Synthesis of a Library of 1,2,3,7-Tetrasubstituted Indolizines using Poly(ethylene glycol) as Soluble Support

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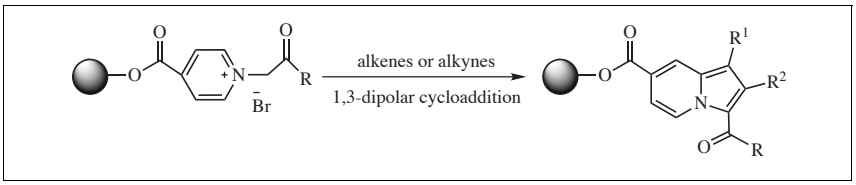

A library of 1,2,3,7-tetrasubstituted indolizines has been synthesized using poly(ethylene glycol) (PEG) as soluble polymer support. The PEG-bound pyridinium salts reacted with alkenes or alkynes in the presence of Et_3N *via* 1,3-dipolar cycloaddition to give PEG-bound indolizine derivatives, which were cleaved by 1 % KCN/MeOH to afford 1,2,3,7-tetrasubstituted indolizines in good to excellent yields.

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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 adamatane derivatives [12].

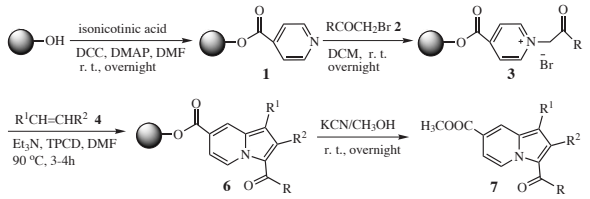
The methods for synthesis of indolizine are classified mainly as Scholtz and Tschitschibabin reaction, 1,3-dipolar cycloaddition and 1,5-dipolar cyclization [13]. Recently there was reported to synthesize indolizines bearing $[Os_3(\mu\text{-}H)_2(CO)_{10}]$ by the rearrangement of diyne [14]. Although 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 pyridinum 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-trisubstitiuted 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 characteristc 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.

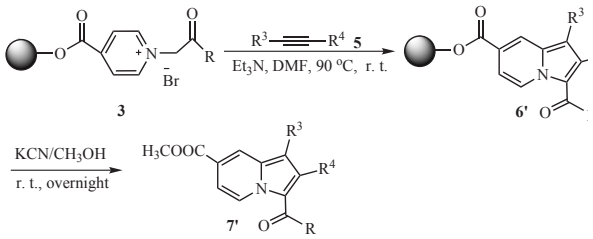
Table 1

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

Entry	R	R^1	R^2	Yeild(%)	
				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_2NPh	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.

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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. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Varian Unity INOVA 600 spectrometer in $CDCl_3$ 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 PEG_{3400} (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 Et_2O (500 mL), washing with cold anhydrous Et_2O (100 mL × 3) and drying under vacuum, to give a white solid **1**, 10.26 g (98%); IR: CH_2 2882 (strong), C=O 1729 (strong) cm^{-1}; ^{1}H 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(CH_2CH_2O)$_n$-).

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 CH_2Cl_2 (40 mL) was stirred at r.t. overnight. After precipitation from cold anhydrous Et_2O (500 mL), the suspension was filtered, washed with cold anhydrous Et_2O (100 mL × 3) and dried to give yellow solid **3a**, 10.70 g (97%) or orange solid **3b**, 10. 92 g (96%); **3a**: IR: CH_2 2868 (strong), C=O 1731 (strong), C=O 1651 (strong) cm^{-1}; ^{1}H 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, *CH_2*COCH$_3$), 4.60-3.16 (m, 4nH, -O(CH_2CH_2O)$_n$-), 2.05 (s, 3H, CH_2CO*CH_3*); **3b**: IR: CH_2 2883 (strong), C=O 1731 (strong), C=O 1652 (strong) cm^{-1}; ^{1}H NMR: δ 8.84 (d, 2H, pyridinyl protons, J = 4.5 Hz), 7.98 (d, 2 H, 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, *CH_2*COPh), 4.63-3.27 (m, 4nH, -O(CH_2CH_2O)$_n$-).

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 Et_3N (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 CH_2Cl_2 (50 mL) and washed with a 0.02% solution of Na_2CO_3 in H_2O (15 mL). The solution was dried over $MgSO_4$, filtered, concentrated and precipitated with cold anhydrous Et_2O (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 Et_2O 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}; ^{1}H 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); ^{13}C 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, OCH_3 53.3, CH_3 31.3.

