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Dedicated to Prof. Bogdan C. Simionescu, on the occasion of his 70th anniversary. The authors acknowledge the long and fruitful collaboration with Prof. Simionescu, as well as his contribution in developing and opening the "Petru Poni" Institute to almost all fields of earth and life sciences.

SIMPLE ONE-POT THREE COMPONENT SYNTHESIS OF SYMMETRICALLY SUBSTITUTED 7,7'-BISINDOLIZINES

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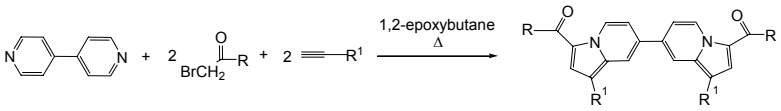
By one-pot, three components reaction of one equivalent of 4,4'-bipyridine with two equivalents of substituted phenacyl bromides and two equivalents of non-symmetrical electron-deficient alkynes in 1,2-epoxybutane at reflux temperature new symmetrically substituted 7,7'-bisindolizines were directly obtained. This novel and efficient synthetic methodology led to a range of symmetrically substituted 7,7'-bisindolizines in good yields.



INTRODUCTION

Sequential transformations and multicomponent processes have become increasingly interesting for economical and ecological reasons. The one-pot, multicomponent reactions provide opportunities for developing novel lead structures for pharmaceuticals and novel molecule-based materials.[1-3]

Indolizine and bisindolizine derivatives have received a considerable attention due to their biological activities,[4-12] and particularly to their well-known fluorescence properties.[13-17] The general synthetic route towards 7,7'-bisindolizine derivatives is based on 1,3-dipolar cycloaddition reactions[18-20] of 4,4'-bipyridinium *N*-ylides with activated carbon-carbon multiple bonds. Usually, 4,4'-bipyridinium *N*-ylides are unstable compounds and they are generated *in situ* from the corresponding pre-prepared 4,4'-bipyridinium salts in the presence of an organic or inorganic base in various solvents,[21,22] or in the presence of potassium fluoride on alumina, without solvent, under microwave irradiation.[23,24] An interesting approach towards indolizine and bisindolizine derivatives is based on a consecutive

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Sonogashira coupling combined with the 1,3-dipolar cycloaddition.[25] However, the combination of solvents, strong bases and long reaction time led usually to small yields of 7,7'-bisindolizines because of side reactions. Considering their increasing importance as fluorophores in biolabeling and fluorescence microscopy we have been seeking a simple and efficient procedure towards new symmetrically substituted 7,7'-bisindolizine derivatives.

Our group has developed a regiospecific, clean and simple one-pot, three component synthetic strategy towards *N*-bridgehead heterocyclic systems based on consecutive quaternization, *in situ* generation of a heterocyclic *N*-ylide, 1,3-dipolar cycloaddition and aromatization sequence.[26-38] As part of our constant interest in this research field we report here an efficient and simple one-pot, three-components synthetic procedure leading directly to symmetrically substituted 7,7'-bisindolizine derivatives in good yields.

RESULTS AND DISCUSSION

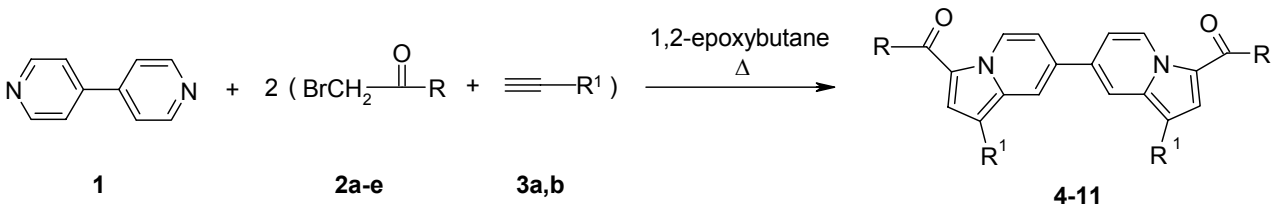
One of the resourceful synthetic methods towards 7,7'-bisindolizine scaffold is based on 1,3-dipolar cycloaddition of pyridinium-*N*-ylides, offering both high yields and regioselectivity.[18-24] We found that the direct reaction of one equivalent of 4,4'-bipyridine **1** with two equivalents of substituted phenacyl bromides **2a-e** and two equivalents of activated alkynes **3a,b** in 1,2-epoxybutane, at reflux temperature, led directly to new symmetrically substituted 7,7'-bisindolizines **4-11** in good yields.

The synthesized 7,7'-bisindolizines **4-11** are presented in Table 1.

