# Substituted Indolizines by 1,3-Dipolar Cycloaddition Reactions
## IV. 7-Benzyl-indolizines

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*The new indolizine derivatives **6a-f** and **7a-f** containing a benzyl group grafted on the pyridine ring were obtained by reaction of N-phenacylpyridinium bromides **3** with ethyl propiolate or 1-butyn-3-one as acetylenic dipolarophiles in 1,2-epoxypropane as reaction medium. Structural proof for the compounds was provided by elemental analysis and NMR spectroscopy, including COSY and HETCOR experiments.*

*Keywords: indolizine, pyridinium-1-methylide, 1,3-dipolar cycloaddition*

Recently, we described the synthesis of new 7-substituted indolizines [1, 2]. The field of synthesis of pyrroloazines, although is a relatively old one, has also proven to be one of the most versatile and lucrative. This is due to the rising interest for novel fluorophores in the past decades for the use in LEDs (light emitting diodes) and other electronic devices. To these relatively new applications, the classical use of fluorophores in bio-labeling and fluorescence microscopy has been expanded. Some of the most versatile scaffolds are indolizine [3-10] and azaindolizine [5, 11-14] derivatives. Attaching different substituents on this relatively simple system can increase the bio-availability and/or alter the quantum yield and the fluorescence spectra. Furthermore, by obtaining indolizines substituted at the 7 position, can be obtained a wide range of new highly selective chemosensors by attaching them to a cyclodextrin moiety, respectively [15, 16].

One of the most versatile synthetic methods for obtaining the indolizine derivatives are 1,3-dipolar cycloaddtions between pyridinium *N*-ylides and activated (electron deficient) alkynes or alkenes in the presence of an oxidant reagent, offering both high yields and regioselectivity [17-25].

Herein we present the synthesis of new indolizines, containing a benzyl group grafted on the pyridine ring, by 1,3-dipolar cycloaddition reactions of pyridinium *N*-ylides with acetylenic non-symmetrical dipolarofiles, ethyl propiolate and butyne-3-one. By introducing the benzyl substituent on the pyridine ring and by varying the substituents on the pyrrole moiety, it may be possible to obtain a finer tuning of the optical properties of indolizine derivatives.

### Experimental part

Melting points were determined on a Boëtius hot plate and are uncorrected. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for $^1$H and 75 MHz for $^{13}$C. Supplementary evidence was given by HETCOR and COSY experiments.

*General procedure for synthesis of 4-benzyl-pyridinium bromides 3*

10 Mmol 4-benzyl-pyridine and 10 mmol phenacyl bromide in 30 mL of methanol were refluxed for 2 h and then were kept at room temperature until the next day. The pyridinium bromides **3** obtained were collected on the filter and washed with chloroform and purified by recrystallization from methanol.

*4-Benzyl-1-(2-phenyl-2-oxoethyl)-pyridinium bromide **(3a)***. The product was recrystallized from methanol and pale yellow crystals with mp 186-8°C were obtained; Yield 79 %. Anal. Calcd. $C_{20}H_{18}BrNO$: N 3.80. Found N 4.07. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 4.23 (s, 2H, $CH_2$Ph); 7.09 (s, 2H, $CH_2$); 7.19-7.23 (m, 2H, H-2", H-6"); 7.38-7.44 (m, 5H, H-3', H-5', H-3", H-4", H-5"); 7.50-7.57 (m, 1H, H-4'); 7.71 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 8.06-8.09 (m, 2H, H-2', H-6'); 9.20 (d, 2H, *J* = 6.7 Hz, H-2, H-6). $^1$H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.30 (s, 2H, $CH_2$Ph); 6.35 (s, 2H, $CH_2$); 7.22-7.25 (m, 3H, H-2", H-4", H-6"); 7.40-7.45 (m, 2H, H-3", H-5"); 7.50-7.55 (m, 2H, H-3', H-5'); 7.67-7.71 (m, 1H, H-4'); 7.80 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 7.99-8.03 (m, 2H, H-2', H-6'); 8.58 (d, 2H, *J* = 6.7 Hz, H-2, H-6).

$^{13}$C-NMR (75 MHz, $CDCl_3$+TFA) δ: 41.8 ($CH_2$Ph); 66.2 ($CH_2$); 116.3, 117.1 (C-4', CN); 127.9, 128.1, 128.6, 129.3, 129.4, 129.6 (C-3, C-5, C-2', C-3', C-5', C-6', C-2", C-3", C-4", C-5", C-6") 132.5 (C-1'); 134.9 (C-1"); 135.8 (C-4'); 145.4 (C-2, C-6); 163.4 (C-4); 190.0 (COAr).