Anal. Calcd. for $C_{25}H_{18}NO_4F$: 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}; ^{1}H 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); ^{13}C 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, OCH_3 53.1, CH_3 31.4, CH_3 31.2.

Anal. Calcd. for $C_{20}H_{17}NO_4$: 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}; ^{1}H 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); ^{13}C 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, OCH_3 53.4, CH_3 28.0.

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: 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: CH_2 2923 (medium), C=O 1715 (strong), C=O 1626 (strong) cm^{-1}; ^{1}H NMR: δ 10.02 (d, 1 H, 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, CH_2, J = 6.0Hz), 2.66-2.63 (m, 5H, CH_2 and $COCH_3$), 2.29 (t, 2H, CH_2, J = 6.0 Hz); ^{13}C 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, OCH_3 53.2, CH_2 38.9, CH_3 31.4, CH_2 25.6, CH_2 24.7.

Anal. Calcd. for $C_{16}H_{15}NO_4$: 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-phenoxyl-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}; ^{1}H 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); ^{13}C 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, OCH_3 53.1, CH_3 31.3.

Anal. Calcd. for $C_{31}H_{22}NO_5F$: 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: CH_3 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), ^{13}C 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, OCH_3 53.1, CH_3 31.5.

Anal. Calcd. for $C_{25}H_{18}NBrO_4$: 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); ^{13}C 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, OCH_3 53.2, CH_3 29.8, CH_3 29.7.

Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.46, H, 4.65, N, 4.31. Found: C, 66.56, H, 4.73, N, 4.44.

Methyl 1,3-dibenzoyl-3-(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); ^{13}C 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, OCH_3 53.2.

Anal. Calcd. for $C_{30}H_{20}NO_4F$: 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); ^{13}C 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, OCH_3 53.2, CH_3 31.3.

Anal. Calcd. for $C_{25}H_{19}NO_4$: 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); ^{13}C 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, OCH_3 53.4.

Anal. Calcd.. for $C_{18}H_{12}N_2O_3$: 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: CH_2 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, CH_2, J = 5.4, 6.0 Hz), 2.40 (t, 2H, CH_2, J = 6.0 Hz), 1.97 (t, 2H, CH_2, J = 6.0 Hz); ^{13}C 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, OCH_3 53.1, CH_3 39.2, CH_3 25.7, CH_3 25.1.

Anal. Calcd. for $C_{21}H_{17}NO_4$: 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-phenoxyl-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); ^{13}C 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, OCH_3 53.2.

Anal. Calcd. for $C_{36}H_{24}FNO_5$: 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 (NO_2) 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, OCH_3 53.2.

Anal. Calcd. for $C_{30}H_{19}N_2O_6$: 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}; ^{1}H 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, OCH_3 53.2.

Anal. Calcd. for $C_{31}H_{20}N_2O_4$: 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 Et_3N (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 CH_2Cl_2 (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: CH_3 2924 (medium), C=O 1723 (strong), C=O 1699 (strong) cm^{-1}; ^{1}H 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, OCH_3 53.3, OCH_3 52.2, CH_3 30.2.

Anal. Calcd. for $C_{14}H_{13}NO_5$: 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: CH_3 2957 (medium), C=O 1722 (strong), C=O 1705 (strong), C=O 1652 (strong) cm^{-1}; ^{1}H 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, OCH_3 53.9, OCH_3 53.3, OCH_3 52.5, CH_3 29.0.

Anal. Calcd. for $C_{16}H_{15}NO_7$: 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: CH_3 2953 (medium), C=O 1729 (strong), C=O 1712 (strong), C=O 1628 (strong) cm^{-1}; ^{1}H 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, OCH_3 53.2, CH_3 52.1.

Anal. Calcd. for $C_{19}H_{15}NO_5$: 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: CH_3 2952 (strong), C=O 1725 (strong), C=O 1629 (strong), C=O 1599 (strong) cm^{-1}; ^{1}H 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, OCH_3 53.3, OCH_3 52.8, OCH_3 52.5.

Anal. Calcd. for $C_{21}H_{17}NO_7$: C, 63.80, H, 4.33, N, 3.54. Found: C, 63.81, H, 4.39, N, 3.53.

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