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Ultrasound-assisted 1,3-dipolar cycloaddition and cyclopropanation reactions for the synthesis of bis-indolizine and bis-cyclopropane derivatives†

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Ultrasound irradiation can promote the 1,3-dipolar cycloaddition reaction of 2-chloropyridinium ylides with 2-benzylidenemalononitrile or 2,2′-(1,4-phenylenebis(methanylylidene))dimalononitrile, to afford the indolizine and bis-indolizine derivatives respectively. While the reaction of pyridinium ylides with 2-benzylidenemalononitrile or 2,2′-(1,4-phenylenebis(methanylylidene))dimalononitrile under ultrasound irradiation provided, in an unusual manner, cyclopropane and bis-cyclopropane derivatives, respectively. These cycloaddition and cyclopropanation reactions were carried out in the presence of triethylamine, in acetonitrile, at room temperature.

Introduction

Ultrasound irradiation has increasingly been used as a green approach for accelerating organic synthesis reactions.[1–3] The main advantages of this method in comparison to common laboratory techniques are reduction of the reaction time, increased reaction efficiency, high product purity, improved selectivity, reduced byproduct formation, and use of milder reaction conditions.[4,5] More recently, ultrasound irradiation has been used for the regioselective synthesis of pyrrolidine Lobelia alkaloid analogues,[6] for one-pot synthesis of various ionic liquids,[7] and as a clean and practical protocol for the synthesis of polyfunctionalized heterocyclic compounds.[8]

It is not surprising that the synthesis of polyfunctionalized heterocyclic compounds has received substantial attention, because polyfunctionalized heterocyclic compounds play important roles in the synthesis of a large number of biologically active molecules.[9–12] In recent years, a great deal of research into polyfunctionalized heterocyclic compounds has allowed the synthesis of bis-heterocyclic compounds that show various biological activities, such as antibacterial, fungicidal, tuberculostatic, and antiamoebic properties.[13–16] Among these aforementioned compounds, indolizine and cyclopropane derivatives have received much attention in recent years, due to their notable molecular structures and important biological activities.

Indolizine derivatives possess numerous diverse biological and pharmacological applications, and these applications have made them interesting heterocyclic compounds to work on.[17–19] Many substituted indolizines have shown biological activities, such as anti-inflammatory,[20] antioxidant,[21] anticancer,[22] antitubercular,[23] antimicrobial,[24] and analgesic[25] activities, *etc*. In addition, some indolizine derivatives are being used to produce organic fluorescent substances,[26] dyes[27] *etc*. In addition, cyclopropanes also play a prominent role in organic synthesis as they are present in biologically active compounds and various natural compounds, such as terpenes, pheromones and fatty acid metabolites.[28,29] Moreover, they have been used for the preparation of molecules with diverse functional groups.[30]

Herein, we report a new method for the synthesis of indolizine (**8a–c**) and bis-indolizine derivatives (**7a–c**), using a 1,3-dipolar cycloaddition reaction of 2-chloropyridinium bromides (**6a–c**) with electron-deficient olefins, such as 2-benzylidenemalononitrile (**4**) and 2,2′-(1,4-phenylenebis(methanylylidene))-dimalononitrile (**2**). The reaction is performed under ultrasound irradiation, in the presence of triethylamine and acetonitrile. We also study the reaction of pyridinium bromides (**1a–c**) with these electron-deficient olefins, from which cyclopropane (**5a–c**) and bis-cyclopropane derivatives (**3a–c**) are formed, through cyclopropanation.