*4-Benzyl-1-[2-(4-fluorophenyl)-2-oxoethyl]-pyridinium bromide **(3b)***. The product was recrystallized from methanol/diethylether and colorless crystals with mp 185-6°C were obtained; Yield 76 %. Anal. Calcd. $C_{20}H_{17}BrFNO$: N 3.63. Found N 3.88. $^1$H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.30 (s, 2H, $CH_2$Ph); 6.43 (s, 2H, $CH_2$); 7.17-7.24 (m, 4H, H-3', H-5', H-2", H-6"); 7.36-7.44 (m, 3H, H-3", H-4", H-5"); 7.78 (d, 2H, *J* = 6.7 Hz, H-3, H-5); ); 8.11 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.62 (d, 2H, *J* = 6.7 Hz, H-2, H-6).

*4-Benzyl-1-[2-(4-chlorophenyl)-2-oxoethyl]-pyridinium bromide **(3c)***. The product was recrystallized from methanol and colorless crystals with mp 271-2°C were obtained; Yield 88 %. Anal. Calcd. $C_{20}H_{17}BrClNO$: N 3.48. Found N 8.57. $^1$H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.31 (s, 2H, $CH_2$Ph); 6.37 (s, 2H, $CH_2$); 7.22-7.25 (m, 2H, H-2", H-6"); 7.37-7.44 (m, 3H, H-3", H-4", H-5"); 7.68 (d, 2H, *J* = 8.5 Hz, H-3', H-5'); 7.81 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 7.91 (d, 2H, *J* = 8.5 Hz, H-2', H-6'); 8.59 (d, 2H, *J* = 6.7 Hz, H-2, H-6). $^{13}$C-NMR (75 MHz, $CDCl_3$+TFA) δ: 41.8 ($CH_2$Ph); 66.2 ($CH_2$); 127.8 (C-3, C-5); 128.1 (C-4"); 129.3; 129.6 (C-2", C-3", C-5", C-6"); 129.7, 130.1 (C-2', C-3', C-5', C-6'); 131.1 (C-1'); 134.9 (C-1"); 142.4 (C-4'); 145.5 (C-2, C-6); 163.4 (C-4); 188.7 (COAr).

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*4-Benzyl-1-[2-(4-bromophenyl)-2-oxoethyl]-pyridinium bromide* ***(3d)***. The product was recrystallized from methanol and colorless crystals with mp 283-5°C were obtained; Yield 96 %. Anal. Calcd. $C_{20}H_{17}Br_2NO$: N 3.13. Found N 3.44. $^1$H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.33 (s, 2H, $CH_2Ph$); 6.36 (s, 2H, $CH_2$); 7.22-7.25 (m, 2H, H-2", H-6"); 7.38-7.46 (m, 3H, H-3", H-4", H-5"); 7.72, 7.92 (2d, 4H, *J* = 8.6 Hz, H-2', H-3', H-5', H-6'); 7.82 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 8.64 (d, 2H, *J* = 6.7 Hz, H-2, H-6). $^{13}$C-NMR (75 MHz, $CDCl_3$+TFA) δ: 41.8 ($CH_2Ph$); 66.1 ($CH_2$); 127.9 (C-3, C-5); 128.2 (C-4"); 129.3; 129.6 (C-2", C-3", C-5", C-6"); 130.0, 132.8 (C-2', C-3', C-5', C-6'); 131.4, 131.5 (C-1', C-4'); 134.9 (C-1"); 145.4 (C-2, C-6); 163.6 (C-4); 189.0 (COAr).

*4-Benzyl-1-[2-(4-nitrophenyl)-2-oxoethyl]-pyridinium bromide* ***(3e).*** The product was recrystallized from methanol and pale yellow crystals with mp 240-2°C were obtained; Yield 84 %. Anal. Calcd. $C_{20}H_{17}BrN_2O_3$: N 6.78. Found N 8.01. $^1$H-NMR (300 MHz, $CDCl_3$+TFA) δ: 4.36 (s, 2H, $CH_2Ph$); 6.36 (s, 2H, $CH_2$); 7.23-7.26 (m, 2H, H-2", H-6"); 7.38-7.46 (m, 3H, H-3", H-4", H-5"); 7.87 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 8.27, 8.39 (2d, 4H, *J* = 8.8 Hz, H-2', H-3', H-5', H-6'); 8.60 (d, 2H, *J* = 6.7 Hz, H-2, H-6).

