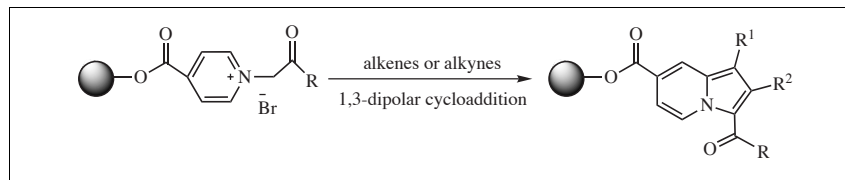


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Received August 28, 2005



A library of 1,2,3,7-tetrasubstituted indolizines has been synthesized using poly(ethylene glycol) (PEG) as soluble polymer support. The PEG-bound pyridinium salts reacted with alkenes or alkynes in the presence of Et₃N *via* 1,3-dipolar cycloaddition to give PEG-bound indolizine derivatives, which were cleaved by 1 % KCN/MeOH to afford 1,2,3,7-tetrasubstituted indolizines in good to excellent yields.

J. Heterocyclic Chem., **43**, 781 (2006).

Introduction.

In recent years, the synthesis of small organic molecules on soluble polymeric supports has become a significant field of interest in particular its application in the field of combinatorial chemistry [1]. It combines the advantages of the conventional liquid-phase synthesis and easy separation/purification of the products in solid-phase synthesis. Moreover, the soluble polymer-bound species allow using routine analytical methods (NMR, TLC or IR) to monitor the reaction process and to determine the structures of products attached to polymer support directly.

In particular, among the soluble supports, poly(ethylene glycol) (PEG) are the most interesting polymers because they can be easily functionalized with different spacers or reactive groups and are commercially available, inexpensive, non-toxic, highly resistant to drastic physical and chemical conditions, and are also soluble in a wide variety of solvents and easily precipitated from ether [2]. Because of their advantages, PEG and its monomethyl analogs are also known to be a rapid and recoverable reaction media for Heck reaction [3], Baylis-Hillman reaction [4], asymmetric dihydroxylation [5], asymmetric aldol condensation [6], and cross-coupling reactions [7] *etc.*

Indolizine derivatives are a well-known class of heterocycles that are very attractive due to their versatility in a large number of applications and their important biological and medical properties. For example, recently they were as potent inhibitors [8] and dyes [9] and exhibited acute antibacterial and antifungal activities [10] *etc.* In addition, they were used to synthesize novel meso-substituted indolizine porphyrins [11] and a new class of

fluorescent β -cyclodextrines to be chemosensors and to detect volatile organic molecules and adamantane derivatives [12].

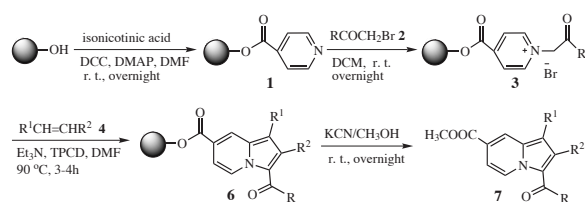
The methods for synthesis of indolizine are classified mainly as Scholtz and Tschitschibabin reaction, 1,3-dipolar cycloaddition and 1,5-dipolar cyclization [13]. Recently there was reported to synthesize indolizines bearing [Os₃(μ -H)₂(CO)₁₀] by the rearrangement of diyne [14]. Although there are many methods, the second one has been widely utilized in the synthesis of indolizines. The synthesis of indolizines on solid support by this method was also reported [15].

Results and Discussion.

We have already described PEG-bound pyridinium-type salts in which PEG was attached to N atom of pyridine using bromoacetyl bromide as the reagent utilized to synthesize a linker [16]. In an extension of our work on PEG-bound pyridinium salt, herein we report that isonicotinic acid attached to PEG employing esterification, followed to react with bromides to afford PEG-bound pyridinium salts. The salts, respectively, reacted with alkenes or alkynes *via* 1,3-dipolar cycloaddition to give PEG-bound indolizine derivatives, followed by cleavage to obtain 1,2,3,7-tetrasubstituted indolizines. For comparison to our synthesis of 1,2,3-trisubstituted indolizines [16a], the synthesis of 1,2,3,7-tetrasubstituted ones had three variable groups. Commercially available difunctional PEG 3400 was chosen as a soluble polymer support.

