1598, 1457, 1246, 1196, 1163, 1026, 820, 763. MS (EI): m/z (%) 355 (100) [M^+], 326 (24), 298 (53), 284 (13), 272 (16), 227 (9), 214 (18), 187 (5), 163 (4), 149 (6). Anal. Calcd for $C_{22}H_{13}NO_4$: C, 74.37; H, 3.66; N, 3.94. Found: C, 74.32; H, 3.69; N, 3.96%.

3H,7H,12H-Benzo[5,6]isoindolo[1,2,3-de]quinolizine-3,7,12-trione (9). Yield: 78%; red solid; mp 292–294 °C. 1H NMR (300 MHz, $CDCl_3$): δ 7.18 (s, 1H), 7.46–7.62 (m, 5H), 7.68–7.80 (m, 2H), 8.03 (dd, J = 7.8, 1.2 Hz, 1H), 8.13 (t, J = 8.1 Hz, 1H), 8.28 (dd, J = 7.2, 1.2 Hz, 1H), 8.72 (dd, J = 7.2, 1.2 Hz, 1H), 9.28 (dd, J = 8.4, 1.1 Hz, 1H). IR (KBr): 1729, 1668, 1641, 1599, 1511, 1453, 1396, 1266, 1237, 939, 719, 702. MS (EI): m/z (%) 375 (100) [M^+], 289 (5), 207(9), 149(3), 105 (4), 91(6). Anal. Calcd for $C_{25}H_{13}NO_3$: C, 80.00; H, 3.47; N, 3.73. Found: C, 80.02; H, 3.50; N, 3.71%.

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Notes and references

- (a) Heterocyclic Systems with Bridgehead Nitrogen Atom (Part 1), W. L. Mosby, Ed.; in *The Chemistry of Heterocyclic Compounds*, Wiley-interscience: New York, NY, 1961; Vol. 1; (b) F. J. Swinborne, J. H. Hunt and G. Klinkert, *Adv. Heterocycl. Chem.*, 1978, **23**, 103; (c) W. Flisch, *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky and C. W. Rees, ed.; Pergamon: Oxford, 1984; Vol. 4, p 443.
- (a) K. Fukui, T. Yonezawa, C. Nagata and H. Shirgu, *J. Chem. Phys.*, 1954, **22**, 1433; (b) A. N. Kost, R. S. Sagitullin and S. P. Gromov, *Heterocycles Special Issue*, 1977, **7**, 997; (c) E. Cane, C. Pizzarini, R. Tarroni and A. Trombetti, *J. Chem. Soc., Faraday Trans.*, 1995, **91**, 3741; (d) D. A. Meiboroda, E. V. Babaev and K. Jug, *J. Org. Chem.*, 1997, **62**, 7100; (e) E. V. Babaev, V. V. Simonyan, K. Y. Pasichnichenko, V. M. Nosova, A. V. Kisin and K. Jug, *J. Org. Chem.*, 1999, **64**, 9057.
- (a) M. C. Wani, A. W. Nicholas and M. E. Wall, *J. Med. Chem.*, 1987, **30**, 2317; (b) A. Furstner and J. W. J. Kennedy, *Chem.-Eur. J.*, 2006, **12**, 7398; (c) A. Decor, B. Monse, M. T. Martin, A. Chiaroni, S. Thoret, D. Guenard, F. Gueritte and O. Baudoin, *Bioorg. Med. Chem.*, 2006, **14**, 2314; (d) K. Olden, P. Breton, K. Grzegorzewski, Y. Yasuda, B. L. Gause, O. A. Creaipe, S. A. Newton and S. L. White, *Pharmacol. Ther.*, 1991, **50**, 285; (e) J. P. Jaffrezou, T. Levade, O. Thurneyssen, M. Chiron, C. Bordier, M. Attal, P. Chatelain and G. Laurent, *Cancer Res.*, 1992, **52**, 1352; (f) K. Koya, L. Sun, M. Ono, W. Ying, H. Li, WO 2003022846 A1, 2003; *Chem. Abstr.*, 2003, **138**, 238174; (g) P. B. Ahrens and H. Ankel, *J. Biol. Chem.*, 1987, **262**, 7575; (h) M. Bols, V. H. Lillelund, H. H. Jensen and X. Liang, *Chem. Rev.*, 2002, **102**, 515; (i) W. H. Pearson and L. Guo, *Tetrahedron Lett.*, 2001, **42**, 8267; (j) N. Asano, R. J. Nash, R. J. Molyneux and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1645; (k) V. W. Sasak, J. M. Ordovas, A. D. Elbein and R. W. Berninger, *Biochem. J.*, 1985, **232**, 759.