Results and discussion

The most common synthetic route to indolizines is through a 1,3-dipolar cycloaddition reaction, using cycloimmonium ylides, such as pyridinium ylides, along with a reagent containing an activated double or triple bond. However, when 2-benzy-

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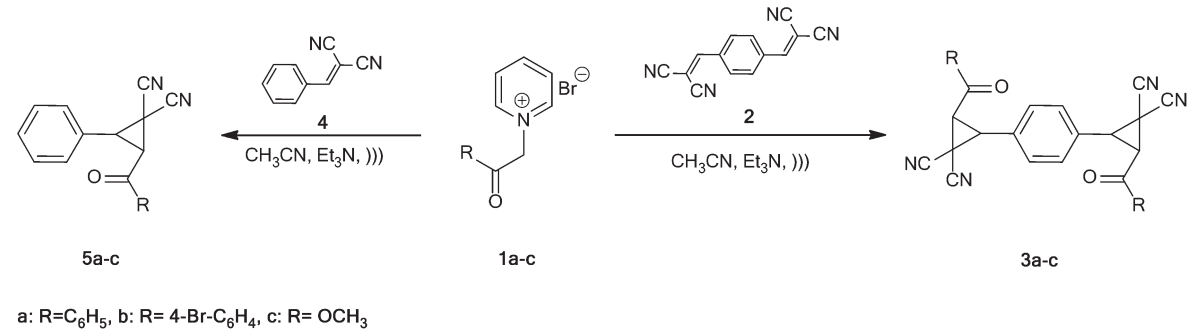
lidenemalononitrile (**4**) was used as the activated double bond component in a reaction with pyridinium bromides **1a–c**, cyclopropane derivatives (**5a–c**) were produced.[31] The reaction of pyridinium bromides with 2,2′-(1,4-phenylenebis(methanylylidene))dimalononitrile (**2**) was also investigated, which led, as might be expected, to the formation of bis-cyclopropane derivatives (**3a–c**). These reactions were conducted at room temperature, under ultrasound irradiation, using triethylamine as the base and acetonitrile as the solvent (Scheme 1).

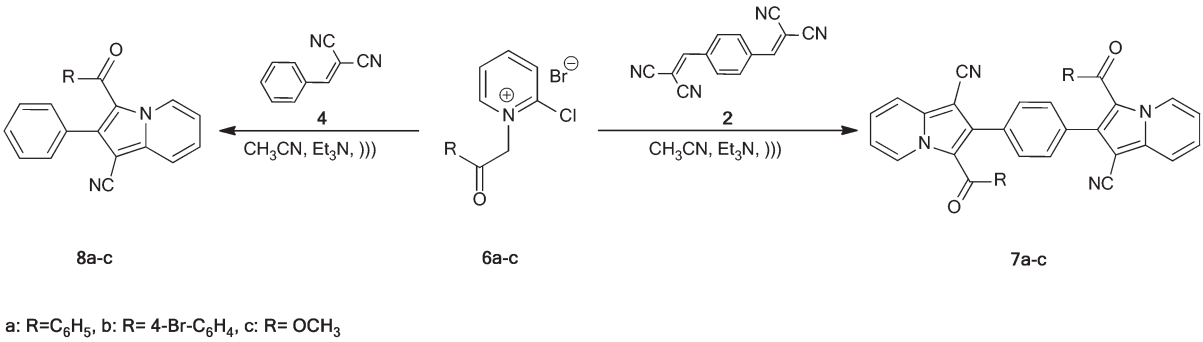
On the other hand, reaction of 2-chloropyridinium bromides (**6a–c**) with 2-benzylidenemalononitrile (**4**) or 2,2′-(1,4-phenylenebis(methanylylidene))dimalononitrile (**2**), under the same conditions, resulted in the formation of indolizine (**8a–c**) and bis-indolizine (**7a–c**) derivatives respectively (Scheme 2).