*4-Benzyl-1-[2-(4-methoxyphenyl)-2-oxoethyl]-pyridinium bromide* ***(3f)***. The product was recrystallized from methanol and colorless crystals with mp 259-261°C were obtained; Yield 84 %. Anal. Calcd. $C_{21}H_{20}BrNO_2$: N 3.52. Found N 3.72. $^1$H-NMR (300 MHz, $CDCl_3$+TFA) δ: 3.90 (s, 3H, MeO); 4.30 (s, 2H, $CH_2Ph$); 6.43 (s, 2H, $CH_2$); 7.01 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 7.20-7.23 (m, 2H, H-2", H-6"); 7.36-7.44 (m, 3H, H-3", H-4", H-5"); 7.78 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 8.06 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.62 (d, 2H, *J* = 6.7 Hz, H-2, H-6). $^{13}$C-NMR (75 MHz, $CDCl_3$+TFA) δ: 41.8 ($CH_2Ph$); 55.7 (OMe); 66.0 ($CH_2$); 114.7 (C-3', C-5'); 125.5 (C-1'); 127.6 (C-3, C-5); 128.1 (C-4"); 129.3; 129.5 (C-2", C-3", C-5", C-6"); 131.3 (C-2', C-6'); 134.9 (C-1"); 145.4 (C-2, C-6); 162.9 (C-4); 165.6 (C-4'); 187.9 (COAr).

*General procedure for synthesis of 7-benzyl-indolizines 6 and 7*

5 Mmol of 4-benzyl-pyridinium bromide **3** were suspended in 50 mL 1,2-epoxypropane, 7 mmol of ethyl propiolate or 1-butyne-3-one were added and the mixture was stirred at room temperature for 20 days (with protection against moisture). The solvent was partly removed under reduced pressure then 8-10 mL of methanol was added under stirring and the mixture was left over night at room temperature. The solid was filtered off, washed with a mixture of methanol-diethyl ether (1:2) and recrystallized from chloroform/diethyl ether.

*3-Benzoyl-7-benzyl-1-carboethoxy-indolizine* ***(6a)***. Yellow crystals with mp 158-160°C were obtained; Yield 41 %. Anal. Calc. $C_{25}H_{21}NO_3$: C 78.31; H 5.52; N 3.65. Found C 78.62; H 5.81; N 3.88. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, *J* = 7.1 Hz, Me); 4.10 (s, 2H, $CH_2Ph$); 4.34 (q, 2H, *J* = 7.1 Hz, $CH_2$); 6.92 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.24-7.29 (m, 3H, H-2", H-4", H-6"); 7.31-7.40 (m, 2H, H-3", H-5"); 7.48-7.58 (m, 3H, H-3', H-4', H-5'); 7.77-7.81 (m, 2H, H-2', H-6'); 7.78 (s, 1H, H-2); 8.21 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 9.85 (dd, *J* = 7.1, 1.0 Hz, H-5). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 14.4 (Me); 41.7 ($CH_2Ph$); 60.2 ($CH_2$); 105.7 (C-1); 116.9 (C-8); 118.2 (C-6); 122.2 (C-3); 126.7 (C-4"); 128.3, 128.8, 128.9, 129.0, 129.3 (C-2, C-5, C-2', C-3', C-5', C-6', C-2", C-3", C-5", C-6"); 131.4 (C-4'); 138.8 (C-1"); 139.8 (C-1'); 140.2 (C-8a); 142.2 (C-7); 163.8 (COO); 182.6 (COAr).