As shown in Scheme 1, PEG was coupled with isonicotinic acid using 3.0 equiv of dicyclohexyl carbodiimide (DCC) and 0.3 equiv of 4-dimethylaminopyridine (DMAP) in dry dimethyl formamide (DMF) at r. t. overnight to get

Scheme 1



PEG-bound pyridine **1**. The IR spectroscopy of **1** exhibited characteristic C=O absorption band at 1729 cm^{-1} and an O-H absorption band was not observed, furthermore, ^1H NMR spectroscopy of **1** showed that the signals of the pyridine protons were at δ 8.67 and 7.82 ppm. Treatment of **1** with bromides **2** overnight, followed by precipitation and washing with cold anhydrous Et_2O to afford the PEG-bound pyridinium salts **3**. TLC showed the absence of excess reagent and any by-products. The salts **3**, respectively, were treated with 3.0 equiv of alkenes **4**, 0.5 equiv of tetrakis(pyridine) cobalt(II) dichromate (TPCD) and 2.0 equiv of Et_3N in dry DMF at 90° for 3-4 h to afford PEG-bound indolizines **6**. In this reaction, **3** were deprotonated by Et_3N to give the resonance-stabilized PEG-bound pyridinium ylides, 1,3-dipoles, that readily underwent a 1,3-dipolar cycloaddition with **4** to the dihydroindolizines, followed by aromatization using oxidant TPCD to get PEG-bound indolizines as the expected cycloadduct. TPCD, a bimetallic coordination compound, was a mild and versatile oxidant [17] and was used widely in organic synthesis [18] including the synthesis of indolizines [19]. Compounds **6** were cleaved from PEG by 1% KCN in methanol solution at r.t. overnight to give, after purification by column chromatography, indolizines **7a1-7** and **7b1-7** in all overall yields of 48-91% (Table 1), which were unambiguously confirmed by IR, ^1H and ^{13}C NMR spectra and elemental analyses.

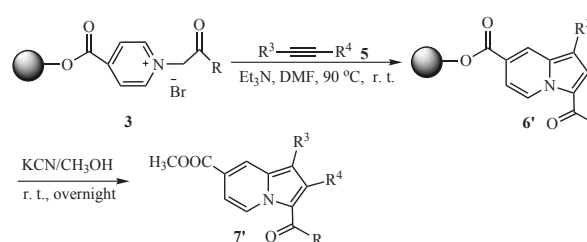
Table 1

Synthesis of indolizines **7a1-7** and **7b1-7** on soluble support.

Entry	R	R^1	R^2	Yield(%)	
				6 ^[a]	7 ^[b]
a1	Me	COPh	4-FPh	97	78
a2	Me	COMe	Ph	98	88
a3	Me	CN	H	97	85
a4	Me	2,3-cyclohexanone		99	90
a5	Me	COPh	(4-F-3-OPh)Ph	97	50
a6	Me	COPh	4-BrPh	96	65
a7	Me	COMe	2-furyl	96	48
b1	Ph	COPh	4-FPh	99	91
b2	Ph	COMe	Ph	96	80
b3	Ph	CN	H	98	82
b4	Ph	2,3-cyclohexanone		97	72
b5	Ph	COPh	(4-F-3-OPh)Ph	96	70
b6	Ph	COPh	3-O ₂ NPh	97	81
7b7	Ph	COPh	3-NCPh	97	75

[a] Based on a step of the reaction; [b] Based on the loading capacity of PEG.

Scheme 2



In order to extend the scope of the application of PEG-bound pyridinium salts [16], the similar reaction of PEG-bound pyridinium salts **3** with alkynes **5** was also carried out. As shown in Scheme 2, **3** reacted with **5** in the presence of Et_3N in DMF at 90° for 3 h to generate PEG-bound indolizines **6'**, followed by the same method of cleavage and purification to afford indolizines **7'** in all overall yields of 62-92% (Table 2). The structures of **7'** were confirmed by IR, ^1H and ^{13}C NMR spectra and elemental analyses. In a step in the reaction of **6'**, PEG-bound pyridinium ylides reacted with **5** by a 1,3-dipolar cycloaddition, followed by aromatization to give the PEG-bound indolizines but not adding TPCD.

Table 2

Synthesis of indolizines **7'a1-2** and **7'b1-2** on soluble support.

Entry	R	R^3	R^4	Yield(%)	
				6' ^[a]	7' ^[b]
a1	Me	H	COOMe	98	62
a2	Me	COOMe	COOMe	97	75
b1	Ph	H	COOMe	99	92
b2	Ph	COOMe	COOMe	97	74

[a] Based on a step of the reaction; [b] Based on the loading capacity of PEG.

Conclusion

We have successfully demonstrated polymer-supported methodology for the efficient synthesis of 1,2,3,7-tetrasubstituted indolizines. In each step of the reaction sequence, the PEG-bound intermediates were purified by simple precipitation and washing by cold anhydrous Et_2O . The pure products are usually obtained in good to excellent yields after easy purification. Synthesis and screening of focused combinatorial libraries may lead to the discovery of interesting biological activities.

Acknowledgements.

This work was supported by Sichuan Agriculture University and the National Natural Sciences Foundation of China (NO: 20372019).