In the same one-pot, three components reaction, starting from one equivalent of 4,4'-bipyridine **1** with one equivalent of each substituted phenacyl bromides **2a-e** and one equivalent of each activated alkynes **3a,b** in 1,2-epoxybutane at reflux temperature, mixtures of about 25% 7,7'-bisindolizines **4-11** and 35% of corresponding 7-pyridinylindolizines were obtained in every experiment. These data were evidenced by the HPLC analyses of all crude reaction products. 7-Pyridinylindolizines can only be obtained from monoquaternary salts of 4,4'-bipyridine and activated alkynes in the presence of 1,2-epoxybutane or in the presence of bases in an appropriate solvent.

Our data suggest that one of the possible reaction pathways implies the intermediate formation of the 4,4'-monopyridinium salts A by the reactions of 4,4'-bipyridine 1 with substituted phenacyl bromides 2 from which the corresponding pyridinium *N*-ylides are generated *in situ* in the presence of 1,2-epoxybutane. The 1,3-dipolar cycloaddition of the pyridinium *N*-ylides with activated alkynes 3 led directly to the 7-pyridylindolizines B. In a further sequence, 7-pyridyl-indolizines B react with another equivalent of substituted phenacyl bromides 2 with the formation of the indolizinium salts C which react with another equivalent of active alkynes *via* corresponding indolizinium *N*-ylides leading directly to symmetrically substituted 7,7'-bisindolizines 4-11. This reaction pathway is probably concurrent with the one in which 4,4'-dipyridinium salts D are formed among 4,4'-monopyridinium salts A and react in the further step with activated alkynes *via* corresponding mono- and dipyridinium-ylides, generated *in situ* in the presence of 1,2-epoxybutane leading finally to 7,7'-bisindolizines 4-11 (Scheme 2). 4,4'-Dipyridinium salts have been previously reported.[39]

The structure of the synthesized bisindolizines was confirmed by elemental analysis, IR and NMR spectroscopy. The IR spectra present the bands of the main functional groups decorating the bisindolizine system. The C=O groups in the benzoyl moiety appear at 1613-1624 cm^{-1} lower than typical range due to conjugation within the extended bisindolizine system. The ester C=O groups in 4-9 appear at 1696-1708 cm^{-1} while the corresponding IR band for the C=O in the acetyl group is present at ~1650 cm^{-1}.



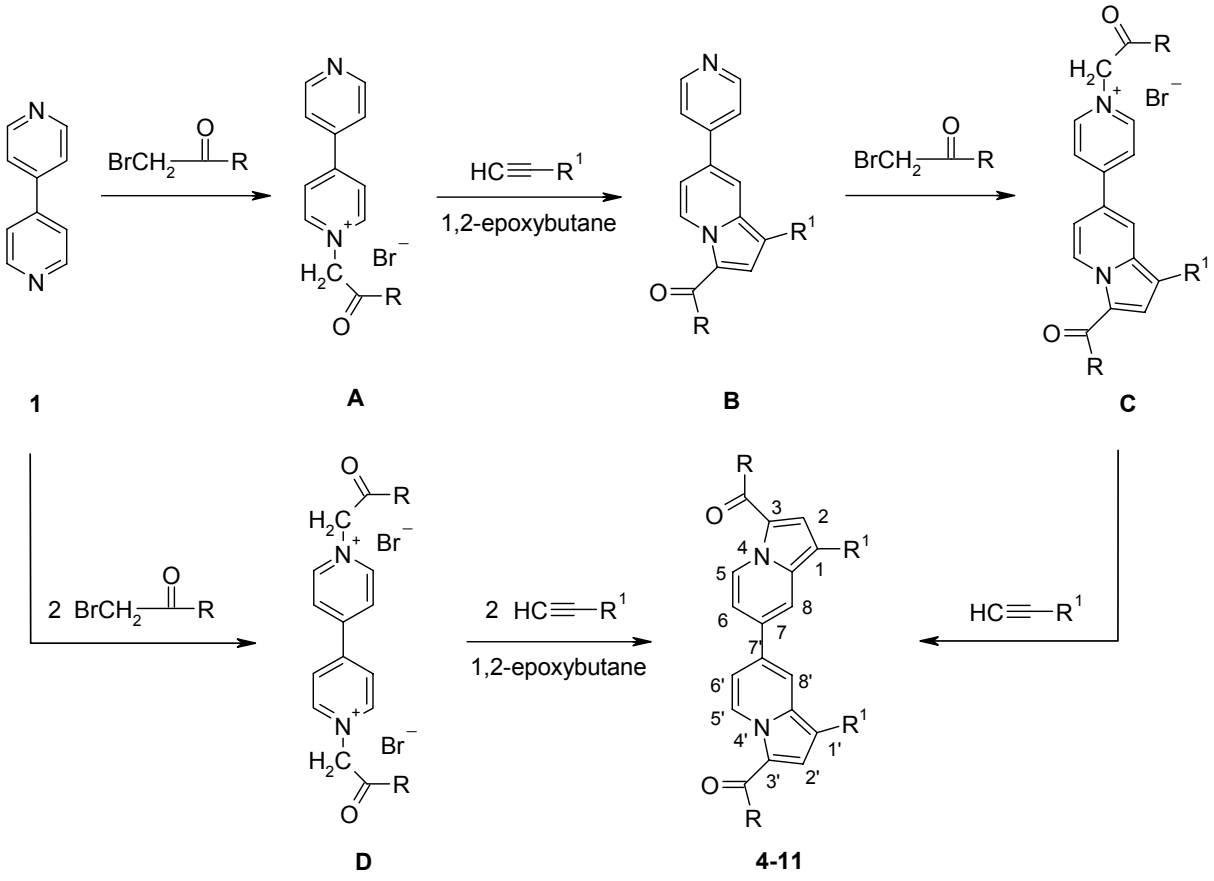
Scheme 1 – The synthetic route towards 7,7'-bisindolizines.