*7-Benzyl-1-carboethoxy-3-(4-fluorobenzoyl)-indolizine* ***(6b)***.Yellow crystals with mp 145-6°C were obtained; Yield 42 %. Anal. Calcd. $C_{25}H_{20}FNO_3$: N 3.49. Found N 3.63. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, *J* = 7.1 Hz, Me); 4.10 (s, 2H, $CH_2Ph$); 4.35 (q, 2H, *J* = 7.1 Hz, $CH_2$); 6.92 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.17-7.37 (m, 7H, Ph, H-3', H-5'); 7.75 (s, 1H, H-2); 7.84 (dd, *J* = 8.8, 5.4 Hz, H-2', H-6'); 8.21 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 8.38 (d, 2H, *J* = 8.9 Hz, H-2', H-6'); 9.80 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 14.4 (Me); 41.7 ($CH_2Ph$); 60.1 ($CH_2$); 105.8 (C-1); 115.3 (d, *J* = 21.9 Hz, C-3', C-5'); 117.0 (C-8); 118.3 (C-6); 122.0 (C-3); 126.8 (C-4"); 128.9 (C-2, C-5); 128.8, 129.0 (C-2", C-3", C-5", C-6"); 131.2 (d, *J* = 9.0 Hz, C-2', C-6'); 136.0 (d, *J* = 3.0 Hz, C-1'); 138.8 (C-1", benzyl); 140.2 (C-8a); 142.3 (C-7); 164.1 (COO); 164.7 (d, *J* = 253.5 Hz, C-4'); 183.8 (COAr).

*7-Benzyl-1-carboethoxy-3-(4-chlorobenzoyl)-indolizine* ***(6c)***. Yellow crystals with mp 138-140°C were obtained; Yield 43 %. Anal. Calcd. $C_{25}H_{20}ClNO_3$: C 71.85; H 4.82; Cl 8.48; N 3.35. Found C 71.11; H 5.12; Cl 8.87; N 3.57. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, *J* = 7.1 Hz, Me); 4.10 (s, 2H, $CH_2Ph$); 4.35 (q, 2H, *J* = 7.1 Hz, $CH_2$); 6.92 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.23-7.25 (m, 2H, H-2", H-6"); 7.27-7.36 (m, 2H, H-3", H-5"); 7.47 (d, 2H, *J* = 8.5 Hz, H-3', H-5'); 7.74 (s, 1H, H-2); 7.75 (d, 2H, *J* = 8.5 Hz, H-2', H-6'); 8.22 (dd, 1H, *J* = 1.9, 1.0, Hz, H-8); 9.81 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

*7-Benzyl-1-carboethoxy-3-(4-bromobenzoyl)-indolizine* ***(6d)***. Yellow crystals with mp 146-8°C were obtained; Yield 41 %. Anal. Calcd. $C_{25}H_{20}BrNO_3$: C 64.95; H 4.36; Br 17.28; N 3.03. Found C 65.21; H 4.67; Br 17.60; N 3.31. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, *J* = 7.1 Hz, Me); 4.09 (s, 2H, $CH_2Ph$); 4.34 (q, 2H, *J* = 7.1 Hz, $CH_2$); 6.91 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.23-7.29 (m, 2H, H-2", H-6"); 7.31-7.40 (m, 2H, H-3", H-5"); 7.63, 7.67 (2d, 4H, *J* = 8.6 Hz, H-2', H-3', H-5', H-6'); 7.73 (s, 1H, H-2); 8.21 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 9.81 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 14.4 (Me); 41.9 ($CH_2Ph$); 60.0 ($CH_2$); 106.3 (C-1); 117.0 (C-8); 118.4 (C-6); 122.3 (C-3); 126.1 (C-4'); 126.8 (C-4"); 128.8, 129.1 (C-2", C-3", C-5", C-6"); 129.0 (C-2, C-5); 130.4; 131.7 (C-2', C-3', C-5', C-6'); 138.8, 138.9 (C-1', C-1"); 140.5 (C-8a); 142.4 (C-7); 163.9 (COO); 183.8 (COAr).

*7-Benzyl-1-carboethoxy-(4-nitrobenzoyl)-indolizine* ***(6e).*** Yellow crystals with mp 180-1°C were obtained; Yield 72 %. Anal. Calcd. $C_{25}H_{20}N_2O_5$: C 70.09; H 4.71; N 6.54. Found C 70.33; H 4.94; N 6.77. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, *J* = 7.1 Hz, Me); 4.13 (s, 2H, $CH_2Ph$); 4.35 (q, 2H, *J* = 7.1 Hz, $CH_2$); 6.99 (dd, 1H, *J* = 7.2, 2.0 Hz, H-6); 7.23-7.37 (m, 5H, $PhCH_2$); 7.70 (s, 1H, H-2); 7.93 (d, 2H, *J* = 8.9 Hz, H-3', H-5'); 8.24 (dd, 1H, *J* = 2.0, 1.0 Hz, H-8); 8.38 (d, 2H, *J* = 8.9 Hz, H-2', H-6'); 9.86 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 41.8 ($CH_2Ph$); 60.2 ($CH_2$); 106.7 (C-1); 117.6 (C-8); 118.4 (C-6); 121.6 (C-3); 123.6 (C-3', C-5'); 126.7 (C-4"); 128.9, 129.0, 129.4, 129.7 (C-2, C-5, C-2', C-6', C-2", C-3", C-5", C-6"); 138.6 (C-1"); 140.7 (C-8a); 143.3 (C-7); 145.4 (C-1'); 149.3 (C-4'); 163.8 (COO); 182.6 (COAr).

