Regioselective synthesis of 3-acylindolizines and benzo- analogues *via* 1,3-dipolar cycloadditions of *N*-ylides with maleic anhydride†

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3-Acylindolizines (**5a–5f**) and their benzo- analogues 1-acylpyrrolo[1,2-*a*]quinolines (**6a–6f**) and 1-acylpyrrolo[2,1-*a*]isoquinolines (**7a–7i**) are regioselectively synthesized by a convenient one pot reaction of the corresponding pyridinium (quinolinium, isoquinolinium) ylide with maleic anhydride (MA) in the presence of the mild oxidant tetrakispyridinecobalt(II) dichromate (TPCD). These reactions proceed *via* a tandem reaction sequence of 1,3-dipolar cycloaddition of azomethine ylide with MA, anhydride hydrolysis and oxidative bisdecarboxylation of the primary cycloadducts followed by dehydrogenative aromatization of the dihydroindolizines. TPCD serves as both decarboxylation and dehydrogenation reagent in the reactions. These results show that TPCD is a promising new reagent for bisdecarboxylation of aliphatic carboxylates.

Introduction

Indolizines and hydrogenated indolizines are widely found in the indolizidine alkaloids.[1] These natural and many synthetic indolizines have a diversity of biological activity and are playing an increasingly important role in developing new pharmaceuticals for the treatment of cancer,[2] cardiovascular diseases[3] and HIV infection.[4] The special electronic structure and reactivity caused by the bridgehead nitrogen atom is of long standing theoretical interest.[5] The high fluorescence quantum yield of indolizine derivatives in the UV-visible region have also received much research attention in designing novel classes of dyes, biological markers[6] and electroluminescent materials.[7]

Pyrrolo[1,2-*a*]quinolines and pyrrolo[2,1-*a*]isoquinolines are 5,6- and 7,8- benzo-fused indolizines, respectively. These structures occur in several marine alkaloids (gephyrotoxin,[8a] lamellarines,[8b] jamtines,[8c] *etc.*) with anti-inflammatory,[9a] cardiovascular,[9b] antidepressant,[9c] anticancer[9d,e] and HIV-1 integrase inhibiting activity.[9f]

For these theoretical and practical reasons, the synthesis of indolizines,[10] pyrrolo[1,2-*a*]quinolines[11] and pyrrolo[2,1-*a*]isoquinolines[12] has drawn much recent research interest. Various synthetic methods for indolizines and benzo-indolizines have been reported. These include, among the more general approaches, the reactions of 2-alkylpyridine with an aldehyde (the Schöltz reaction)[13] or with an α-haloketone (the Tschitschibabin reaction),[14] 1,3-dipolar cycloadditions of pyridinium (quinolinium, isoquinolinium) methylides with electron deficient acetylenes[15] or alkenes,[16,17] 1,5-dipolar cyclizations[18] and metal-catalyzed intramolecular C–N bond formation of alkynyl pyridines or propargylic pyridines.[19] Despite these advances, a comprehensive structure–activity relationship (SAR) study in drug and optoelectronic material design has raised a growing demand for new chemo- and regioselective synthetic strategies that allow access to indolizines with a well-defined substitution pattern, while many present synthetic methodology have severe limitations in achieving this. Recently, 3-monofunctionalized indolizines have received much attention because of their occurrence in alkaloids and their biological properties.[20] However, in the above mentioned general synthetic approaches towards indolizines, the Tschitschibabin reaction cannot be used to synthesize the 1,2-unsubstituted indolizines, and the pyridinium ylide 1,3-dipolar cycloadditions require the olefinic or acetylenic dipolarophiles to have one or two electron withdrawing substituent(s) and are also not suitable for the synthesis of 3-indolizines except in a few cases using special alkene substrates not easily accessible such as nitroketene dithioacetals.[21] As a result, the synthesis of 3-indolizines proves to be rather difficult. Recently, several successful syntheses for 3-indolizines relying on other strategies have been reported. Therefore, 3-aminoindolizines were synthesized by Pd/Cu-catalyzed cross-coupling–cycloisomerization reactions of propargyl amines or amides with 2-bromopyridines.[22] Reaction of pyridine silylated vinylacetylenes with alcohol in the presence of an inorganic base afforded 3-alkoxymethylindolizines.[23] 3-Alkynylindolizines were synthesized by palladium-catalyzed reactions of indolizine with alkynyl bromides.[24] 3-Alkylindolizines can be obtained by copper-promoted cyclization of alkynyl pyridines,[25] while palladium catalyzed regioselective Heck arylation of indolizines leads to 3-arylindolizines.[26] More recently, 3-acylindolizines were synthesized by intermolecular cyclization of picolinium salts and a methoxymethylene-dimethyl ammonium salt.[27] Because direct Friedel–Crafts acylation of the indolizines is hampered by low regioselectivity and low yield,[28] and the unsubstituted indolizine

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used for acylation needs to be prepared,[21,28a] general and regioselective synthetic methods of 3-acylindolizines from easily available starting materials are highly desirable. We report here a convenient synthesis of 3-acylindolizines and their benzo- analogues by the more general 1,3-dipolar cycloaddition reactions of pyridinium (quinolinium, isoquinolinium) ylide by using maleic anhydride as the olefinic substrate. This strategy has overcome the inherent shortcomings of the 1,3-dipolar cycloadditions using conventional alkynes and alkenes in accessing the 1,2-unsubstituted indolizines by taking advantage of the novel tandem bisdecarboxylation–dehydrogenation reactions of the primary cycloadducts under the action of the mild oxidant tetrakispyridinecobalt(II) dichromate [$Py_4Co(HCrO4)_2$] (TPCD).[17a,b]