EXPERIMENTAL

All organic solvents and bases were dried by standard methods. PEG3400 (Aldrich, 3015-3685) and PEG-bound compounds were melted in vacuum at 80° for about 30 min before use, to remove any trace of moisture. Melting points were measured on a X-6 digital melting point apparatus and uncorrected. IR spectra were recorded on an IR-Spectrum One spectrometer (Perin Elmer), using KBr pellets. ¹H NMR (600 MHz) and ¹³C NMR (150 MHz) spectra were recorded on a Varian Unity INOVA 600 spectrometer in CDCl₃ using TMS (0.03 %) as internal standard. Elemental analyses were done on a PE 2400 CHN analyzer.

Preparation of PEG-bound Pyridine (**1**).

To a solution of PEG₃₄₀₀ (10.00 g, 5.88 mmoles-OH) in dry DMF (50 mL) were added isonicotinic acid (2.17 g, 17.64 mmoles), DCC (3.63 g, 17.64 mmoles) and DMAP (0.22 g, 1.76 mmoles) and stirred at r.t. overnight. The solvent was evaporated under vacuum, followed by precipitation with cold anhydrous Et₂O (500 mL), washing with cold anhydrous Et₂O (100 mL × 3) and drying under vacuum, to give a white solid **1**, 10.26 g (98%); IR: CH₂ 2882 (strong), C=O 1729 (strong) cm⁻¹; ¹H NMR: δ 8.67 (d, 2H, pyridinyl protons, J = 4.2 Hz), 7.82 (d, 2H, pyridinyl protons, J = 4.2 Hz), 4.40-3.06 (m, 4nH, -O(CH₂CH₂O)_n-).

General Procedure for Preparation of PEG-bound Pyridinium Salts (**3**).

A solution of **1** (10.26 g, 2.84 mmoles), bromoacetone **2a** (1.39 g, 10.15 mmoles) or phenacyl bromide **2b** (2.02 g, 10.15 mmoles) in dry CH₂Cl₂ (40 mL) was stirred at r.t. overnight. After precipitation from cold anhydrous Et₂O (500 mL), the suspension was filtered, washed with cold anhydrous Et₂O (100 mL × 3) and dried to give yellow solid **3a**, 10.70 g (97%) or orange solid **3b**, 10.92 g (96%); **3a**: IR: CH₂ 2868 (strong), C=O 1731 (strong), C=O 1651 (strong) cm⁻¹; ¹H NMR: δ 8.80 (d, 2H, pyridinyl protons, J = 4.5 Hz), 7.89 (d, 2H, pyridinyl protons, J = 4.5 Hz), 5.88 (s, 2H, CH₂COCH₃), 4.60-3.16 (m, 4nH, -O(CH₂CH₂O)_n-), 2.05 (s, 3H, CH₂COCH₃); **3b**: IR: CH₂ 2883 (strong), C=O 1731 (strong), C=O 1652 (strong) cm⁻¹; ¹H NMR: δ 8.84 (d, 2H, pyridinyl protons, J = 4.5 Hz), 7.98 (d, 2H, pyridinyl protons, J = 4.5 Hz), 7.52 (d, 2H, phenyl protons, J = 7.2 Hz), 7.65 (t, 1H, phenyl proton, J = 7.8 Hz), 7.53 (dd, 2H, phenyl protons, J = 7.2, 7.8 Hz), 6.47 (s, 2H, CH₂COPh), 4.63-3.27 (m, 4nH, -O(CH₂CH₂O)_n-).

Typical Procedure for Preparation of Indolizines (**7**).

A solution of **3** (0.50 mmoles), **4** (4.00 mmoles), TPCD (0.30 g, 0.50 mmoles) and Et₃N (0.20 g, 2.00 mmoles) in dry DMF (30 mL) was stirred at 90° for 3-4 h. After the solvent was evaporated under vacuum, the residue was added CH₂Cl₂ (50 mL) and washed with a 0.02% solution of Na₂CO₃ in H₂O (15 mL). The solution was dried over MgSO₄, filtered, concentrated and precipitated with cold anhydrous Et₂O (300 mL) to afford PEG-bound indolizines **6**. The products **6** were treated with a 1% solution of KCN in MeOH (30 mL) and stirred at r.t. overnight, evaporated MeOH and precipitated with cold anhydrous Et₂O to get the crude products, which were purified by column chromatography on silica gel (EtOAc-petroleum ether, 1: 4-1: 2) to give the pure indolizines **7**.

Methyl 3-acetyl-1-benzoyl-2-(4-fluorophenyl)-7-indolizinecarboxylate (**7a1**).

This compound was obtained as yellow green crystals, mp 197°; IR: C=O 1723 (strong), C=O 1625 (strong) cm⁻¹; ¹H NMR: δ 9.98 (d, 1H, 5-H, J = 7.2 Hz), 8.59 (d, 1H, 8-H, J = 1.8 Hz), 7.59 (dd, 1H, 6-H, J = 1.8, 7.2 Hz), 7.49 (d, 2H, phenyl protons, J = 7.8 Hz), 7.37 (t, 1H, phenyl proton, J = 7.2 Hz), 7.21-7.19 (m, 4H, phenyl protons), 6.91 (dd, 2H, phenyl protons, J = 7.2, 7.8 Hz), 3.94 (s, 3H, COOMe), 2.00 (s, 3H, COMe); ¹³C NMR: δ C=O 192.8, C=O 190.9, C=O 165.6, 139.4, 138.9, 137.1, 132.8, 132.7, 132.6, 130.3, 129.7, 128.6, 128.4, 128.2, 123.5, 121.7, 118.6, 115.7, 114.8, OCH₃ 53.3, CH₃ 31.3.