As shown in Scheme 3, in these reactions the first step is a Knoevenagel condensation, which takes place to form the 2,2′-(1,4-phenylenebis(methanylylidene))dimalononitrile (**2**). For the synthesis of the bis-cyclopropane derivatives (**3a–c**), Michael addition of a pyridinium ylides (**I**), which were prepared *in situ* from the corresponding pyridinium bromides (**1a–c**) using triethylamine, to 2,2′-(1,4-phenylenebis(methanylylidene))dimalononitrile (**2**) can lead to the formation of intermediate **II**. In the following cyclization step, intramolecular substitution of the pyridine group by the carbanion can occur, to generate the corresponding cyclopropane (**III**). The final bis-cyclopropane derivatives (**3a–c**) were then formed following a repetition of the above steps. However, the 1,3-dipolar cycloaddition reaction of 2-chloropyridinium ylides (**IV**), which were prepared *in situ* from the corresponding 2-chloropyridinium bromides (**6a–c**) using triethylamine, with 2,2′-(1,4-phenylenebis(methanylylidene))dimalononitrile (**2**) formed intermediate **V**. The elimination of HCN and HCl from intermediate **V** can then follow, to provide the indolizine derivatives (**VI**). Finally, the bis-indolizine derivatives (**7a–c**) are formed.

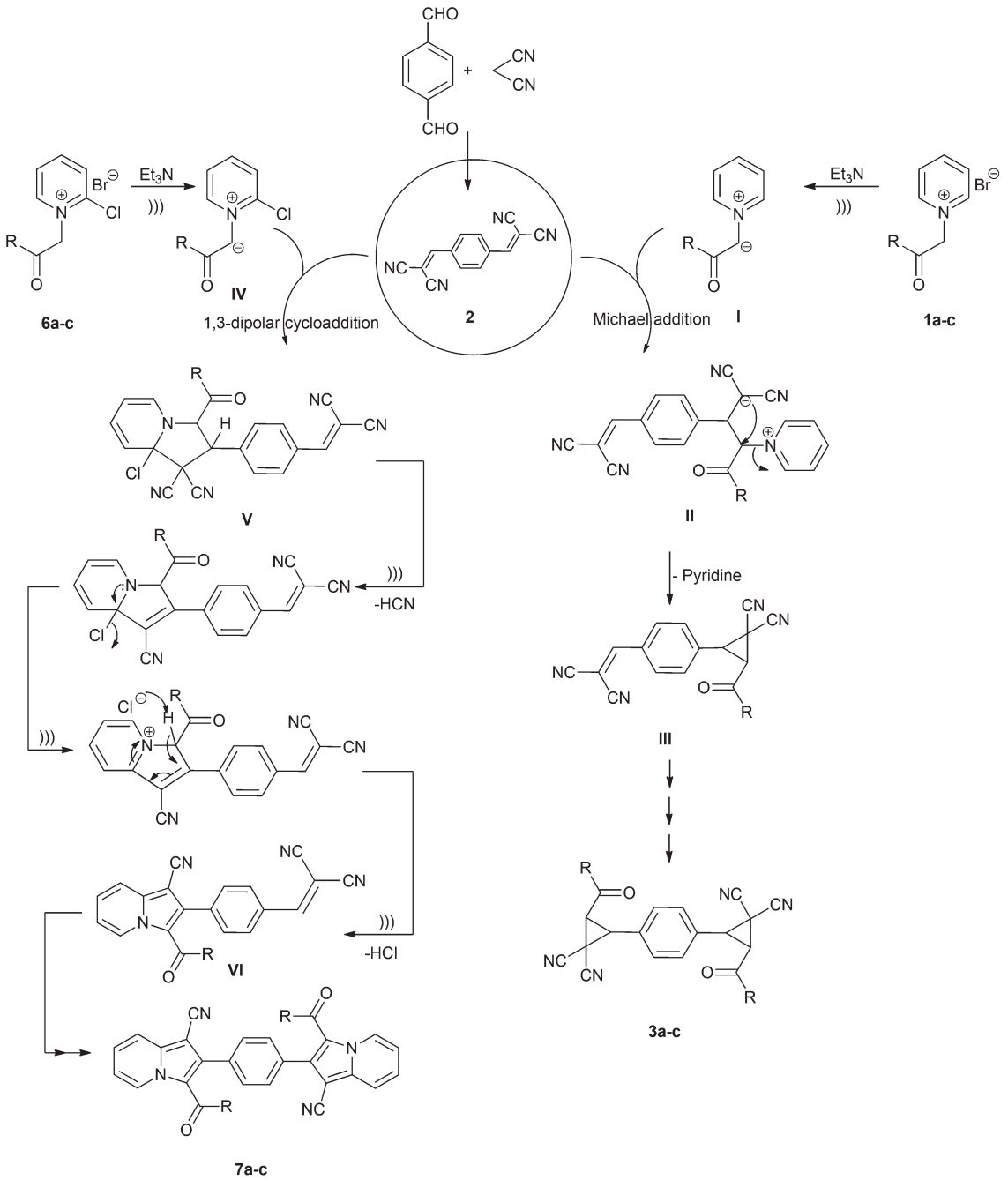
The structures of compounds **3a–c**, **7a–c** and **8a–c** were determined on the basis of their elemental analysis, mass spectrum, and ^{1}H, ^{13}C NMR and IR spectroscopic data. The IR spectrum of **3a** showed the presence of CN by a band in the region of 2208 cm^{-1}, and showed one sharp band at 1655 cm^{-1} due to vibration of the carbonyl (C═O) group. The ^{1}H NMR spectrum of **3a** indicated two types of aliphatic protons, by signals at 3.06 and 1.16 ppm. The aryl proton signals appeared at 7.95–7.19 ppm (14H, m). The ^{13}C NMR of compound **3a** showed two signals at 190.3 and 114.2 ppm, which were attributed to the carbonyl and CN carbons respectively. The signals for the eighteen aromatic carbons appeared at 153.9–126.8 ppm. These signals appeared along with three upfield shifted aliphatic carbon atom signals at 45.6, 28.9 and 8.6 ppm. The structure of compound **8a** was also established on the basis of spectral data. The IR spectrum of this compound showed the presence of CN by a band in the region of 2208 cm^{-1}, and showed a sharp band at 1648 cm^{-1} due to the carbonyl (C═O) group. The ^{1}H NMR spectrum of **8a** showed fourteen aryl protons, which appeared at 7.99–6.97 ppm. The ^{13}C NMR of compound **8a** showed two signals at 190.0 and 114.7 ppm, which were due to the carbonyl (C═O) and nitrile (CN) carbons respectively. The aromatic carbon signals appeared at 154.7–118.0 ppm.