Results and discussion

A recent advance in using the 1,3-dipolar cycloadditions of pyridinium ylide for the indolizine synthesis is to apply alkenes to replace alkynes (such as dimethyl acetylenedicarboxylate) as the dipolarophile.[16,17] An efficient approach in this respect is to use electron deficient alkenes in combination with the mild oxidant TPCD to effect the dehydroaromatization of the primary tetrahydroindolizine product.[17] Although these [3+2] cycloadditions are widely used for the indolizine synthesis, they are not applicable for the synthesis of 1,2-unsubstituted indolizines because the alkene dipolarophiles have to bear at least one electron-withdrawing group. However, we have found that when maleic anhydride was used as the dipolarophile, 3-monofunctionalized indolizines can be synthesized *via* oxidative bisdecarboxylation during the reaction course. Therefore, under the established reaction conditions for carrying out the TPCD-mediated 1,3-dipolar cycloadditions of the pyridinium ylide with electron deficient alkenes with DMF as the solvent and sodium carbonate as the base,[17a,b] reaction of 1-phenacylpyridinium salt (**1a**) (Chart 1) with maleic anhydride (**4**) in the presence of TPCD and sodium carbonate in DMF at 90 °C for 10 h gave the 3-benzoylindolizine **5a** in 43% yield. However, it was found that using potassium carbonate as the base and shortening the reaction time to 3 h led to an improved yield of 55%. Furthermore, if the reaction was carried out under a nitrogen atmosphere, the yield was raised to 71%. Reactions of

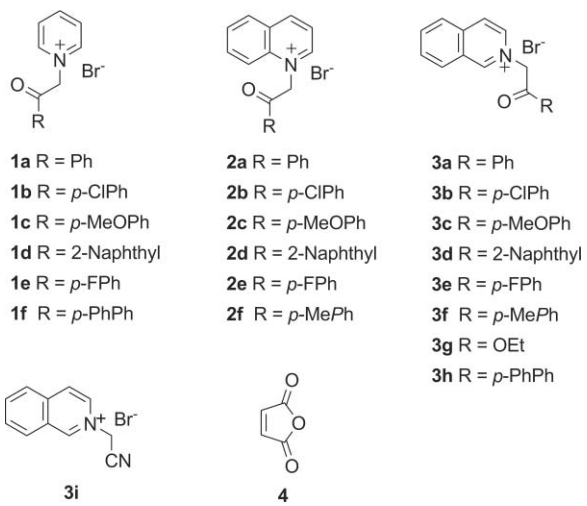


Chart 1

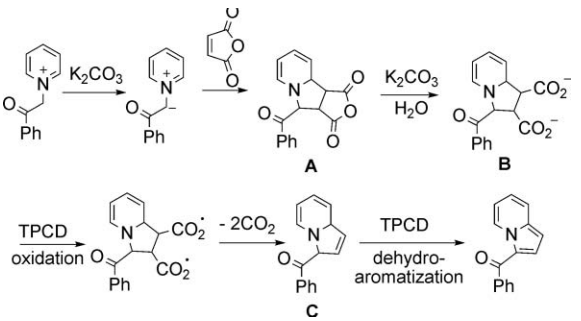
Table 1 Synthesis of 3-acylindolizines[a]

Pyridinium salt	Product	Yield (%)[b]
1a R = Ph	**5a** R = Ph	71 (65)[c]
1b R = *p*-ClPh	**5b** R = *p*-ClPh	78 (71)[c]
1c R = *p*-MeOPh	**5c** R = *p*-MeOPh	75 (66)[c]
1d R = 2-Naphthyl	**5d** R = 2-Naphthyl	68
1e R = *p*-FPh	**5e** R = *p*-FPh	83
1f R = *p*-PhPh	**5f** R = *p*-PhPh	73

[a] All the reactions were carried out under N_2 atmosphere, with **1** (1 mmol), **4** (2 mmol), TPCD (1 g) and potassium carbonate (0.483 g) in DMF at 90 °C for 3 h. [b] Isolated yield by silica gel column chromatography. [c] In parentheses are the yields when using MnO_2 as an oxidant.

pyridinium salts **1b–1f** (Chart 1) with **4** under the same conditions under a nitrogen atmosphere similarly afforded the corresponding 3-acylindolizines **5b–5f**, respectively (Table 1).

These reactions are proposed to proceed by a mechanism as shown in Scheme 1.



Scheme 1

The *N*-ylide generated by deprotonation of the pyridinium salt with potassium carbonate as a base takes part in a 1,3-dipolar cycloaddition with maleic anhydride to give the primary product **A**. Hydrolysis of **A** in the presence of the base and adventitious water in the solvent gives the dicarboxylate **B**, which undergoes oxidative bisdecarboxylation under the action of TPCD to give the dihydroindolizine **C**. Further dehydroaromatization of **C** by TPCD leads to the 3-acylindolizine **5a**. As a proof of the proposed mechanism and as a variation of this synthetic protocol, we examined the reaction of **1a** with maleic acid in the presence of potassium carbonate and TPCD in DMF at 90 °C for 3 h under N_2 atmosphere and found that, this indeed gave the 3-benzoylindolizine **5a**, albeit in lower yield (57%).

These results show that, as a mild oxidant, TPCD is not only useful to achieve dehydroaromatization for partly hydrogenative *N*-heterocycles, but is also an effective decarboxylation reagent for carboxylates, and it performs these two functions in the above mentioned reactions, leading to one pot tandem reactions to give the 1,2-unsubstituted indolizines.