Table 1

New synthesized 7,7'-bisindolizine derivatives

Compound	R	R^1	mp (°C)	Yield (%) *
4	4-FC_6H_4	CO_2Et	293-296	41
5	4-ClC_6H_4	CO_2Et	308-310 (269-270) [24]	48
6	3-$NO_2C_6H_4$	CO_2Et	315-317	53
7	3,4-$(MeO)_2C_6H_3$	CO_2Et	285-286	63
8	2-naphthyl	CO_2Et	301-303	46
9	4-FC_6H_4	$COCH_3$	356-358	65
10	4-ClC_6H_4	$COCH_3$	> 360	67
11	3-$NO_2C_6H_4$	$COCH_3$	> 360	62

* isolated products



Scheme 2 – The reaction pathway.

The number of ^{1}H-NMR signals and their multiplicity confirms the quaternization and further 1,3-dipolar cycloaddition took place at both pyridyl moieties as no free pyridine signals were observed. Thus in the ^{1}H-NMR spectra the main features are the signals of H-5/5', H-6/6' and H-8/8' which appear as three doublets, of which the most deshielded being H-5/5' in the range 9.9-10.1 ppm. The signal of the H-8/8' proton appears more deshielded in the case of compounds **9-11** than in **4-8** most possible this being the spatial influence of the C=O group in the acetyl moiety. The ^{13}C-NMR spectra are also in agreement with the proposed structures. The individual ^{1}H- and ^{13}C- chemical shifts have been unambiguously assigned based on additional 2D NMR experiments (COSY, HSQC and HMBC).

EXPERIMENTAL

General information. Melting points were measured on a Boëtius hot plate microscope and are uncorrected. IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets. The NMR spectra of compounds **5-8** and **10** were

recorded on a Varian Gemini 300 BB instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. The NMR spectra of compounds **4**, **9** and **11** were recorded on a Bruker Avance III 400 instrument operating at 400 and 100 MHz for ^{1}H and ^{13}C nuclei respectively. Samples were recorded with either a 5 mm multinuclear inverse detection z-gradient probe (^{1}H spectra and all H-C 2D experiments) or with a 5 mm four nuclei direct detection z-gradient probe (^{1}H and ^{13}C spectra). Chemical shifts are reported in δ units (ppm) and were referenced to internal TMS for ^{1}H chemical shifts and to the internal deuterated solvent for ^{13}C chemical shifts ($CDCl_3$ referenced at 77.0 ppm). Unambiguous 1D NMR signal assignments were made based on 2D NMR homo- and heterocorrelation. H,H-COSY, H,C-HSQC and H,C-HMBC experiments, recorded using standard pulse sequences in the version with z-gradients, as delivered by Bruker with TopSpin 2.1 PL6 spectrometer control and processing software.

Elemental analyses for C, H and N were obtained on a COSTECH Instruments EAS32. Satisfactory microanalyses for all new compounds were obtained. The high performance liquid chromatography (HPLC) analyses were performed on an Agilent Chromatograph 1200 Series at room temperature by isocratic elution of acetonitrile on an Agilent Zorbax SB-C18 (250x4.6) column with flow rate 1.0 mL/min. Elution was monitored at 400 nm. 4,4'-Bipyridine, 2-bromoacetophenones, 2-bromoacetonaphthone and activated alkynes were purchased from Sigma Aldrich and used without further purification.