Anal. Calcd. for C₂₅H₁₈NO₄F: C, 72.28, H, 4.37, N, 3.37. Found: C, 72.30, H, 4.34, N, 3.40.

Methyl 1,3-diacetyl-2-phenyl-7-indolizinecarboxylate (**7a2**).

This compound was obtained as yellow spiculate crystals, mp 212°; IR: C=O 1718 (strong), C=O 1624 (strong) cm⁻¹; ¹H NMR: δ 10.03 (d, 1H, 5-H, J = 7.2 Hz), 9.29 (d, 1H, 8-H, J = 1.8 Hz), 7.62 (dd, 1H, 6-H, J = 1.8, 7.2 Hz), 7.54-7.43 (m, 5H, phenyl protons), 3.99 (s, 3H, COOMe), 1.90 (s, 3H, COMe), 1.86 (s, 3H, COMe); ¹³C NMR: δ C=O 195.5, C=O 190.8, C=O 165.8, 140.3, 137.4, 136.1, 130.2, 129.5, 129.4, 129.4, 128.7, 123.8, 123.0, 118.2, 115.4, OCH₃ 53.1, CH₃ 31.4, CH₃ 31.2.

Anal. Calcd. for C₂₀H₁₇NO₄: C, 71.63, H, 5.11, N, 4.18. Found: C, 71.66, H, 5.10, N, 4.20.

Methyl 3-acetyl-1-cyano-7-indolizinecarboxylate (**7a3**).

This compound was obtained as yellow solid, mp 215°; IR: CN 2223 (strong), C=O 1711 (strong), C=O 1650 (strong) cm⁻¹; ¹H NMR: δ 9.86 (d, 1H, 5-H, J = 7.2 Hz), 8.47 (d, 1H, 8-H, J = 1.2 Hz), 7.81 (s, 1H, H-2), 7.59 (dd, 6-H, J = 1.2, 7.2 Hz), 3.98 (s, 3H, COOMe), 2.60 (s, 3H, COMe); ¹³C NMR: δ C=O 188.3, C=O 165.0, 139.8, 129.4, 128.6, 127.3, 124.8, 120.1, 115.3, 114.8, 88.2, OCH₃ 53.4, CH₃ 28.0.

Anal. Calcd. for C₁₃H₁₀N₂O₃: C, 64.46, H, 4.16, N, 11.56. Found: C, 64.61, H, 4.20, N, 11.58.

Methyl 2,3-cyclohexanone-7-indolizinecarboxylate (**7a4**).

This compound was obtained as yellow crystals, mp 188°; IR: CH₂ 2923 (medium), C=O 1715 (strong), C=O 1626 (strong) cm⁻¹; ¹H NMR: δ 10.02 (d, 1H, 5-H, J = 7.2 Hz), 9.09 (s, 1H, 8-H), 7.59 (d, 1H, 6-H, J = 7.2 Hz), 3.98 (s, 3H, COOMe), 3.25 (t, 2H, CH₂, J = 6.0 Hz), 2.66-2.63 (m, 5H, CH₂ and COCH₃), 2.29 (t, 2H, CH₂, J = 6.0 Hz); ¹³C NMR: δ C=O 194.4, C=O 189.0, C=O 165.7, 142.8, 136.5, 129.5, 129.1, 122.3, 121.6, 115.4, 114.8, OCH₃ 53.2, CH₂ 38.9, CH₃ 31.4, CH₂ 25.6, CH₂ 24.7.

Anal. Calcd. for C₁₆H₁₃NO₄: C, 67.36, H, 5.30, N, 4.91. Found: C, 67.42, H, 5.35, N, 4.93.

Methyl 3-acetyl-4-benzoyl-2-(3-phenoxy-4-fluorophenyl)-7-indolizinecarboxylate (**7a5**).

This compound was obtained as light yellow solid; IR: C=O 1722 (strong), C=O 1623 (strong), C=O 1589 (strong) cm⁻¹; ¹H NMR: δ 9.98 (d, 1H, 5-H, J = 7.2 Hz), 8.63 (s, 1H, 8-H), 7.61 (d, 1H, 6-H, J = 7.2 Hz), 7.55 (d, 2H, phenyl protons, J = 7.8 Hz), 7.48 (t, 1H, phenyl proton, J = 7.2 Hz), 7.35-7.29 (m, 4H, phenyl protons), 7.14 (t, 1H, phenyl proton, J = 7.2 Hz), 7.05 (d, 2H, phenyl protons, J = 9.6 Hz), 6.94 (d, 1H, phenyl proton, J = 6.6 Hz), 6.82 (d, 2H, phenyl protons, J = 7.8 Hz), 3.96 (s, 3H, COOMe), 2.08 (s, 3H, COMe); ¹³C NMR: δ C=O 192.6, C=O

190.7, C=O 165.5, 157.1, 154.5, 152.9, 144.3, 141.3, 139.3, 138.5, 137.8, 137.1, 132.8, 131.3, 130.3, 129.8, 128.6, 128.3, 127.4, 124.1, 124.0, 123.3, 121.7, 118.1, 114.9, OCH₃ 53.1, CH₃ 31.3.