Diels–Alder reactions of maleic anhydride with cyclic dienes followed by oxidative bisdecarboxylation of the cycloadduct have been applied for the synthesis of several bicyclic dienes.[29] The bisdecarboxylation process was conducted either electrolytically[30]

Table 2 Synthesis of 1-acylpyrrolo[1,2-*a*]quinolines[a]

Quinolinium salt	Product	Yield (%)[b]
2a R = Ph	**6a** R = Ph	78
2b R = *p*-ClPh	**6b** R = *p*-ClPh	86
2c R = *p*-MeOPh	**6c** R = *p*-MeOPh	80
2d R = 2-Naphthyl	**6d** R = 2-Naphthyl	73
2e R = *p*-FPh	**6e** R = *p*-FPh	89
2f R = *p*-MePh	**6f** R = *p*-MePh	82

[a] All the reactions were carried out under N_2 atmosphere, with **2** (1 mmol), **4** (2 mmol), TPCD (1 g) and potassium carbonate (0.483 g) in DMF at 90 °C for 6 h. [b] Isolated yield by silica gel column chromatography.

or with chemical oxidants such as lead oxide,[31] lead tetraacetate,[32] copper(II) oxide,[33] *etc*. Although electrolytic decarboxylation gave rather high yields of the alkene products, chemical oxidants usually resulted in low yield of the bisdecarboxylation products because of the harsh reaction conditions or the strongly oxidizing character of the oxidants which led to the further oxidation of the alkene products. Our own experiments showed that using lead tetraacetate instead of TPCD in the reaction of the pyridinium ylide with maleic anhydride under otherwise the same reaction conditions (heating in DMF at 90 °C for 3 h with potassium carbonate as base) resulted in a complicated reaction mixture, from which no significant amount of the desired 3-acylindolizine could be detected. However, we have found that newly prepared manganese dioxide can be used to replace TPCD under these reaction conditions to effect the decarboxylation to give the 3-acylindolizines. However, the yields are significantly lower (Table 1, yields in parentheses). An additional advantage of TPCD over MnO_2 is the ease of its preparation and storage,[19a,b] while MnO_2 has to be prepared by cumbersome procedures and to be used when it is newly prepared, and loses its activity quickly upon storage. Therefore, the successful one pot synthesis of our target compounds has taken advantage of TPCD's mild oxidizing ability that is well tolerated by such highly π-electron excessive and easily oxidizable substrates as indolizines.

Reactions of the *N*-ylides derived from the quinolinium salts **2a–2f** and from the isoquinolinium salts **3a–3i** with maleic anhydride under similar conditions were further investigated. The reactions of the ylides derived from **2a–2f** afforded the corresponding 1-acylpyrrolo[1,2-*a*]quinoline products **6a–6f**, leaving C2 and C3 in the pyrrole ring unsubstituted (Table 2). The structure of product **6e** is unambiguously established on the basis of an X-ray crystallographic analysis (Fig. 1).

It is noteworthy that, among the more general synthesis of benzo-indolizines, the Tschitschibabin reaction can not be used for the synthesis of pyrrolo[1,2-*a*]quinoline derivatives because the reaction of 2-methylquinoline with either phenacyl bromide or α-chloroacetate gives merely the corresponding 2-methylquinoline hydrohalide.[34] Although several syntheses of pyrrolo[1,2-*a*]quinolines have been reported,[11] more general and convenient one pot synthetic methods are still needed. Our results and other recent reports[11b,17a,d] showed that, [3+2] cycloaddition of the *N*-ylide with electron deficient alkenes in the presence of TPCD serves as a convenient and regioselective one pot

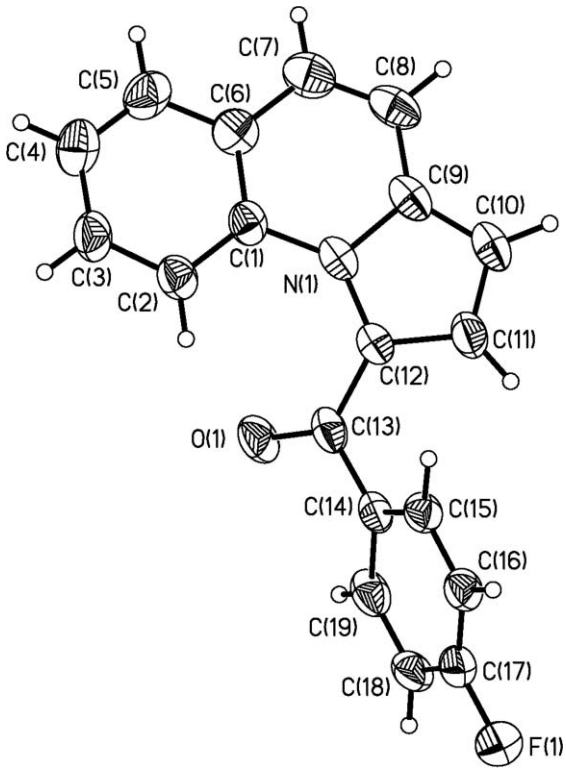


Fig. 1 ORTEP drawing of **6e**.

synthesis of pyrrolo[1,2-*a*]quinoline derivatives, and these 1,3-dipolar cycloadditions with maleic anhydride as a dipolarophile turned out to be a general regioselective synthetic approach to the 1-acylpyrrolo[1,2-*a*]quinolines.

Similar reactions of the isoquinolinium ylides derived from the isoquinolinium salts **3a–3i** with maleic anhydride under the same conditions gave the corresponding 2,3-unsubstituted 1-acylpyrrolo[2,1-*a*]isoquinolines **7a–7i** in satisfactory yields (Table 3). Therefore, these reactions prove to be a general and convenient synthetic approach toward the previously unknown 1-acylpyrrolo[1,2-*a*]quinolines and 1-acylpyrrolo[2,1-*a*]isoquinolines.