*7-Benzyl-1-carbethoxy-(4-methoxybenzoyl)-indolizine* ***(6f)***. Yellow crystals with mp 122-4 °C were obtained; Yield 44 %. Anal. Calcd. $C_{26}H_{23}NO_4$: C 75.53; H 5.61; N 3.39. Found C 75.82; H 5.97; N 3.67. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, *J* = 7.1 Hz, Me); 3.90 (s, 3H, MeO); 4.09 (s, 2H, $CH_2Ph$); 4.35 (q, 2H, *J* = 7.1 Hz, $CH_2$); 6.88 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.01 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 7.23-7.29 (m, 3H, H-2", H-4", H-6"); 7.31-7.37 (m, 2H, H-3", H-5"); 7.78 (s, 1H, H-2); 7.83 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.20 (dd, 1H, *J* = 1.9, 1.0 Hz, H-8); 9.78 (dd, 1H, *J* = 7.2, 1.0 Hz, H-5).

*1-Acetyl-7-benzyl-3-benzoyl-indolizine* ***(7a)***. Yellow crystals with mp 175-7°C were obtained; Yield 50 %. Anal. Calc. $C_{24}H_{19}NO_2$: 81.56; H 5.42; N 3.96. Found C 81.90; H 5.71; N 4.24. δ: 2.50 (s, 3H, MeCO); 4.13 (s, 2H, $CH_2Ph$);

6.98 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.23-7.36 (m, 5H, benzyl); 7.51-7.60 (m, 3H, H-3', H-4', H-5'); 7.67 (s, 1H, H-2); 7.80-7.83 (m, 2H, H-2', H-6'); 8.55 (dd, 1H, *J* = 1.9, 0.8 Hz, H-8); 9.85 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5).

*1-Acetyl-7-benzyl-3-(4-fluorobenzoyl)-indolizine* ***(7b)*** Yellow crystals with mp 177-9°C were obtained; Yield 46 %. Anal. Calcd. $C_{24}H_{18}FNO_2$: N 3.77. Found N 4.03. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 2.50 (s, 3H, MeCO); 4.11 (s, 2H, $CH_2Ph$); 6.96 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.18-7.37 (m, 7H, 5H benzyl, H-3', H-5'); 7.63 (s, 1H, H-2); 7.84 (dd, *J* = 8.8, 5.4 Hz, H-2', H-6'); 8.34 (d, 2H, *J* = 8.9 Hz, H-3', H-5'); 8.52 (dd, 1H, *J* = 1.9, 0.8 Hz, H-8); 9.80 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 27.7 (MeCO); 41.7 ($CH_2Ph$); 114.4 (C-1); 115.5 (d, *J* = 21.9 Hz, C-3', C-5'); 117.9 (C-6); 119.3 (C-8); 121.8 (C-3); 126.8 (C-4"); 128.9 (C-2, C-5); 128.8, 129.0 (C-2", C-3", C-5", C-6"); 131.1 (d, *J* = 9.0 Hz, C-2', C-6'); 136.0 (d, *J* = 3.0 Hz, C-1'); 138.8 (C-1", benzyl); 139.8 (C-8a); 143.8 (C-7); 164.7 (d, *J* = 253.5 Hz, C-4'); 183.8 (COAr); 193.0 (COMe).

*1-Acetyl-7-benzyl-3-(4-chlorobenzoyl)-indolizine* ***(7c)***. Yellow crystals with mp 190-192°C were obtained; Yield 51 %. Anal. Calcd. $C_{24}H_{18}ClNO_2$: C 74.32; H 4.68; Cl 9.14; N 3.61. Found C 74.64; H 4.99; Cl 9.50; N 3.87. $^1$H-NMR (300 MHz, $CDCl_3$+TFA) δ: 2.66 (s, 3H, MeCO); 4.20 (s, 2H, $CH_2Ph$); 7.25-7.36 (m, 6H, H-6, H-2", H-3", H-4", H-5", H-6"); 7.58 (d, 2H, *J* = 8.5 Hz, H-3', H-5'); 7.73 (d, 2H, *J* = 8.5 Hz, H-2', H-6'); 7.83 (s, 1H, H-2); 8.54 (bs, 1H, H-8); 9.82 (d, 1H, *J* = 7.1, 0.8 Hz, H-5).