Scheme 1 Synthesis of cyclopropane and bis-cyclopropane derivatives.



Scheme 2 Formation of indolizine and bis-indolizine derivatives.



Scheme 3 Proposed mechanism for the synthesis of cyclopropane, bis-cyclopropane, indolizine and bis-indolizine derivatives.

Conclusions

In summary, we have reported an efficient procedure for the reaction of pyridinium or 2-chloropyridinium ylides with 2-benzylidenemalononitrile, which leads to the synthesis of cyclopropane or indolizine derivatives. Reaction of these ylides with 2,2′-(1,4-phenylenebis(methanylylidene))dimalononitrile generated bis-cyclopropane or bis-indolizine derivatives. The reactions were carried out in the presence of triethylamine, in acetonitrile, under ultrasound irradiation at room temperature. The developed procedure offers several advantages, including high yields, operational simplicity, mild reaction conditions and a very simple product separation process, which makes it a useful practical process for the synthesis of these compounds.

Experimental section

General methods

Melting points were measured on an Electrothermal-9100 apparatus and are uncorrected. IR spectra were recorded on a

Bruker FT-IR Tensor 27 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer. Ultrasonication was performed in a Bandelin-Sonorex Ultrasonic Bath (Super RK) with a frequency of 100 kHz. The internal dimensions of the ultrasonic tank were 240 × 140 × 100 mm with a liquid holding capacity of 3 L. Pyridinium[32] and 2-chloropyridinium bromides[33] were prepared according to literature procedures.