General procedure for the synthesis of 7,7'-bisindolizines. To a solution of 0.39 g (2.5 mmol) of 4,4'-bipyridine in 50 mL of 1,2-epoxybutane 5 mmol of phenacyl bromide and 5.5 mmol of activated alkyne were added and the reaction mixture was heated at reflux temperature for 24 hours. The solvent was partly evaporated *in vacuo*, 5-10 mL of MeOH was added under stirring and the mixture was left over night in the refrigerator. The solid formed was filtered, washed on the filter with 2-3 mL of MeOH, then with Et_2O and recrystallized from $CHCl_3$ or $CHCl_3$/MeOH.

***Diethyl 3,3'-bis(4-fluorobenzoyl)-7,7'-bisindolizine-1,1'-dicarboxylate* (4)** Orange crystals. ^{1}H-NMR (400 MHz, $CDCl_3$+TFA, δ ppm): 1.48 (t, 6H, *J* = 6.8 Hz, 2Me), 4.49 (q, 4H, *J* = 6.8 Hz, $2CH_2$), 7.26 (t, 4H, $^3J_{H,H} = {}^3J_{H,F}$ = 8.6 Hz, H-3Ph), 7.62 (dd, 2H, *J* = 7.4, 1.9 Hz, H-6/H-6'), 7.86 (dd, 4H, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,F}$ = 5.4 Hz, H-2Ph), 7.92 (s, 2H, H-2/H-2'), 8.82 (d, 2H, *J* = 1.2 Hz, H-8/H-8'), 10.03 (d, 2H, *J* = 7.2 Hz, H-5/H-5'). ^{13}C-NMR (100 MHz, $CDCl_3$+TFA, δ ppm): 14.3 (2Me), 61.7 ($2CH_2$), 108.2 (C-1/C-1'), 114.5 (C-6/C-6'), 116.1 (d, $^2J_{C,F}$ = 22 Hz, 4C, C-3Ph, C-5Ph), 117.2 (C-8/C-8'), 122.7 (C-3/C-3'), 130.3 (C-5/C-5'), 131.6 (C-2/C-2'), 131.7 (d, $^3J_{C,F}$ = 9 Hz, 4C, C-2Ph, C-6Ph), 134.5 (d, $^4J_{C,F}$ = 3 Hz, 2C, C-1Ph), 137.9 (C-7/C-7'), 140.7 (C-8a/C-8a'), 165.1 (2COO), 165.4 (d, $^1J_{C,F}$ = 255 Hz, 2C, C-4Ph), 185.7 (2COAr). IR (KBr, cm^{-1}): 2980, 1695, 1624, 1599, 1528, 1495, 1340, 1231, 1208, 1157, 1080, 1046. Anal. Calcd. for $C_{36}H_{26}F_2N_2O_6$ (620.60): C, 69.67; H, 4.22; N, 4.51. Found: C, 69.73; H, 4.27; N, 4.44.

***Diethyl 3,3'-bis(4-chlorobenzoyl)-7,7'-bisindolizine-1,1'-dicarboxylate* (5).** Yellow greenish crystals. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA, δ ppm): 1.50 (t, 6H, *J* = 7.1 Hz, 2Me), 4.49 (q, 4H, *J* = 7.1 Hz, $2CH_2$), 7.57 (d, 4H, *J* = 8.5 Hz, H-3Ph/H-5Ph), 7.68 (dd, 2H, *J* = 7.4, 1.6 Hz, H-6/H-6'), 7.77 (d, 4H, *J* = 8.5 Hz, H-2Ph/H-6Ph), 7.96 (s, 2H, H-2/H-2'), 8.83 (dd, 2H, *J* = 1.6, 1.0 Hz, H-8/H-8'), 10.06 (dd, 2H, *J* = 7.4, 1.0 Hz, H-5/H-5'). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA, δ ppm):14.3 (2Me), 62.4 ($2CH_2$), 108.9 (C-1/C-1'), 115.1 (C-6/C-6'), 117.5 (C-8/C-8'), 122.8 (C-3/C-3'), 130.8 (C-5/C-5'), 129.4; 130.7 (8C, C-2Ph, C-3Ph, C-5Ph, C-6Ph), 132.7 (C-2/C-2'), 136.4, 139.7 (4C , C-1Ph, C-4Ph), 138.7 (C-7/C-7'), 141.3 (C-8a/C-8a'), 165.9 (2COO), 186.5 (2COAr). IR (KBr, cm^{-1}): 2986, 1702, 1617, 1590, 1529, 1473, 1449, 1342, 1227, 1198, 1050, 1047.