*1-Acetyl-7-benzyl-3-(4-bromobenzoyl)-indolizine* ***(7d)***. Yellow crystals with mp 183-5°C were obtained; Yield 40 %. Anal. Calcd. $C_{24}H_{18}BrNO_2$: C 66.68; H 4.20; Br 18.48; N 3.24. Found C 66.97; H 4.51; Br 18.81; N 3.52. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 2.50 (s, 3H, MeCO); 4.11 (s, 2H, $CH_2Ph$); 6.98 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.23-7.29 (m, 3H, H-2", H-4", H-6"); 7.31-7.36 (m, 2H, H-3", H-5"); 7.62 (s, 1H, H-2); 7.68 (s, 4H, H-2', H-3', H-5,' H-6'); 8.55 (dd, 1H, *J* = 1.9, 0.8 Hz, H-8); 9.81 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 27.7 (MeCO); 41.8 ($CH_2Ph$); 114.6 (C-1); 118.0 (C-6); 119.3 (C-8); 121.7 (C-3); 126.2 (C-4'); 126.8 (C-4"); 128.8, 128.9, 130.0 (C-2, C-5, C-2", C-3", C-5", C-6"); 130.4; 131.7 (C-2', C-3', C-5', C-6'); 138.7, 138.8 (C-1', C-1"); 139.9 (C-8a); 144.0 (C-7); 183.9 (COAr); 193.0 (COMe).

*1-Acetyl-7-benzyl-3-(4-nitrobenzoyl)-indolizine* ***(7e)***.Yellow crystals with mp 169-171°C were obtained; Yield 75 %. Anal. Calcd. $C_{24}H_{18}N_2O_4$: C 72.35; H 4.55; N 7.03. Found C 72.60; H 4.81; N 7.30. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 2.50 (s, 3H, MeCO); 4.13 (s, 2H, $CH_2Ph$); 7.03 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.23-7.29 (m, 3H, H-2", H-4", H-6"); 7.31-7.36 (m, 2H, H-3", H-5"); 7.59 (s, 1H, H-2); 7.94 (d, 2H, *J* = 8.7 Hz, H-3', H-5'); 8.38 (d, 2H, *J* = 8.7 Hz, H-2', H-6'); 8.57 (dd, 1H, *J* = 1.9, 0.8 Hz, H-8); 9.86 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 27.7 (MeCO); 41.8 ($CH_2Ph$); 115.1 (C-1); 118.4 (C-6); 119.4 (C-8); 121.3 (C-3); 123.7 (C-3', C-5'); 126.8 (C-4"); 128.8, 128.9 (C-5, C-2", C-3", C-5", C-6"); 129.3 (C-2); 129.6 (C-3', C-5'); 138.6 (C-1", benzyl); 140.2 (C-8a); 144.7 (C-7); 145.3 (C-1'); 149.3 (C-4'); 182.5 (COAr); 192.9 (COMe).

*1-Acetyl-7-benzyl-3-(4-methoxybenzoyl)-indolizine* ***(7f)***. Yellow crystals with mp 179-181°C were obtained; Yield 48 %. Anal. Calcd. $C_{25}H_{21}NO_3$: C 78.31; H 5.52; N 3.65. Found C 78.66; H 5.80; N 3.87. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 2.50 (s, 3H, MeCO); 3.91 (MeO); 4.11 (s, 2H, $CH_2Ph$); 6.93 (dd, 1H, *J* = 7.2, 1.9 Hz, H-6); 7.03 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 7.23-7.29 (m, 3H, H-2", H-4", H-6"); 7.31-7.36 (m, 2H, H-3", H-5"); 7.67 (s, 1H, H-2); 2); 7.83 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.53(dd, 1H, *J* = 1.9, 0.8 Hz, H-8); 9.77 (dd, 1H, *J* = 7.2, 0.8 Hz, H-5). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 27.7 (MeCO); 41.8 ($CH_2Ph$); 55.5 (MeO); 113.7 (C-3', C-5'); 114.1 (C-1); 117.5 (C-6); 119.2 (C-8); 122.2 (C-3); 126.7 (C-4"); 128.5, 128.7, 128.9 (C-2, C-5, C-2", C-3", C-5", C-6"); 131.0 (C-2', C-6'); 132.3 (C-1'); 139.0 (C-1", benzyl); 139.5 (C-8a); 143.3 (C-7); 162.4 (C-4'); 184.3 (COAr); 193.1 (COMe).