Typical procedure for the preparation of compounds (3, 7, 8a–c). A solution of 2-benzylidenemalononitrile (**4**) (2 mmol) or 2,2′-(1,4-phenylenebis(methanylylidene))dimalononitrile (**2**) (1 mmol), pyridinium (**1a–c**) or 2-chloropyridinium bromide (**6a–c**) (2 mmol) and triethylamine (0.2 mL) in acetonitrile (10 mL) were irradiated at room temperature for 20–35 min (the progress of the reaction was monitored by TLC, with hexane–ethyl acetate used as an eluent). The reaction mixture was diluted with 50 mL of water and the resulting precipitate was collected by filtration. The crude product was recrystallized using dichloromethane–*n*-hexane (1 : 2) to give the pure solid sample for analysis.

3,3′-(1,4-Phenylene)bis(2-benzoylcyclopropane-1,1-dicarbonitrile) (3a). Black powder, yield: 89%. m.p. 270 °C (dec.). IR (KBr, ν_{max}/cm^{-1}): 2208 (CN), 1655 (C═O), 1593, 1523 (C═C). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_{ppm}: 7.95–7.19 (m, 14H, CH–Ar), 3.06 (d, 2H, ^3J = 4 Hz, CH), 1.16 (d, 2H, ^3J = 4 Hz, CH). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_{ppm}: 190.3 (C═O), 153.9, 130.6, 129.4, 128.7, 127.8, 126.8, 114.2 (CN), 45.6 (CH), 28.9 (CH), 8.6 (C). MS (*m*/*z*): 466 (M$^+$) (1), 462 (6), 394 (3), 368 (18), 319 (16), 273 (13), 218 (7), 174 (41), 121 (8), 105 (63), 77 (100). Anal. calcd for $C_{30}H_{18}N_4O_2$: C, 77.24; H, 3.89; N, 12.01%. Found: C, 77.07; H, 3.72; N, 11.84%.

3,3′-(1,4-Phenylene)bis(2-(4-bromobenzoyl)cyclopropane-1,1-dicarbonitrile) (3b). Black powder, yield: 88%. m.p. 300 °C (dec.). IR (KBr, ν_{max}/cm^{-1}): 2192 (CN), 1657 (C═O), 1625, 1577 (C═C). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_{ppm}: 8.97–7.89 (m, 12H, CH–Ar), 3.91 (d, 2H, ^3J = 4 Hz, CH), 2.09 (d, 2H, ^3J = 4 Hz, CH). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_{ppm}: 190.0 (C═O), 146.4, 146.2, 132.5, 132.2, 130.1, 127.8, 113.5 (CN), 37.2 (CH), 30.6 (CH), 14.7 (C). MS (*m*/*z*): 624 (M + 2) (1), 622 (M$^+$) (1), 604 (12), 552 (9), 481 (2), 436 (4), 393 (6), 339 (28), 313(29), 286 (41), 236 (33), 183 (29), 127 (27), 97 (41), 79 (100). Anal. calcd for $C_{30}H_{16}Br_2N_4O_2$: C, 57.72; H, 2.58; N, 8.97%. Found: C, 57.55; H, 2.43; N, 8.80%.

Dimethyl 3,3′-(1,4-phenylene)bis(2,2-dicyanocyclopropanecarboxylate) (3c). Brown powder, yield: 89%. m.p. 119 °C (dec.). IR (KBr, ν_{max}/cm^{-1}): 2258 (CN), 1737 (C═O), 1614, 1523 (C═C). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_{ppm}: 7.01 (s, 2H, CH–Ar), 6.71 (s, 2H, CH–Ar), 3.86 (d, 2H, ^3J = 4 Hz, CH), 2.24 (s, 3H, OCH_3), 1.61 (d, 2H, ^3J = 4 Hz, CH). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_{ppm}: 166.1 (C═O), 131.1, 129.1, 112.3 (CN), 53.2 (OCH_3), 37.5 (CH), 32.1 (CH), 14.0 (C). MS (*m*/*z*): 374 (M$^+$) (2), 330 (28), 285 (11), 271 (100), 230 (28), 202 (74), 165 (39), 127 (14), 105 (11), 77 (11). Anal. calcd for $C_{20}H_{14}N_4O_4$: C, 64.17; H, 3.77; N, 14.97%. Found: C, 63.98; H, 3.60; N, 14.79%.