Table 3 Synthesis of 1-acylpyrrolo[2,1-*a*]isoquinolines[a]

Isoquinolinium salt	Product	Yield (%)[b]
3a R = Ph	**7a** R = Ph	80
3b R = *p*-ClPh	**7b** R = *p*-ClPh	88
3c R = *p*-MeOPh	**7c** R = *p*-MeOPh	83
3d R = 2-Naphthyl	**7d** R = 2-Naphthyl	77
3e R = *p*-FPh	**7e** R = *p*-FPh	92
3f R = *p*-MePh	**7f** R = *p*-MePh	83
3g R = OEt	**7g** R = OEt	67
3h R = *p*-PhPh	**7h** R = *p*-PhPh	82
3i CN in place of COR	**7i** CN in place of COR	63

[a] All the reactions were carried out under N_2 atmosphere, with **3** (1 mmol), **4** (2 mmol), TPCD (1 g) and potassium carbonate (0.483 g) in DMF at 90 °C for 6 h. [b] Isolated yield by silica gel column chromatography.

Conclusions

In summary, 1,2-unsubstituted 3-acylindolizines, 2,3-unsubstituted 1-acylpyrrolo[1,2-*a*]quinolines and 1-acylpyrrolo[2,1-*a*]-isoquinolines have been regioselectively synthesized by reactions of the corresponding pyridinium (quinolinium, isoquinolinium) ylide with maleic anhydride in the presence of the mild oxidant TPCD. These syntheses proceed *via* tandem reactions involving [3+2] cycloaddition, bisdecarboxylation of the primary cycloadduct and further dehydroaromatization of the dihydroindolizines (and their benzo- analogues). TPCD serves both as a decarboxylation and a dehydroaromatization reagent in the reactions. This strategy provides a general synthesis of 3-acylindolizines and their benzo- analogues *via* easily accessible starting materials by a simple one pot procedure. The results reveal that TPCD is not only an efficient dehydrogenative reagent for partly hydrogenated heterocycles as previously known, but is also a promising new decarboxylation reagent for aliphatic carboxylates, whose mild oxidation ability can be tolerated by such highly sensitive products as indolizines. It is anticipated that this strategy to use maleic anhydride as a dipolarophile (or a dienophile) in a reaction sequence of 1,3-dipolar cycloaddition with an azomethine ylide (or Diels–Alder reaction with a diene) followed by oxidative decarboxylation and dehydrogenation of the primary cycloadduct under the action of TPCD would be of general utility for the regioselective synthesis of other bridgehead nitrogen atom heterocycles (or other cyclic compounds) with a distinct substitution pattern.

Experimental

General

Melting points are uncorrected. ^{1}H NMR spectra were measured on a Bruker DPX 300 spectrometer at 300 MHz with $CDCl_3$ 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 Hertz. ^{13}C NMR spectra were measured on a Bruker Avance 300 spectrometer at 75 MHz with $CDCl_3$ 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 240C analyzer. For X-ray crystallographic analysis, the X-ray diffraction intensities and the unit cell parameters were determined on a Siemens P4 diffractometer employing graphite-monochromated (Mo-Kα) radiation ($\lambda = 0.71073$ Å) and operating in the ω-2θ scan mode. Data collection and cell refinement were performed with XSCANS. Structures were solved by direct methods and refined by full-matrix least-squares on F^2 with SHELXTL. Non-hydrogen atoms were refined by anisotropic displacement parameters, and the positions of all H-atoms were fixed geometrically and included in estimated positions using a riding model.

Crystallographic data (excluding structure factors) for the structure in this paper is available as ESI.† CCDC 602715.

General procedure for the preparation of 3-acylindolizines (5a-5f)

A mixture of 1-phenacyl pyridinium salt **1** (1 mmol), maleic anhydride **4** (0.196 g, 2 mmol), TPCD (1 g) and potassium carbonate (0.483 g, 3.5 mmol) in DMF (15 ml) was heated at 90 °C under N_2 atmosphere for 3 h with magnetic stirring. The reaction course was monitored by TLC. After the reaction was completed, 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 **5**.

3-Benzoylindolizine (5a). Yield: 158 mg, 71%. Yellow solid from petroleum ether–ethyl acetate, mp 90–92 °C (lit:[27] 91–92 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.54 (d, $J = 4.5$ Hz, 1H), 6.96 (t, $J = 6.9$ Hz, 1 H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.36 (d, $J = 4.5$ Hz, 1H), 7.47–7.60 (m, 4H), 7.82 (d, $J = 7.2$ Hz, 2H), 9.99 (d, $J = 6.9$ Hz, 1H). IR (KBr): 1595, 1566, 1467, 1388, 1357, 1234, 1130, 1053, 872, 772, 756. MS (EI): m/z (%) 221 (100) [M$^+$], 193 (66), 192 (46), 144 (91), 116 (61), 89 (16), 77 (11). Anal. Calcd for $C_{15}H_{11}NO$: C, 81.45; H, 4.98; N, 6.33. Found: C, 81.40; H, 5.01; N, 6.35.