***Diethyl 3,3'-bis(3-nitrobenzoyl)-7,7'-bisindolizine-1,1'-dicarboxylate* (6).** Brown crystals. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA, δ ppm): 1.42 (t, 6H, *J* = 7.1 Hz, 2Me), 4.50 (q, 4H, *J* = 7.1 Hz, $2CH_2$), 7.65 (dd, 2H, *J* = 7.4, 1.6 Hz, H-6/H-6'), 7.75 (t, 2H, *J* = 8.0 Hz, H-5Ph), 7.66 (s, 2H, H-2/H-2'), 8.08-8.11 (m, 2H, H-4Ph), 8.44-8.46 (m, 2H, H-6Ph), 8.58 (t, 2H *J*=1.8 Hz, H-2Ph), 8.80 (dd, 2H, *J* = 1.6, 1.0 Hz, H-8/H-8'), 10.03 (dd, 2H, *J* = 7.4, 1.0 Hz, H-5/H-5'). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA, δ ppm):14.2 (2Me), 62.4 ($2CH_2$), 109.0 (C-1/C-1'), 115.2 (C-6/C-6'), 117.6 (C-8/C-8'), 122.5 (C-3/C-3'), 130.7 (C-5/C-5'), 124.0, 126.9, 130.3, 134.7 (8C, C-2Ph, C-4Ph, C-5Ph, C-6Ph), 132.2 (C-2/C-2'), 139.9, 148.3 (4C, C-1Ph, C-4Ph), 138.7, (C-7/C-7'), 141.3 (C-8a/C-8a'), 165.6 (2COO), 184.3 (2COAr). IR (KBr, cm^{-1}): 2979, 1708, 1617, 1532, 1475, 1451, 1345, 1200, 1075, 1045. Anal. Calcd. for $C_{36}H_{26}N_4O_{10}$ (674.61): C, 64.09; H, 3.88; N, 8.30. Found: C, 63.99; H, 3.92; N, 8.34.

***Diethyl 3,3'-bis(3,4-dimethoxybenzoyl)-7,7'-bisindolizine-1,1'- dicarboxylate* (7).** Dark beige crystals. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA, δ ppm): 1.45 (t, 6H, *J* = 7.1 Hz, 2Me), 3.93, 3.97 (2s, 12H, 4MeO), 4.47 (q, 4H, *J* = 7.1 Hz, $2OCH_2$), 7.02 (d, 2H, *J* = 8.6 Hz, H-5Ph), 7.36 (d, 2H, *J* = 0.8 Hz, H-2Ph), 7.46 (dd, 2H, *J* = 7.4, 1.7 Hz, H-6/H-6'), 7.61 (dd, 2H, *J* = 8.6, 1.6 Hz, H-6Ph), 7.98 (s, 2H, H-2/H-2'), 8.75 (dd, 2H, *J* = 1.7, 1.0 Hz, H-8/H-8'), 9.94 (dd, 2H, *J* = 7.4, 1.0 Hz, H-5/H-5'). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA, δ ppm):14.2 (2Me); 56.4 (4 OMe), 62.6 ($2CH_2$), 108.6 (C-1, C-1'), 110.1, 112.3 (4C, C-2Ph, C-5Ph), 115.0 (C-6/C-6'), 117.5 (C-8/C-8'), 123.0 (C-3/C-3'), 125.3 (2C, C-6Ph), 130.6 (2C, C-1Ph), 130.8 (C-5/C-5'), 133.0 (C-2/C-2'), 138.7 (C-7/C-7'), 141.3 (C-8a/C-8a'), 148.9, 153.2 (4C, C-3Ph, C-4Ph), 166.3 (2COO), 186.7 (2COAr). IR (KBr, cm^{-1}): 2979, 1700, 1615, 1578, 1527, 1475, 1450, 1342, 1269, 1196, 1140, 1083, 1023. Anal. Calcd. for $C_{40}H_{36}N_2O_{10}$ (704.72): C, 68.17; H, 5.15; N, 3.97. Found: C, 68.24; H, 5.09; N, 3.92.

***Diethyl 3,3'-bis(2-napthoyl)-7,7'-bisindolizine-1,1'-dicarboxylate* (8).** Brown crystals. ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 1.43 (t, 6H, *J* = 7.1 Hz, 2Me), 4.43 (q, 4H, *J* = 7.1 Hz, $2CH_2$), 7.54-7.64 (m, 6H, H-6/H-6', 4H-Napht), 7.93-8.03 (m, 10H, H-2, H-2', 8H-Napht), 8.36 (s, 2H, 2H-Napht), 8.87 (dd, 2H, *J* = 1.6, 1.0, Hz, H-8/H-8'), 10.08 (dd, 2H, *J* = 7.4, 1.0 Hz, H-5/H-5'). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA, δ ppm):14.3 (2Me), 62.3 ($2CH_2$), 108.8 (C-1/C-1'), 115.0 (C-6/C-6'), 117.5 (C-8/C-8'), 123.2 (C-3/C-3'), 130.8 (C-5/C-5'), 125.0, 127.5, 128.1, 128.9, 129.1, 129.5, 131.0 (14C-Napht), 133.1 (C-2/C-2'), 132.5, 135.1, 135.5 (6Cq-Napht), 138.7 (C-7/C-7'), 141.2 (C-8a/C-8a'), 165.9 (2COO), 187.9 (2COAr). IR (KBr, cm^{-1}): 2981, 1702, 1606, 1528, 1470, 1444, 1330, 1255, 1192, 1079, 1044. Anal. Calcd. for $C_{44}H_{32}N_2O_6$ (684.73): C, 77.18; H, 4.71; N, 4.09. Found: C, 77.10; H, 4.66; N, 4.00.