2,2′-(1,4-Phenylene)bis(3-benzoylindolizine-1-carbonitrile) (7a). Orange powder, yield: 92%. m.p. 326–328 °C. IR (KBr, ν_{max}/cm^{-1}): 2192 (CN), 1654 (C═O), 1593, 1536 (C═C). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_{ppm}: 7.96–7.78 (m, 8H, CH–Ar), 7.72 (t, 2H, ^3J = 8 Hz, CH–Ar), 7.60 (t, 4H, ^3J = 8 Hz, CH–Ar), 7.34 (t, 2H, ^3J = 8 Hz, CH–Ar), 7.28 (s, 4H, CH–Ar), 6.96 (t, 2H, ^3J = 8 Hz, CH–Ar).^{13}C NMR (100 MHz, DMSO-d$_6$) δ_{ppm}: 189.7 (C═O), 154.8, 143.5, 141.4, 140.5, 136.5, 135.4, 133.4, 132.7, 130.9, 130.7, 129.7, 128.6, 121.0, 117.9, 114.6 (CN). MS (*m*/*z*): 566 (M$^+$) (3), 552 (9), 524 (8), 436 (6), 368 (19), 313 (35), 286 (72), 236 (43), 205 (35), 155 (100), 105 (52), 77 (60). Anal. calcd for $C_{38}H_{22}N_4O_2$: C, 80.55; H, 3.91; N, 9.89%. Found: C, 80.36; H, 3.75; N, 9.71%.

2,2′-(1,4-Phenylene)bis(3-(4-bromobenzoyl)indolizine-1-carbonitrile) (7b). Brown powder, yield: 91%. m.p. 269–270 °C. IR (KBr, ν_{max}/cm^{-1}): 2208 (CN), 1667 (C═O), 1625, 1580 (C═C). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_{ppm}: 7.97–6.93 (m, 20H, CH–Ar). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_{ppm}: 189.1 (C═O), 154.8, 143.8, 141.4, 140.4, 136.3, 136.2, 134.4, 133.5, 131.7, 130.9, 130.7, 126.7, 121.0, 117.9, 114.7 (CN). MS (*m*/*z*): 724 (M + 2) (1), 722 (M$^+$) (1), 648 (2), 578 (5), 478 (10), 436 (15), 340 (31), 286 (100), 253 (30), 200 (16), 183 (100), 155 (83), 123 (45), 107 (25), 91 (46), 75 (35). Anal. calcd for $C_{38}H_{20}Br_2N_4O_2$: C, 63.00; H, 2.78; N, 7.73%. Found: C, 62.81; H, 2.62; N, 7.58%.

Dimethyl 2,2′-(1,4-phenylene)bis(1-cyanoindolizine-3-carboxylate) (7c). Yellow powder, yield: 90%. m.p. 290 °C (dec.). IR (KBr, ν_{max}/cm^{-1}): 2208 (CN), 1734 (C═O), 1614, 1539 (C═C). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_{ppm}: 8.12–6.87 (m, 12H, CH–Ar), 3.72 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_{ppm}: 161.3 (C═O), 154.7, 142.1, 141.0, 131.3, 130.6, 130.0, 129.3, 120.8, 120.2, 114.6, 113.4 (CN), 53.6 (OCH_3). MS (*m*/*z*): 474 (M$^+$) (1), 406 (8), 331 (100), 286 (25), 246 (42), 202 (13), 176 (24), 155 (22), 119 (12), 101 (13), 83 (13). Anal. calcd for $C_{28}H_{18}N_4O_4$: C, 70.88; H, 3.82; N, 11.81%. Found: C, 70.71; H, 3.67; N, 11.66%.