3-(4-Chlorobenzoyl)indolizine (5b). Yield: 199 mg, 78%. Yellow solid from petroleum ether–ethyl acetate, mp 123–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (d, $J = 4.7$ Hz, 1H), 6.97 (td, $J = 7.0$, 1.3 Hz, 1 H), 7.23 (td, $J = 6.8$, 1.1 Hz, 1H), 7.32 (d, $J = 4.7$ Hz, 1H), 7.48 (dt, $J = 9.0$, 2.1 Hz, 2H), 7.60 (d, $J = 8.7$ Hz, 1H), 7.76 (dt, $J = 9.0$, 2.1 Hz, 2H), 9.96 (d, $J = 7.1$ Hz, 1H). IR (KBr): 1603, 1589, 1563, 1469, 1394, 1361, 1234, 1052, 879, 750. MS (EI): m/z (%) 255 (100) [M$^+$], 227 (13), 226 (2), 192 (12), 144 (57), 116 (27), 89 (9). Anal. Calcd for $C_{15}H_{10}NOCl$: C, 70.59; H, 3.92; N, 5.49. Found: C, 70.63; H, 3.89; N, 5.47.

3-(4-Methoxybenzoyl)indolizine (5c). Yield: 189 mg, 75%. Pale yellow solid from petroleum ether–ethyl acetate, mp 140–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.54 (d, $J = 4.5$ Hz, 1H), 6.92 (t, $J = 6.9$ Hz, 1H), 7.00 (d, $J = 9.0$ Hz, 2H), 7.17 (t, $J = 7.8$ Hz, 1H), 7.37 (d, $J = 4.5$ Hz, 1H), 7.56 (t, $J = 9.0$ Hz, 1H), 7.83 (d, $J = 8.7$ Hz, 2H), 9.93 (d, $J = 7.2$ Hz, 1H). IR (KBr): 1601, 1569, 1505, 1463, 1384, 1352, 1236, 1168, 879, 751. MS (EI): m/z (%) 251 (100) [M$^+$], 223 (8), 222 (11), 208 (48), 144 (37), 116 (22), 89 (13). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.49; H, 5.18; N, 5.58. Found: C, 76.55; H, 5.22; N, 5.56.

3-(2-Naphthoyl)indolizine (5d). Yield: 184 mg, 68%. Yellow solid from petroleum ether–ethyl acetate, mp 141–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.58 (d, $J = 4.6$ Hz, 1H), 6.99 (t, $J = 7.0$ Hz, 1 H), 7.23 (t, $J = 7.8$ Hz, 1H), 7.43 (d, $J = 4.6$ Hz, 1H), 7.58–7.62 (m, 3H), 7.92–7.99 (m, 4H), 8.31 (s, 1H), 10.03 (d, $J = 7.0$ Hz, 1H). IR (KBr): 1583, 1567, 1469, 1385, 1356, 1240, 1120, 1051, 817, 768, 758. MS (EI): m/z (%) 271 (100) [M$^+$], 243 (11), 242 (20), 144 (17), 127 (9), 116 (10), 89 (4). Anal. Calcd for $C_{19}H_{13}NO$: C, 84.13; H, 4.80; N, 5.17. Found: C, 84.19; H, 4.85; N, 5.13.

3-(4-Fluorobenzoyl)indolizine (5e). Yield: 198 mg, 83%. Pale yellow solid from petroleum ether–ethyl acetate, mp 92–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.55 (d, $J = 4.5$ Hz, 1H), 6.96 (td, $J = 6.9$, 1.0 Hz, 1H), 7.15–7.22 (m, 3H), 7.32 (d, $J = 4.5$ Hz, 1H), 7.58 (d, $J = 9.0$ Hz, 1H), 7.82–7.86 (m, 2H), 9.95 (d, $J = 7.2$ Hz, 1H). IR (KBr): 1607, 1586, 1503, 1471, 1361, 1235, 752. IR (KBr): 1607, 1601, 1586, 1503, 1471, 1361, 1235, 1155, 1051, 833, 753. MS (EI): m/z (%) 239 (100) [M$^+$], 211 (67), 210 (32), 144 (92), 116 (73), 89 (20). Anal. Calcd for $C_{15}H_{10}NOF$: C, 75.31; H, 4.18; N, 5.86. Found: C, 75.37; H, 4.21; N, 5.89.

3-(4-Phenylbenzoyl)indolizine (5f). Yield: 216 mg, 73%. Yellow solid from petroleum ether–ethyl acetate, mp 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (d, J = 4.5 Hz, 1H), 6.97 (td, J = 6.9, 1.1 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.39–7.53 (m, 4H), 7.59 (d, J = 9.0 Hz, 1H), 7.67–7.74 (m, 4H), 7.92 (d, J = 8.4 Hz, 2H), 9.95 (d, J = 6.8 Hz, 1H). IR (KBr): 1592, 1578, 1469, 1387, 1356, 1235, 879, 768, 752, 740. MS (EI): m/z (%) 297 (100) [M$^+$], 269 (57), 268 (43), 152 (23), 144 (59), 116 (26), 89 (8). Anal. Calcd for $C_{21}H_{15}NO$: C, 84.85; H, 5.05; N, 4.71. Found: C, 84.80; H, 5.08; N, 4.73.

General procedure for the preparation of 1-acylpyrrolo[1,2-*a*]quinolines (6a–6f)

A mixture of quinolinium salt **2** (1 mmol), maleic anhydride **4** (0.196 g, 2 mmol), TPCD (1 g) and potassium carbonate (0.483 g, 3.5 mmol) in DMF (15 ml) was heated under N_2 atmosphere at 90 °C for 6 h with magnetic stirring. The reaction was monitored by TLC. After the reaction was completed, 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**.