***1,1'-Diacetyl-3,3'-bis(4-fluorobenzoyl)-7,7'-bisindolizine* (9).** Yellow crystals. ^{1}H-NMR (400 MHz, $CDCl_3$+TFA, δ ppm): 2.40 (s, 6H, 2Me), 6.97 (t, 4H, $^3J_{H,H} = {}^3J_{H,F}$ = 8.6 Hz, H-3Ph), 7.48 (dd, 2H, *J* = 7.4, 2.0 Hz, H-6/H-6'), 7.63 (s, 2H, H-2/H-2'), 7.58 (dd, 4H, $^3J_{H,H}$ = 8.8 Hz, $^4J_{H,F}$ = 5.3 Hz, H-2Ph), 8.79 (dd, 2H, *J* = 2.0, 0.6 Hz, H-8/H-8'), 9.73 (dd, 2H, *J* = 7.3, 0.6 Hz, H-5/H-5'). ^{13}C-NMR (100 MHz, $CDCl_3$+TFA, δ ppm): 28.6 (2Me), 118.0 (C-1/C-1'), 118.2 (C-6/C-6'), 118.5 (d, $^2J_{C,F}$ = 22 Hz, 4C, C-3Ph, C5-Ph), 120.9 (C-8/C-8'), 126.0 (C-3/C-3'), 132.9 (C-5/C-5'), 134.1 (d, $^3J_{C,F}$ = 9 Hz, 4C, C-2Ph, C-6Ph), 134.8 (C-2/C-2'), 137.0 (d, $^4J_{C,F}$ = 3 Hz, 2C, C-1Ph), 142.3 (C-7/C-7'), 143.2 (C-8a/C-8a'), 168.1 (d, $^1J_{C,F}$ = 254 Hz, 2C, C-4Ph), 188.6 (2COAr), 200.2 (2COMe). IR (KBr, cm^{-1}): 1651, 1613, 1517, 1473, 1422, 1334, 1229, 1190, 1153. Anal. Calcd. for $C_{34}H_{22}F_2N_2O_4$ (560.55): C, 72.85; H, 3.95; N, 5.00. Found: C, 72.92; H, 3.99; N, 4.94.

***1,1'-Diacetyl-3,3'-bis(4-chlorobenzoyl)-7,7'-bisindolizine* (10) Py-419.** Khaki crystals. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA, δ: 2.68 ppm) (s, 6H, 2Me), 7.60 (d, 4H, *J* = 8.5 Hz, H-3Ph/H-5Ph), 7.77-7.81 (m, 6H, H-6/H-6', H-2Ph/H-6Ph), 7.93 (s, 2H, H-2/H-2'), 9.10 (dd, 2H, *J* = 1.6, 1.0 Hz, H-8/H-8'), 10.08 (dd, 2H, *J* = 7.4, 1.0 Hz, H-5/H-5'). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA, δ ppm):26.7 (Me), 116.0 (C-1/C-1'), 116.4 (C-6/C-6'), 117.9 (C-8/C-8'), 123.5 (C-3/C-3'), 130.9 (C-5/C-5'), 129.6, 130.6 (8C, C-2Ph, C-3Ph, C-5Ph, C-6Ph), 133.3 (C-2/C-2'), 136.3, 140.4 (4C, C-1Ph, C-4Ph), 140.0 (C-7/C-7'), 141.2 (C-8a/C-8a'), 186.9 (2COAr), 198.3 (2CO). IR (KBr, cm^{-1}): 1652, 1616, 1530, 1473, 1431, 1341, 1227, 1196, 1175. Anal. Calcd. for $C_{34}H_{22}Cl_2N_2O_4$ (593.45): C, 68.81; H, 3.74; N, 4.72. Found: C, 68.90; H, 3.79; N, 4.66.