3-Benzoyl-2-phenylindolizine-1-carbonitrile (8a). Yellow powder, yield: 94%. m.p. 223–225 °C. IR (KBr, ν_{max}/cm^{-1}): 2208 (CN), 1648 (C═O), 1593, 1571 (C═C). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_{ppm}: 7.99–7.90 (m, 3H, CH–Ar), 7.84 (t, 1H, ^3J = 8 Hz, CH–Ar), 7.72 (t, 1H, ^3J = 4 Hz, CH–Ar), 7.64–7.22 (m, 8H, CH–Ar), 6.98 (t, 1H, ^3J = 8 Hz, CH–Ar). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_{ppm}: 190.0 (C═O), 154.7, 147.8, 144.8, 141.7, 140.5, 135.7, 135.3, 132.5, 132.2, 130.5, 130.5, 129.6, 129.5, 128.6, 120.9, 118.0, 114.7 (CN). MS (*m*/*z*): 322 (M$^+$) (12), 304 (6), 266 (57), 244 (100), 207 (17), 161 (28), 129 (12), 105 (36), 77 (41). Anal. calcd for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69%. Found: C, 81.80; H, 4.22; N, 8.52%.

3-(4-Bromobenzoyl)-2-phenylindolizine-1-carbonitrile (8b). Yellow powder, yield: 93%. m.p. 180 °C (dec.). IR (KBr, ν_{max}/cm^{-1}): 2192 (CN), 1648 (C═O), 1616, 1580 (C═C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 7.95 (t, 1H, ^3J = 4 Hz, CH–Ar), 7.93 (t, 1H, ^3J = 4 Hz, CH–Ar), 7.81 (s, 1H, CH–Ar), 7.72 (t, 1H, ^3J = 4 Hz, CH–Ar), 7.70 (t, 1H, ^3J = 4 Hz, CH–Ar), 7.53–7.22 (m, 6H, CH–Ar), 7.95 (t, 1H, ^3J = 4 Hz, CH–Ar), 6.64–6.60 (m, 1H,

CH–Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 188.7 (C═O), 156.0, 145.2, 141.6, 140.3, 137.9, 136.4, 134.4, 132.7, 132.1, 131.4, 130.7, 130.2, 129.7, 127.9, 122.5, 117.6, 113.3 (CN). MS (*m*/*z*): 402 (M + 2) (10), 400 (M^+) (11), 340 (5), 287 (10), 244 (100), 217 (14), 185 (26), 157 (23), 129 (8), 102 (5), 76 (10). Anal. calcd for $C_{22}H_{13}BrN_2O$: C, 65.85; H, 3.27; N, 6.98%. Found: C, 65.67; H, 3.13; N, 6.79%.

Methyl 1-cyano-2-phenylindolizine-3-carboxylate (8c). Yellow powder, yield: 91%. m.p. 160–162 °C. IR (KBr, ν_{max}/cm^{-1}): 2192 (CN), 1731 (C═O), 1628, 1542 (C═C). ^{1}H NMR (400 MHz, DMSO-d_6) δ_{ppm}: 8.07 (d, 1H, ^3J = 4 Hz, CH–Ar), 7.79–7.45 (m, 6H, CH–Ar), 7.28 (d, 1H, ^3J = 4 Hz, CH–Ar), 6.90 (t, 1H, ^3J = 4 Hz, CH–Ar), 3.70 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm}: 161.3 (C═O), 156.0, 145.8, 142.3, 139.8, 131.4, 130.9, 130.5, 129.9, 129.5, 127.8, 120.2, 118.5, 113.3 (CN), 52.7 (OCH_3). MS (*m*/*z*): 276 (M^+) (5), 272 (8), 244 (100), 217 (41), 167 (18), 143 (95), 129 (35), 102 (35), 78 (17). Anal. calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14%. Found: C, 73.71; H, 4.20; N, 9.93%.

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