1-Benzoylpyrrolo[1,2-*a*]quinoline (6a). Yield: 211 mg, 78%. Yellow solid from petroleum ether–ethyl acetate, mp 93–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.55 (d, J = 4.3 Hz, 1H), 7.22 (d, J = 4.3 Hz, 1H), 7.40–7.45 (m, 3H), 7.52–7.57 (m, 3H), 7.63 (t, J = 7.3 Hz, 1H), 7.73 (dd, J = 7.7, 1.0 Hz, 1H), 8.09 (d, J = 7.1 Hz, 2H), 8.20 (d, J = 8.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.3, 139.5, 139.4, 133.7, 132.2, 130.1, 128.9, 128.6, 128.5, 128.2, 128.0, 125.7, 125.0, 124.6, 120.1, 117.9, 104.0. IR (KBr): 1614, 1597, 1575, 1452, 1337, 1207, 871, 811, 719. MS (EI): m/z (%) 271 (100) [M$^+$], 243 (20), 242 (15), 194 (34), 166 (25), 77 (6). Anal. Calcd for $C_{19}H_{13}NO$: C, 84.13; H, 4.80; N, 5.17. Found: C, 84.10; H, 4.83; N, 5.18.

1-(4-Chlorobenzoyl)pyrrolo[1,2-*a*]quinoline (6b). Yield: 262 mg, 86%. Yellow solid from petroleum ether–ethyl acetate, mp 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (d, J = 4.4 Hz, 1H), 7.22 (d, J = 4.4 Hz, 1 H), 7.40–7.46 (m, 3H), 7.50–7.58 (m, 3H), 7.73 (dd, J = 7.8, 1.4 Hz, 1H), 8.02 (d, J = 8.5 Hz, 2H), 8.15 (d, J = 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.8, 139.7, 138.5, 137.9, 133.7, 131.4, 129.0, 128.7, 128.6, 128.1, 126.0, 125.0, 124.8, 120.1, 117.9, 104.3. IR (KBr): 1626, 1611, 1587, 1454, 1399, 1329, 1089, 1054, 879, 806, 750. MS (EI): m/z (%) 305 (100) [M$^+$], 277 (15), 276 (6), 194 (32), 166 (24), 139 (4). Anal. Calcd for $C_{19}H_{12}NOCl$: C, 74.75; H, 3.93; N, 4.59. Found: C, 74.80; H, 3.95; N, 4.61.

1-(4-Methoxybenzoyl)pyrrolo[1,2-*a*]quinoline (6c). Yield: 242 mg, 80%. Yellow solid from petroleum ether–ethyl acetate, mp 109–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H), 6.55 (d, J = 4.3 Hz, 1H), 7.03 (dt, J = 8.8, 2.0 Hz, 2H), 7.19 (d, J = 4.3 Hz, 1H), 7.36–7.43 (m, 3H), 7.51 (td, J = 7.2, 1.5 Hz, 1H), 7.71 (dd, J = 7.8, 1.5 Hz, 1H), 8.09 (dd, J = 9.0, 1.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.8, 163.1, 138.8, 133.7, 132.4, 131.9, 128.6, 128.4, 127.9, 127.7, 125.1, 125.0, 124.5, 120.0, 118.0, 113.6, 103.8, 55.5. IR (KBr): 1600, 1556, 1453, 1338, 1261, 1168, 1025, 881, 808, 755. MS (EI): m/z (%) 301 (100) [M$^+$], 273 (7), 272 (14), 258 (10), 194 (13), 166 (18), 135 (11), 77 (5). Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.73; H, 4.98; N, 4.65. Found: C, 79.77; H, 4.95; N, 4.66.

1-(2-Naphthoyl)pyrrolo[1,2-*a*]quinoline (6d). Yield: 235 mg, 73%. Yellow solid from petroleum ether–ethyl acetate, mp 135–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (d, J = 4.2 Hz, 1H), 7.28 (d, J = 4.2 Hz, 1H), 7.41–7.44 (m, 3H), 7.52–7.67 (m, 3H), 7.75 (d, J = 7.7 Hz, 1H), 7.98 (t, J = 9.0 Hz, 3H), 8.16 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 8.6 Hz, 1H), 8.63 (s, 1H). IR (KBr): 1606, 1572, 1555, 1483, 1452, 1335, 1321, 1271, 1052, 893, 810, 759. MS (EI): m/z (%) 321 (100) [M$^+$], 293 (10), 292 (17), 194 (15), 166 (14), 127 (8). Anal. Calcd for $C_{23}H_{15}NO$: C, 85.98; H, 4.67; N, 4.36. Found: C, 86.05; H, 4.71; N, 4.31.

1-(4-Fluorobenzoyl)pyrrolo[1,2-*a*]quinoline (6e). Yield: 258 mg, 89%. Yellow solid from petroleum ether–ethyl acetate, mp 120–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (d, J = 4.5 Hz, 1H), 7.19–7.25 (m, 3H), 7.40–7.45 (m, 3H), 7.54 (td, J = 7.2, 1.5 Hz, 1H), 7.73 (dd, J = 7.8, 1.3 Hz, 1H), 8.09–8.16 (m, 3H). IR (KBr): 1614, 1595, 1452, 1338, 1225, 1156, 879, 812, 754. MS (EI): m/z (%) 289 (100) [M$^+$], 261 (40), 260 (23), 194 (61), 166 (58), 84 (22). Anal. Calcd for $C_{19}H_{12}NOF$: C, 78.89; H, 4.15; N, 4.84. Found: C, 78.84; H, 4.18; N, 4.82.