- 4 (a) R. M. Ruprecht, S. Mullaney, J. Andersen and R. Bronson, *J. Acquired Immune Defic. Syndr.*, 1989, **2**, 149; (b) R. A. Gruters, J. J. Neefjes, M. Tersmette, R. E. Y. de Goede, A. Tulp, H. G. Huisman, F. Miedema and H. L. Ploegh, *Nature*, 1987, **330**, 74; (c) A. Kaspas, G. W. J. Fleet, R. A. Dwek, S. Petursson, S. K. Namgoong, N. G. Ramsden, G. S. Jacob and T. W. Radamacher, *Proc. Natl. Acad. Sci. USA*, 1989, **86**; (d) T. M. Brennen, D. L. Taylor, C. G. Bridges, J. P. Leyda and A. S. Tynms, *Antiviral Res.*, 1995, **26**, 173.
- 5 (a) J. Gubin, H. Vogelaer, H. Inion, C. Houben, J. Lucchetti, J. Mahaux, G. Rosseels, M. Peiren, M. Clinet, P. Polster and P. Chatelain, *J. Med. Chem.*, 1993, **36**, 1425; (b) D. L. J. Clive, D. M. Coltart and Y. Zhou, *J. Org. Chem.*, 1999, **64**, 1447; (c) J. S. Mynderse and D. S. Fukuda, Eur. Patent. Appl. 133038A2, 1985; *Chem. Abstr.*, 1985, **103**, 160306; (d) P. Chatelain, A. Laruel, P. Beaufort, L. Meysmans and M. Clinet, *Cardioscience*, 1992, **3**, 117.
- 6 (a) F. Delattre, P. Woisel, G. Surpateau, F. Cazier and P. Blach, *Tetrahedron*, 2005, **61**, 3939; (b) G. G. Surpateanu, M. Becuwe, N. C. Lungu, P. I. Dron, S. Fourmentin, D. Landy and G. Surpateanu, *J. Photochem. Photobiol. A*, 2007, **185**, 312; (c) G. L. Fletetcher, S. L. Bender and D. H. Wadsworth, U.S. Patent 4,577,024, 1986; *Chem. Abstr.*, 1984, **100**, 122772; (d) H. Sonnenschein, G. Hennrich, U. Resch-Genger and B. Schulz, *Dyes Pigm.*, 2000, **46**, 23; (e) A. V. Retaru, L. D. Druta, T. Deser and T. Mueller, *Helv. Chim. Acta*, 2005, **88**, 1798.
- 7 (a) T. Mitsumori, M. Bendikov, O. Dautel, F. Wudl, T. Shioya, H. Sato and Y. Sato, *J. Am. Chem. Soc.*, 2004, **126**, 16793; (b) Y.-M. Shen, G. Grampp, N. Leesakul, H.-W. Hu and J.-H. Xu, *Eur. J. Org. Chem.*, 2007, 3718; (c) M. K. Bayazit and K. S. Coleman, *J. Am. Chem. Soc.*, 2009, **131**, 10670; (d) P. J. Aittala, O. Cramariuc, T. I. Hukka, M. Vasilescu, R. Bandula and H. Lemmetyinen, *J. Phys. Chem. A*, 2010, **114**, 7094.
- 8 (a) V. Boekelheide and R. J. Windgassen, *J. Am. Chem. Soc.*, 1958, **80**, 2020; (b) R. J. Windgassen, Jr., W. H. Sanders, Jr. and V. Boekelheide, *J. Am. Chem. Soc.*, 1959, **81**, 1459.
- 9 M. A. Jessep and D. Leaver, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1324.
- 10 A. G. King and J. Meinwald, *Chem. Rev.*, 1996, **96**, 1105.
- 11 M. Timmermans, J.-C. Braekman, D. Daloze, J. M. Pasteels, J. Merlin and J.-P. Declercq, *Tetrahedron Lett.*, 1992, **33**, 1281.
- 12 K. D. McCormick, A. B. Attygalle, S. C. Xu, A. Svatos, J. Meinwald, M. A. Houck, C. L. Blankespoor and T. Eisner, *Tetrahedron*, 1994, **50**, 2365.
- 13 X. Shi, A. B. Attygalle, J. Meinwald, M. Houck and T. Eisner, *Tetrahedron*, 1995, **51**, 8711.
- 14 Q. Huang, A. B. Attygalle, J. Meinwald, M. A. Houck and T. Eisner, *J. Nat. Prod.*, 1998, **61**, 598.
- 15 P. Laurent, J. C. Braekman, D. Daloze and J. M. Pasteels, *Tetrahedron Lett.*, 2002, **43**, 7465.
- 16 (a) F. Schröder, S. Franke, W. Francke, H. Baumann, M. Kaib, J. M. Pasteels and D. Daloze, *Tetrahedron*, 1996, **52**, 13539; (b) F. Schröder, V. Sinnwell, H. Baumann and M. Kaib, *Chem. Commun.*, 1996, 2139; (c) F. Schröder, V. Sinnwell, H. Baumann, M. Kaib and W. Francke, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 77; (d) A. E. Ondrus and M. Movassaghi, *Chem. Commun.*, 2009, 4151.
- 17 D. Farquhar, T. T. Gough, D. Leaver, J. F. Miller, J. W. Dick and M. A. Jessep, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2553.
- 18 J. W. Dick, W. K. Gibson, D. Leaver and J. E. Roff, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3150.
- 19 Y. Miki, H. Kinoshita, T. Yoshimaru and S. Takemura, *Heterocycles*, 1987, **26**, 199.
- 20 J. Hu, X. Jiang, T. He, J. Zhou, Y. Hu and H. Hu, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1820.
- 21 (a) X. Wei, Y. Hu and H. Hu, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2487; (b) B. Wang, X. Zhang, Y. Hu and H. Hu, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1571; (c) L. Zhang, F. Liang, L. Sun, Y. Hu and H. Hu, *Synthesis*, 2000, 1733.
- 22 For reviews on the application of tandem reactions involving [3+2] cycloadditions in the synthesis of *N*-heterocycles, see (a) L. F. Tietze and N. Rackelmann, *Pure Appl. Chem.*, 2004, **76**, 1967; (b) M. Pineiro and T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.*, 2009, 5287; (c) S. K. Bur and A. Padwa, *Adv. Heterocycl. Chem.*, 2007, **94**, 1; (d) K. Harju and J. Yli-Kauhaluoma, *Recent Res. Devel. Org. Chem.*, 2004, **8**, 111.
- 23 P. A. Duke, A. Fozard and G. Jones, *J. Org. Chem.*, 1965, **30**, 526.
- 24 Y. Liu, Y. Zhang, Y.-M. Shen, H.-W. Hu and J.-H. Xu, *Org. Biomol. Chem.*, 2010, **8**, 2449.