***1,1'-Diacetyl-3,3'-bis(3-nitrobenzoyl)-7,7'-bisindolizine* (11) Py-447.** Brown crystals. ^{1}H-NMR (400 MHz, $CDCl_3$+TFA, δ ppm): 2.69 (s, 6H, 2Me), 7.80 (dd, 2H, *J* = 7.4, 2.0 Hz, H-6/H-6'), 7.83 (t, 2H, *J* = 8.0 Hz, H-5Ph), 7.84 (s, 2H, H-2/H-2'), 8.18 (dt, 2H, *J* = 7.7, 1.2 Hz, H-4Ph), 8.52 (ddd, 2H, *J* = 8.0, 2.3, 1.0 Hz, H-6Ph), 8.66 (t, 2H, *J* = 2.0 Hz, H-2Ph), 9.11 (dd, 2H, *J* = 2.0, 0.8 Hz, H-8/H-8'), 10.09 (dd, 2H, *J* = 7.3, 0.8 Hz, H-5/H-5'). ^{13}C-NMR (100 MHz, $CDCl_3$+TFA, δ ppm): 26.8 (2Me), 116.1 (C-6/C-6'), 116.3 (C-1/C-1'), 118.8 (C-8/C-8'), 122.8 (C-3/C-3'), 123.8 (2C, C-2Ph), 127.1 (2C,C-6Ph), 130.5 (2C, C-5Ph), 130.7 (C-5/C-5'), 132.2 (C-2/C-2'), 134.6 (2C, C-4Ph), 139.7 (C-7/C-7'), 140.1 (2C, C-1Ph), 140.9 (C-8a/C-8a'), 148.2 (2C-3Ph); 184.2 (2COAr), 197.8 (2COMe). IR (KBr, cm^{-1}): 2090, 1652, 1615, 1525, 1495, 1455, 1336, 1225, 1198. Anal. Calcd. for $C_{34}H_{22}N_4O_8$ (614.56): C, 66.45; H, 3.61; N, 9.12. Found: C, 66.38; H, 3.66; N, 9.19.

CONCLUSIONS

We have developed a convenient and efficient synthetic methodology for symmetrical-substituted 7,7'-bisindolizine derivatives. This consecutive, one-pot, three-component reaction of 4,4'-bipyridine with α-bromocarbonyl compounds and non-symmetrical electron-deficient alkynes, used in a molar ratio of 1:2:2, in 1,2-epoxybutane is a novel methodology that led to a variety of 7,7'-bisindolizine derivatives. Mixtures of 7,7'-bisindolizines and 7-pyridylindolizines were obtained when one equivalent of 4,4'-bipyridine, one equivalent of substituted phenacyl bromides and one equivalent of activated alkynes was heated in 1,2-epoxybutane at reflux temperature. Fluorescence properties of synthesized compounds are investigated.

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REFERENCES

1. A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, **2000**, *39*, 3168-3210.
2. J. Zhu and H. Bienaymé (Eds.), "Multicomponent Reactions", Wiley-VCH, Weinheim, 2005.
3. T. J. J. Müller, *Beilstein J. Org. Chem.*, **2014,** *10,* 115-116.
4. J. Gubin, J. Luchetti, J. Mahaux, D. Nisato, G. Rossels, M. Clinet, P. Polster and P. Chatlain, *J. Med. Chem.*, **1992**, *35*, 981-988.
5. K. Kitadokoro, S. Hagishita, T. Sato, M. Ohtani and K. Miki, *J. Biochem.*, **1998**, *123*, 619-623.
6. S. Medda, P. Jaisankar, R. K. Manna, B. Pal, V. S. Giri and M. K. Basu, M. *J. Drug Target,* **2003**, *11*, 123-128.
7. L.-L. Gundersen, K. E. Malterund, A. H. Negussie, F. Rise, S. Teklu and O. B. Østby, *Bioorg. Med. Chem*., **2003**, *24*, 5409-5415.
8. L. D. Bolle, G. Andrei, R. Snoeck, Y. Zhang, A. V. Lommel, M. Otto, A. Bousseau, C. Roy, E. D. Clercq and L. Naesens, *Biochem. Pharmacol*., **2004**, *67*, 325-336.
9. T. Weide, L. Arve, H. Prinz, H. Waldmann and H. Kesslet, *Bioorg. Med. Chem. Lett*., **2006**, *16*, 59-63.
10. K. Bedjeguelal, H. Bienayme, A. Dumoulin, S. Poigny, P. Schmitt and E. Tam, *Bioorg. Med. Chem. Lett*., **2006**, *16*, 3998-4001.
11. D. A. James, K. Koya, H. Li, G. Liang, Z. Xia, W. Ying, Y. Wu and L. Sun, *Bioorg. Med. Chem. Lett*., **2008**, *18*, 1784-1787.
12. Y.-M. Shen, P.-C. Lu, W. Chen, P.-G. Liu, M.-Z. Zhang and H.-L. Zhu, *Eur. J. Med. Chem*., **2010**, *45*, 3184-3190.
13. A. Vlahovici, I. Druta, M. Andrei, M. Cotlet and R. Dinica, *J. Lumin*., **1999**, *82*, 155-162.
14. A. Vlahovici, M. Andrei and I. Druta, *J. Lumin*., **2002**, *96*, 279-285.
15. H. Sonnenschein, G. Henrich, H. Resch-Genger and B. Schultz, *Dyes Pigments*, **2000**, *46*, 23-27.
16. P. Woisel, G. Surpateanu, F. Cazier and P. Blach, *Tetrahedron*, **2005**, *61*, 3939-3945.
17. M. Vasilescu, R. Bandula, F. Dumitrascu and H. Lemmetyinen, *J. Fluoresc*., **2006**, *16*, 631
18. R. Huisgen, *Angew. Chem., Int. Ed.*, **1963**, *2*, 565-632.
19. I. Zugravescu and M. Petrovanu, "*N*-Ylid Chemistry", Mc-Graw Hill, London, 1976.