1-(4-Methylbenzoyl)pyrrolo[1,2-*a*]quinoline (6f). Yield: 233 mg, 82%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H), 6.55 (d, J = 4.5 Hz, 1H), 7.22 (d, J = 4.5 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.38–7.44 (m, 3H), 7.52 (td, J = 7.2, 1.5 Hz, 1H), 7.73 (dd, J = 7.8, 1.5 Hz, 1H), 8.00 (d, J = 8.1 Hz, 2H), 8.16 (d, J = 8.5 Hz, 1H). IR (KBr): 1625, 1605, 1483, 1454, 1338, 1269, 1176, 1051, 876, 807, 748. MS (EI): m/z (%) 285 (100) [M$^+$], 257 (22), 256 (17), 194 (23), 166 (18), 91 (6). Anal. Calcd for $C_{20}H_{15}NO$: C, 84.21; H, 5.26; N, 4.91. Found: C, 84.27; H, 5.29; N, 4.89.

General procedure for the preparation of 1-acylpyrrolo[2,1-*a*]isoquinolines (7a–7i)

A mixture of isoquinolinium salt **3** (1 mmol), maleic anhydride **4** (0.196 g, 2 mmol), TPCD (1 g) and potassium carbonate (0.483 g, 3.5 mmol) in DMF (15 ml) was heated under N_2 atmosphere at 90 °C for 6 h with magnetic stirring. The reaction was monitored by TLC. After the reaction was completed, 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-Benzoylpyrrolo[2,1-*a*]isoquinoline (7a). Yield: 216 mg, 80%. Colorless solid from petroleum ether–ethyl acetate, mp 140–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (d, J = 4.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 4.5 Hz, 1H), 7.49–7.60 (m, 5H), 7.75 (dd, J = 6.6, 2.4 Hz, 1H), 7.87 (dd, J = 8.1, 1.5 Hz, 2H), 8.20 (dd, J = 6.6, 2.2 Hz, 1H), 9.62 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.4, 140.6, 136.9, 131.2, 129.2, 128.9, 128.2, 128.0, 127.7, 126.9, 126.0, 125.8, 124.6, 123.6, 113.4, 102.0. IR (KBr): 1610, 1573, 1468, 1357, 1234, 1053, 875, 797, 760, 723, 695. MS (EI): m/z (%) 271 (100) [M$^+$], 243 (6), 242 (19), 194 (24), 166 (15), 139 (7), 77 (4). Anal. Calcd for $C_{19}H_{13}NO$: C, 84.13; H, 4.80; N, 5.17. Found: C, 84.09; H, 4.82; N, 5.17.

1-(4-Chlorobenzoyl)pyrrolo[2,1-*a*]isoquinoline (7b). Yield: 268 mg, 88%. Yellow solid from petroleum ether–ethyl acetate,

mp 208–210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, J = 4.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1 H), 7.29 (d, J = 4.5 Hz, 1H), 7.50 (dt, J = 8.6, 2.1 Hz, 2H), 7.58–7.62 (m, 2H), 7.74–7.77 (m, 1H), 7.80 (dt, J = 8.6, 2.1 Hz, 2H), 8.21 (dd, J = 6.6, 2.5 Hz, 1H), 9.59 (d, J = 7.5 Hz,1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.9, 138.9, 137.4, 137.2, 130.5, 129.0, 128.5, 128.2, 127.8, 127.0, 125.8, 125.7, 124.6, 124.4, 123.7, 113.6, 102.2. IR (KBr): 1610, 1590, 1565, 1467, 1452, 1352, 1233, 1088, 878, 806, 756, 748. MS (EI): m/z (%) 305 (100) [M$^+$], 277 (5), 276 (10), 241 (7), 194 (31), 166 (23), 139 (13). Anal. Calcd for $C_{19}H_{12}NOCl$: C, 74.75; H, 3.93; N, 4.59. Found: C, 74.67; H, 3.92; N, 4.58.

1-(4-Methoxybenzoyl)pyrrolo[2,1-*a*]isoquinoline (7c). Yield: 251 mg, 83%. Yellow solid from petroleum ether–ethyl acetate, mp 187–189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.02 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 4.3 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 4.4 Hz, 1H), 7.55–7.62 (m, 2H), 7.73 (dd, J = 6.6, 1.9 Hz, 1H), 7.88 (d, J = 8.7 Hz, 2H), 8.18 (d, J = 7.2 Hz, 1H), 9.55 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.5, 162.3, 133.1, 131.3, 128.8, 127.9, 127.7, 126.9, 125.8, 125.2, 124.8, 123.6, 113.5, 113.1, 101.7, 55.5. IR (KBr): 1604, 1573, 1451, 1353, 1252, 1026, 880, 841, 796, 757. MS (EI): m/z (%) 301 (100) [M$^+$], 273 (3), 272 (11), 258 (4), 194 (8), 166 (8), 139 (3). Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.73; H, 4.98; N, 4.65. Found: C, 79.66; H, 4.95; N, 4.70.

1-(2-Naphthoyl)pyrrolo[2,1-*a*]isoquinoline (7d). Yield: 248 mg, 77%. Yellow solid from petroleum ether–ethyl acetate, mp 216–218 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, J = 4.5 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 4.5 Hz, 1H), 7.56–7.64 (m, 4H), 7.76 (dd, J = 6.6, 2.4 Hz, 1H), 7.93–8.00 (m, 4H), 8.23 (dd, J = 6.6, 2.2 Hz, 1H), 8.37 (s, 1H), 9.65 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.3, 137.9, 137.0, 134.7, 132.5, 129.9, 129.1, 129.0, 128.1, 128.0, 127.8, 127.7, 127.6, 126.9, 126.6, 126.0, 125.9, 125.8, 124.9, 124.7, 123.7, 113.4, 102.0. IR (KBr): 1603, 1590, 1449, 1354, 1242, 1112, 806, 752. MS (EI): m/z (%) 321 (100) [M$^+$], 293 (8), 292 (23), 194 (18), 166 (18), 139 (11), 127 (8), 84 (8). Anal. Calcd for $C_{23}H_{15}NO$: C, 85.98; H, 4.67; N, 4.36. Found: C, 85.95; H, 4.69; N, 4.38.