Anal. Calcd. for C₃₁H₂₂NO₃F: C, 73.36, H, 4.37, N, 2.76. Found: C, 73.42, H, 4.33, N, 2.70.

Methyl 3-acetyl-1-benzoyl-2-(4-bromo)phenyl-7-indolizinecarboxylate (**7a6**).

This compound was obtained as yellow crystals, mp 186°; IR: CH₃ 2952 (medium), C=O 1723 (strong), C=O 1635 (strong), 1598 (strong) cm⁻¹; ¹H NMR: δ 9.97 (d, 1H, 5-H, J = 7.2 Hz), 8.55 (d, 1H, 8-H, J = 0.6 Hz), 7.58 (d, 1H, 6-H, J = 0.6, 7.2 Hz), 7.48 (d, 2H, phenyl protons, J = 7.8 Hz), 7.40 (t, 1H, phenyl proton, J = 7.2 Hz), 7.35 (d, 2H, phenyl protons, J = 8.4 Hz), 7.22 (dd, 2H, phenyl protons, J = 7.2, 7.8 Hz), 7.12 (d, 2H, phenyl protons, J = 8.4 Hz), 3.93 (s, 3H, COOMe), 2.02 (s, 3H, COMe), ¹³C NMR: δ C=O 192.6, C=O 190.8, C=O 165.5, 139.4, 138.7, 137.1, 133.4, 132.6, 131.7, 129.6, 129.1, 128.6, 128.5, 128.2, 123.4, 123.2, 121.7, 118.4, 114.8, OCH₃ 53.1, CH₃ 31.5.

Anal. Calcd. for C₂₅H₁₈NBrO₄: C, 63.04, H, 3.81, N, 2.94. Found: C, 63.10, H, 3.85, N, 3.83.

Methyl 1,3-diacetyl-2-furyl-7-indolizinecarboxylate (**7a7**).

This compound was obtained as yellow solid; IR: C=O 1727 (strong), C=O 1635 (strong) cm⁻¹; ¹H NMR: δ 9.97 (d, 1H, 5-H, J = 7.2 Hz), 9.27 (s, 1H, 8-H), 7.70 (d, 1H, 6-H, J = 7.2 Hz), 7.62 (dd, 1H, furyl proton, J = 1.8, 7.2 Hz), 6.64-6.61 (m, 2H, furyl protons), 3.99 (s, 3H, COOMe), 2.09 (s, 3H, COMe), 2.05 (s, 3H, COMe); ¹³C NMR: δ C=O 195.0, C=O 190.4, C=O 165.6, 145.1, 143.7, 137.0, 129.3, 128.5, 128.1, 124.5, 123.2, 118.9, 115.7, 113.7, 112.4, OCH₃ 53.2, CH₃ 29.8, CH₃ 29.7.

Anal. Calcd. for C₁₈H₁₅NO₅: C, 66.46, H, 4.65, N, 4.31. Found: C, 66.56, H, 4.73, N, 4.44.

Methyl 1,3-dibenzoyl-2-(4-fluorophenyl)-7-indolizinecarboxylate (**7b1**).

This compound was obtained as yellow crystals, mp 146°; IR: C=O 1721 (strong), C=O 1614 (strong) cm⁻¹; ¹H NMR: δ 9.55 (d, 1H, 5-H, J = 7.2 Hz), 8.79 (d, 1H, 8-H, J = 1.2 Hz), 7.60 (dd, 1H, 6-H, J = 1.2, 7.2 Hz), 7.45 (d, 2H, phenyl protons, J = 7.2 Hz), 7.38 (d, 2H, phenyl protons, J = 7.2 Hz), 7.27-7.21 (m, 2H, phenyl protons), 7.10-7.02 (m, 4H, phenyl protons), 6.83 (dd, 2H, phenyl protons, J = 7.2, 7.8 Hz), 6.43 (dd, 2H, phenyl protons, J = 7.2, 8.4 Hz), 3.97 (s, 3H, COOMe); ¹³C NMR: δ C=O 192.9, C=O 188.9, C=O 165.7, 138.9, 138.8, 138.1, 137.6, 133.5, 133.4, 132.6, 132.4, 129.9, 129.5, 128.3, 128.2, 128.0, 127.5, 122.7, 122.1, 117.2, 114.9, 114.7, 114.6, OCH₃ 53.2.