20. A. Padwa, "1,3-Dipolar Cycloaddition Chemistry", John Wiley & Sons, New York, 1984.
21. I. Druta, A, R. Dinica, E. Bacu and I. Humelnicu, *Tetrahedron*, **1998**, *54*, 10811-10818.
22. A. Rotaru, R. Danac and I. Druta, *J. Heterocycl. Chem*., **2004**, *41*, 893-897.
23. R. Dinica and C. Pettinari, *Heterocycl. Comm*., **2001**, *7*, 381-386.
24. R. M. Dinica, I. I. Druta and C. Pettinari, *Synlett*, **2000**, 1013-1015.
25. A. V. Rotaru, I. Druta, T. Oeser and T. J. J. Müller, *Helv. Chim. Acta*, **2005**, *88*, 1798-1812.
26. E. Georgescu, M. R. Caira, F.Georgescu, C. Draghici, M. M. Popa and F. Dumitrascu, *Synlett*, **2009**, 1795-1799.
27. M. R. Caira, E. Georgescu, F. Georgescu, M. M. Popa and F. Dumitrascu, *Arkivoc*, **2009**, 242-253.
28. F. Dumitrascu, M. T. Caproiu, F. Georgescu, C. Draghici, M. M. Popa and E. Georgescu, *Synlett*, **2010**, 2407-2410.
29. F. Dumitrascu, M. M. Caira, E. Georgescu, F. Georgescu, C. Draghici and, M. M. Popa, *Heteroatom Chem.*, **2011**, *22*, 723-729.
30. E. Georgescu, F. Georgescu, M. M. Popa, C. Draghici, L. Tarko and F. Dumitrascu, *ACS Comb. Sci*., **2012**, *14,* 101-107.
31. F. Dumitrascu, E. Georgescu, F. Georgescu, M. M. Popa and D. Dumitrescu, *Molecules*, **2013**, *18*, 2635-2645.
32. E. Georgescu, F. Dumitrascu, F. Georgescu, C. Draghici and L. Barbu, *J. Heterocycl. Chem*., **2013**, *50*, 78-82.
33. A. Nicolescu, C. Deleanu, E. Georgescu, F. Georgescu, A.-M. Iurascu, S. Shova and P. Filip, *Tetrahedron Lett*., **2013**, *54*, 1486-1488.
34. E. Georgescu, A. Nicolescu, F. Georgescu, F. Teodorescu, D. Marinescu, A.-M. Macsim and C. Deleanu, *Beilstein J. Org. Chem.*, **2014,** *10,* 2377-2387.
35. E. Georgescu, A. Nicolescu, F. Georgescu, S. Shova, F. Teodorescu, A.-M. Macsim and C. Deleanu, *Synthesis*, **2015**, *47*, 1643-1655.
36. E. Georgescu, A. Nicolescu, F. Georgescu, F. Teodorescu, S. Shova, A. T. Marinoiu, F. Dumitrascu and C. Deleanu, *Tetrahedron*, **2016**, *72*, 2507-2520.
37. F. Albota, M. R. Caira, C. Draghici, F. Dumitrascu and D. E. Dumitrescu, *Beilstein J. Org. Chem.*, **2016***, 12*, 2503-2510.
38. E. Georgescu, A. Nicolescu, F. Georgescu, S. Shova, B. C. Simionescu and C. Deleanu, *Rev. Roum. Chim.*, **2016**, *61*, 283-290.
39. I. I. Druta, R. M. Dinica, L. Smau and D. Tanase, *Ann. Sci. Univ. Iaşi*, **1995**, *S3*, 123-128.