1-(4-Fluorobenzoyl)pyrrolo[2,1-*a*]isoquinoline (7e). Yield: 267 mg, 92%. Yellow solid from petroleum ether–ethyl acetate, mp 191–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (d, J = 4.5 Hz, 1H), 7.14–7.23 (m, 3H), 7.30 (d, J = 4.5 Hz, 1H), 7.57–7.63 (m, 2H), 7.75 (dd, J = 6.4, 2.4 Hz, 1H), 7.87–7.92 (m, 2H), 8.19 (dd, J = 6.6, 2.4 Hz, 1H), 9.58 (d, J = 7.5 Hz, 1H). IR (KBr): 1612, 1600, 1587, 1466, 1451, 1353, 1229, 1056, 881, 805, 750. MS (EI): m/z (%) 289 (100) [M$^+$], 261 (10), 260 (57), 194 (56), 166 (41), 139 (12). Anal. Calcd for $C_{19}H_{12}NOF$: C, 78.89; H, 4.15; N, 4.84. Found: C, 78.81; H, 4.17; N, 4.81.

1-(4-Methylbenzoyl)pyrrolo[2,1-*a*]isoquinoline (7f). Yield: 236 mg, 83%. Yellow solid from petroleum ether–ethyl acetate, mp 168–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 3H), 7.05 (d, J = 4.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.28–7.35 (m, 3H), 7.56–7.59 (m, 2H), 7.73 (dd, J = 6.7, 1.8 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 8.20 (dd, J = 6.8, 1.5 Hz, 1H), 9.60 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.3, 141.7, 137.8, 136.7, 129.3, 128.9, 127.9, 127.7, 126.9, 125.8, 125.6, 124.8, 124.7, 123.6, 113.2, 101.8, 21.6. IR (KBr): 1599, 1563, 1466, 1452, 1347, 1234, 1051, 878, 748, 739. MS (EI): m/z (%) 285 (100) [M$^+$], 257 (13), 256 (60), 194 (46), 166 (35), 139 (12), 91 (6). Anal. Calcd for $C_{20}H_{15}NO$: C, 84.21; H, 5.26; N, 4.91. Found: C, 84.25; H, 5.23; N, 4.92.

Ethyl pyrrolo[2,1-*a*]isoquinoline-1-carboxylate (7g). Yield: 161 mg, 67%. Colorless solid from petroleum ether–ethyl acetate, mp 95–97 °C (lit:[21] 94 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, J = 6.9 Hz, 3H), 4.42 (q, J = 6.9 Hz, 2H), 7.00–7.02 (m, 2H), 7.47–7.55 (m, 3H), 7.66 (d, J = 7.6 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H), 9.23 (d, J = 7.5 Hz, 1H). IR (KBr): 1688, 1533, 1471, 1452, 1342, 1247, 1179, 1104, 1066, 801, 737. MS (EI): m/z (%) 239 (100) [M$^+$], 211 (44), 194 (30), 167 (27), 166 (16), 139 (6). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.31; H, 5.44; N, 5.86. Found: C, 75.38; H, 5.42; N, 5.83.

1-(4-Phenylbenzoyl)pyrrolo[2,1-*a*]isoquinoline (7h). Yield: 285 mg, 82%. Yellow solid from petroleum ether–ethyl acetate, mp 238–240 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, J = 4.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 4.5 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.57–7.62 (m, 2H), 7.68–7.76 (m, 5H), 7.95 (d, J = 8.1 Hz, 2H), 8.22 (dd, J = 6.6, 2.1 Hz, 1H), 9.64 (d, J = 7.6 Hz, 1H). IR (KBr): 1610, 1579, 1530, 1468, 1451, 1353, 1236, 1055, 880, 796, 760, 739. MS (EI): m/z (%) 347 (100) [M$^+$], 319 (7), 318 (15), 194 (12), 166 (11), 139 (4), 84 (3). Anal. Calcd for $C_{25}H_{17}NO$: C, 86.46; H, 4.90; N, 4.03. Found: C, 86.49; H, 4.95; N, 4.01.

Pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile (7i). Yield: 121 mg, 63%. Colorless solid from petroleum ether–ethyl acetate, mp 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, J = 4.1 Hz, 1H), 7.08 (d, J = 7.4 Hz, 1H), 7.31 (d, J = 4.2 Hz, 1H), 7.51–7.62 (m, 2H), 7.69 (d, J = 7.6 Hz, 1H), 8.06 (d, J = 7.4 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H). IR (KBr): 2217, 1637, 1527, 1455, 1354, 1126, 791, 739. MS (EI): m/z (%) 192 (100) [M$^+$], 165 (14), 164 (9), 139 (5), 138 (5), 96 (6). Anal. Calcd for $C_{13}H_8N_2$: C, 81.25; H, 4.17; N, 14.58. Found: C, 81.35; H, 4.21; N, 14.52.

Procedure for the preparation of 3-acylindolizines (5a-5c) with manganese dioxide as an oxidant

A mixture of the corresponding 1-phenacyl pyridinium salt **1a**, **1b** or **1c** (1 mmol), maleic anhydride **4** (0.196 g, 2 mmol), newly prepared MnO_2 (0.7 g) and potassium carbonate (0.483 g, 3.5 mmol) in DMF (10 ml) was heated at 90 °C under N_2 atmosphere for 3 h with magnetic stirring. The reaction course was monitored by TLC. After the reaction, 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 **5a** (143 mg, 65%), **5b** (181 mg, 71%) or **5c** (165 mg, 66%).

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