Anal. Calcd. for C₃₀H₂₀NO₄F: C, 75.46, H, 4.22, N, 3.98. Found: C, 75.44, H, 4.25, N, 3.90.

Methyl 1-acetyl-3-benzoyl-2-phenyl-7-indolizinecarboxylate (**7b2**).

This compound was obtained as yellow crystals, mp 155°; IR: C=O 1723 (strong), C=O 1645 (strong), C=O 1611 (strong) cm⁻¹; ¹H NMR: δ 9.47 (d, 1H, 5-H, J = 7.2 Hz), 9.21 (d, 1H, 8-H, J = 1.2 Hz), 7.61 (dd, 1H, 6-H, J = 1.2, 7.2 Hz), 7.36 (d, 2H, phenyl protons, J = 7.2 Hz), 7.20 (t, 1H, phenyl protons, J = 7.2 Hz), 7.13-7.04 (m, 7H phenyl protons), 4.01 (s, 3H, COOMe), 1.91 (s, 3H, COMe); ¹³C NMR: δ C=O 196.4, C=O 189.1, C=O 165.8, 139.6, 139.2, 137.3, 134.1, 132.0, 131.4, 129.6, 128.8,

128.6, 128.3, 128.1, 127.6, 123.6, 123.0, 118.1, 114.9, OCH₃ 53.2, CH₃ 31.3.

Anal. Calcd. for C₂₅H₁₉NO₄: C, 75.55, H, 4.82, N, 3.52. Found: C, 75.57, H, 4.88, N, 3.59.

Methyl 3-benzoyl-1-cyano-7-indolizinecarboxylate (**7b3**).

This compound was obtained as light yellow spiculate crystals, mp 211°; IR: CN 2220 (strong), C=O 1731 (strong), C=O 1627 (strong) cm⁻¹; ¹H NMR: δ 9.93 (d, 1H, 5-H, J = 7.2 Hz), 8.55 (d, 1H, 8-H, J = 1.2 Hz), 7.81 (d, 2H, phenyl protons, J = 7.2 Hz), 7.70 (s, 1H, H-2), 7.69 (dd, 1H, 6-H, J = 1.2, 7.2 Hz), 7.64 (t, 1H, phenyl proton, J = 7.8 Hz), 7.54 (dd, 2H, phenyl protons, J = 7.2, 7.8 Hz), 4.03 (s, 3H, COOMe); ¹³C NMR: δ C=O 185.9, C=O 165.0, 140.2, 139.1, 132.9, 129.9, 129.4, 129.4, 129.1, 128.9, 124.5, 120.1, 115.2, 114.8, 88.4, OCH₃ 53.4.

Anal. Calcd. for C₁₈H₁₂N₂O₃: C, 71.50, H, 3.97, N, 9.21. Found: C, 71.50, H, 3.95, N, 9.25.

Methyl 2,3-cyclohexanone-7-indolizinecarboxylate (**7b4**).

This compound was obtained as yellow solid, mp 194°; IR: CH₂ 2919 (medium), C=O 1715 (strong), C=O 1649 (strong), C=O 1614 (strong) cm⁻¹; ¹H NMR: δ 9.68 (d, 1H, 5-H, J = 7.2 Hz), 9.12 (d, 1H, 8-H, J = 1.2 Hz), 7.68 (d, 2H, phenyl protons, J = 7.2 Hz), 7.64-7.60 (m, 2H, 6-H and phenyl proton), 7.52 (dd, 2H, phenyl protons, J = 7.2, 7.8 Hz), 4.00 (s, 3H, COOMe), 2.57 (dd, 2H, CH₂, J = 5.4, 6.0 Hz), 2.40 (t, 2H, CH₂, J = 6.0 Hz), 1.97 (t, 2H, CH₂, J = 6.0 Hz); ¹³C NMR: δ C=O 194.5, C=O 187.7, C=O 165.6, 143.6, 140.9, 136.9, 132.5, 129.5, 129.2, 128.8, 128.6, 121.9, 115.3, OCH₃ 53.1, CH₃ 39.2, CH₂ 25.7, CH₂ 25.1.

Anal. Calcd. for C₂₁H₁₇NO₄: C, 72.61, H, 4.93, N, 4.03. Found: C, 72.69, H, 4.95, N, 4.10.

Methyl 1,3-dibenzoyl-2-(3-phenoxy-4-fluorophenyl)-7-indolizinecarboxylate (**7b5**).

This compound was obtained as yellow crystals, mp 95°; IR: C=O 1723 (strong), C=O 1615 (strong), C=O 1597 (strong) cm⁻¹; ¹H NMR: δ 9.48 (dd, 1H, 6-H, J = 0.6, 7.2 Hz), 8.78 (d, 1H, 8-H, J = 0.6 Hz), 7.59 (d, 1H, 5-H, J = 7.2 Hz), 7.47 (d, 2H, phenyl protons, J = 7.2 Hz), 7.42 (d, 2H, phenyl protons, J = 7.2 Hz), 7.37-7.13 (m, 8H, phenyl protons), 7.08 (t, 1H, phenyl proton, J = 7.2 Hz), 6.68-6.51 (m, 5H, phenyl protons), 3.97 (s, 3H, COOMe); ¹³C NMR: δ C=O 192.6, C=O 188.7, C=O 165.7, 157.0, 154.5, 152.9, 143.2, 141.5, 139.9, 138.9, 138.7, 137.5, 137.0, 132.8, 132.7, 130.6, 130.1, 130.0, 129.4, 128.3, 128.1, 127.3, 124.8, 123.9, 122.5, 122.1, 117.7, 117.2, 114.7, OCH₃ 53.2.

Anal. Calcd. for C₃₆H₂₄FNO₅: C, 75.91, H, 4.25, N, 2.46. Found: C, 75.80, H, 4.33, N, 2.50.

Methyl 1-acetyl-3-benzoyl-2-(3-nitrophenyl)-7-indolizinecarboxylate (**7b6**).

This compound was obtained as yellow solid, mp 185°; IR: C=O 1723 (strong), C=O 1621 (strong), 1534 (NO₂) cm⁻¹; ¹H NMR: δ 9.62 (d, 1H, 5-H, J = 7.2 Hz), 8.80 (d, 1H, 8-H, J = 1.2 Hz), 7.69 (s, 1H, phenyl proton), 7.66-7.63 (m, 2H, 6-H and phenyl proton), 7.44 (d, 2H, phenyl protons, J = 7.2 Hz), 7.36 (d, 2H, phenyl protons, J = 7.2 Hz), 7.23 (t, 2H, phenyl protons, J = 7.8 Hz), 7.15 (dd, 1H, phenyl proton, J = 7.2, 7.8 Hz), 7.08 (dd, 2H, phenyl protons, J = 7.2, 7.8 Hz), 6.99 (dd, 2H, phenyl

protons, $J = 7.2, 7.8$ Hz), 6.94 (t, 1H, phenyl proton, $J = 7.8$ Hz), 3.98 (s, 3 H, COOMe); ^{13}C NMR: δ C=O 192.3, C=O 188.4, C=O 165.5, 147.2, 138.9, 138.9, 137.7, 137.2, 136.6, 135.2, 132.7, 132.4, 129.7, 128.6, 128.4, 128.6, 128.3, 127.7, 126.7, 126.8, 122.9, 122.2, 117.2, 115.1, 115.1, OCH₃ 53.2.

Anal. Calcd. for C₃₀H₁₉N₂O₆: C, 71.57, H, 3.80, N, 5.56. Found: C, 71.63, H, 3.86, N, 5.60.

Methyl 1,3-dibenzoyl-3-(4-cynaophenyl)-7-indolizinecarboxylate (**7b7**).

This compound was obtained as yellow solid, mp 187°; IR: CN 2228 (strong), C=O 1723 (strong), C=O 1621 (strong), 1599 (strong) cm⁻¹; ^1H NMR: δ 9.55 (d, 1 H, 5-H, $J = 7.2$ Hz), 8.76 (s, 1H, 8-H), 7.63 (d, 1H, 6-H, $J = 7.2$ Hz), 7.44 (d, 2H, phenyl protons, $J = 7.8$ Hz), 7.36 (d, 1H, phenyl proton, $J = 7.8$ Hz), 7.31-7.23 (m, 2H, phenyl protons), 7.11-6.99 (m, 8H, phenyl protons), 3.97 (s, 3H, COOMe); ^{13}C NMR: δ C=O 192.3, C=O 188.4, C=O 165.5, 138.8, 138.6, 138.1, 137.6, 136.9, 133.0, 132.8, 132.3, 131.3, 129.9, 129.9, 128.4, 128.4, 127.6, 122.6, 122.2, 118.8, 117.2, 115.3, 115.0, 111.2, OCH₃ 53.2.

Anal. Calcd. for C₃₁H₂₀N₂O₄: C, 76.85, H, 4.16, N, 5.78. Found: C, 76.89, H, 4.21, N, 5.79.

Typical procedure for Preparation of Indolizines (**7'**).

A solution of **3** (0.50 mmole), **5** (4.00 mmoles), and Et₃N (0.20 g, 2.00 mmoles) in DMF (30 mL) was stirred at 90° for 2 h. After the solvent was evaporated under vacuum, the residue was added to CH₂Cl₂ (50 mL), washed, dried, filtered, concentrated, precipitated and cleaved by using the procedure described above for **7** to give crude materials. They were purified by column chromatography on silica gel (EtOAc-petroleum ether, 1: 3-1: 2) to give the pure indolizines **7'**.

Dimethyl 3-acetyl-1,7-indolizinedicarboxylate (**7'a1**).

This compound was obtained as yellow crystals, mp 198°; IR: CH₃ 2924 (medium), C=O 1723 (strong), C=O 1699 (strong) cm⁻¹; ^1H NMR: δ 9.88 (d, 1H, 5-H, $J = 7.2$ Hz), 9.00 (s, 1H, 8-H), 8.054 (s, 1H, 2-H), 7.56 (d, 6-H, $J = 7.2$ Hz), 3.99 (s, 3H, COOMe), 3.98 (s, 3H, COOMe), 2.63 (s, 3H, COMe); ^{13}C NMR: δ C=O 188.8, C=O 164.7, C=O 164.5, 138.1, 129.0, 128.3, 127.0, 124.4, 122.2, 114.7, 108.9, OCH₃ 53.3, OCH₃ 52.2, CH₃ 30.2.

Anal. Calcd. for C₁₄H₁₃NO₅: C, 61.09, H, 4.76, N, 5.09. Found: C, 61.11, H, 4.68, N, 5.10.

Trimethyl 3-acetyl-1,2,7-indolizinetricarboxylate (**7'a2**).

This compound was obtained as light yellow crystals, mp 179°; IR: CH₃ 2957 (medium), C=O 1722 (strong), C=O 1705 (strong), C=O 1652 (strong) cm⁻¹; ^1H NMR: δ 9.95 (d, 1H, 5-H, $J = 7.8$ Hz), 8.96 (d, 1H, 8-H, $J = 1.2$ Hz), 7.60 (dd, 1H, 6-H, $J = 1.2, 7.8$ Hz), 4.06 (s, 3H, COOMe), 4.00 (s, 3H, COOMe), 3.97 (s, 3H, COOMe), 2.55 (s, 3H, COMe); ^{13}C NMR: δ C=O 188.5, C=O 167.2, C=O 165.4, C=O 163.4, 136.6, 132.3, 129.2, 129.2, 122.3, 121.5, 115.5, 107.0, OCH₃ 53.9, OCH₃ 53.3, OCH₃ 52.5, CH₃ 29.0.

Anal. Calcd. for C₁₆H₁₅NO₇: C, 57.66, H, 4.54, N, 4.20. Found: C, 57.70, H, 4.58, N, 4.22.

Dimethyl 3-benzoyl-1,7-indolizinedicarboxylate (**7'b1**).

This compound was obtained as light yellow crystals, mp 186°; IR: CH₃ 2953 (medium), C=O 1729 (strong), C=O 1712

(strong), C=O 1628 (strong) cm⁻¹; ^1H NMR: δ 9.95 (d, 1H, 5-H, $J = 7.2$ Hz), 9.06 (s, 1H, 8-H), 7.89 (s, 1H, 2-H), 7.83 (d, 2H, phenyl protons, $J = 7.2$ Hz), 7.65-7.60 (m, 2H, 6-H and phenyl proton), 7.53 (t, 2H, phenyl protons, $J = 7.8$ Hz), 4.01 (s, 3H, COOMe), 3.95 (s, 3H, COOMe); ^{13}C NMR: δ C=O 186.5, C=O 165.7, C=O 164.5, 139.8, 138.7, 132.4, 129.7, 129.5, 129.1, 129.0, 128.6, 124.1, 122.2, 114.7, 109.2, OCH₃ 53.2, CH₃ 52.1.

Anal. Calcd. for C₁₉H₁₅NO₅: C, 67.65, H, 4.48, N, 4.15. Found: C, 67.66, H, 4.39, N, 4.11.

Trimethyl 3-benzoyl-1,2,7-indolizinetricarboxylate (**7'b2**).

This compound was obtained as yellow green solid, mp 195°; IR: CH₃ 2952 (strong), C=O 1725 (strong), C=O 1629 (strong), C=O 1599 (strong) cm⁻¹; ^1H NMR: δ 9.54 (d, 1H, 5-H, $J = 7.2$ Hz), 9.03 (d, 1H, 8-H, $J = 1.2$ Hz), 7.80 (d, 2H, phenyl protons, $J = 7.8$ Hz), 7.63 (dd, 1H, 6-H, $J = 1.2, 7.2$ Hz), 7.58 (t, 1H, phenyl proton, $J = 7.2$ Hz), 7.47 (dd, 2H, phenyl protons, $J = 7.2, 7.8$ Hz), 4.01 (s, 3H, COOMe), 3.93 (s, 3H, COOMe), 3.32 (s, 3H, COOMe); ^{13}C NMR: δ C=O 187.4, C=O 165.5, C=O 165.2, C=O 163.5, 139.6, 137.1, 132.9, 132.2, 129.2, 128.9, 128.7, 128.4, 122.9, 122.6, 115.2, 107.3, OCH₃ 53.3, OCH₃ 52.8, OCH₃ 52.5.

Anal. Calcd. for C₂₁H₁₇NO₇: C, 63.80, H, 4.33, N, 3.54. Found: C, 63.81, H, 4.39, N, 3.53.

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