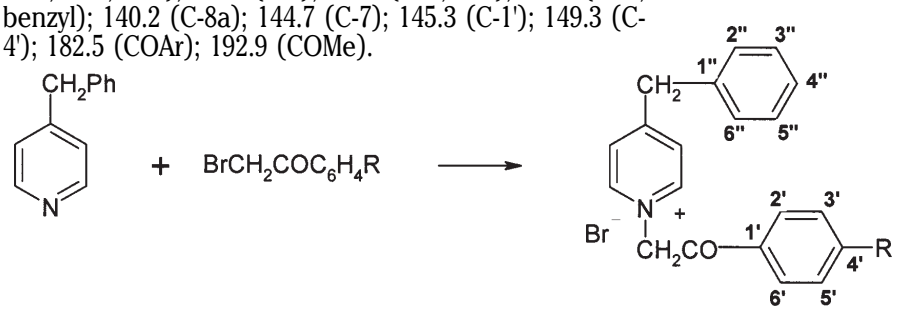
## Results and Discussion

The indolizines **6** and **7** were obtained by 1,3-dipolar cycloaddition reactions between pyridinium *N*-ylides (generated *in situ* from the corresponding pyridinium salts) and activated (electron deficient) alkynes. The pyridinium bromides **3** were prepared by *N*-alkylation of 4-benzyl-pyridine **1** with the corresponding 2-bromoacetophenones **2** in methanol at reflux (scheme 1) and were purified by recrystallization from methanol.

The structure of new cycloimmonium bromides **3** was confirmed by elemental analysis and NMR spectroscopy. In the $^1$H-NMR, recorded in mixture of $CDCl_3$ with trifluoroacetic, the signal for the methylenic protons appears in the range δ = 6.35-6.43 ppm as a sharp singlet. The methylenic protons from the benzyl moiety appear in the range δ= 4.30-4.36 ppm. The protons H-2 and H-6 from the pyridine moiety are deshielded (δ = 8.56-8.64 ppm) in respect with H-3 and H-5 protons from the beta position (δ = 7.78-7.87 ppm), due to the vicinity of the quaternary nitrogen atom.

$^{13}$C-NMR spectra show all the expected signals. The carbon atoms in the á position (δ = ca. 145 ppm) in respect to the quaternary nitrogen atom of the pyridinium ring are deshielded when compared to the carbon atoms in the β positions (δ ~ 128 ppm). Carbon C-4 owes its high chemical shift (δ ~ 163 ppm) to its in γ position in respect to the nitrogen atom and to the strong deshielding effect of the benzyl group. The chemical shifts of the carbonyl groups are in the range 187.9-190.0 ppm.

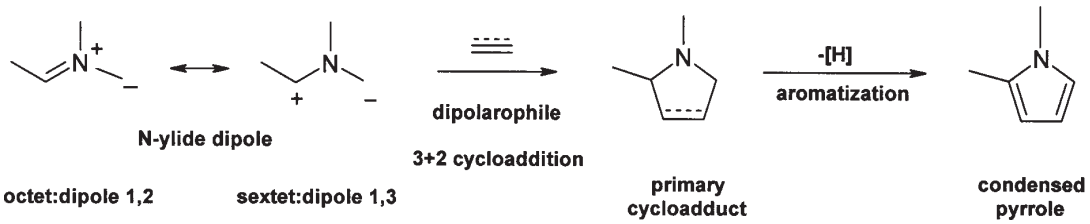
Pyridinium *N*-ylides are heteroaromatic *N*-ylides which are allyl type 1,3-dipoles characterized by four electrons in three parallel $p_z$ orbitals with a sextet structure. The 1,3-dipoles undergo 1,3-dipolar cycloaddition reactions with alkene and alkynes to furnish a diversity of substituted condensed pyrrole rings, which are difficult or impossible to be obtained by others methods, making them very useful synthetic tools.




1 2 3

Scheme 1

R: a = H; b = F; c = Cl; d = Br; e = $NO_2$; f = OMe



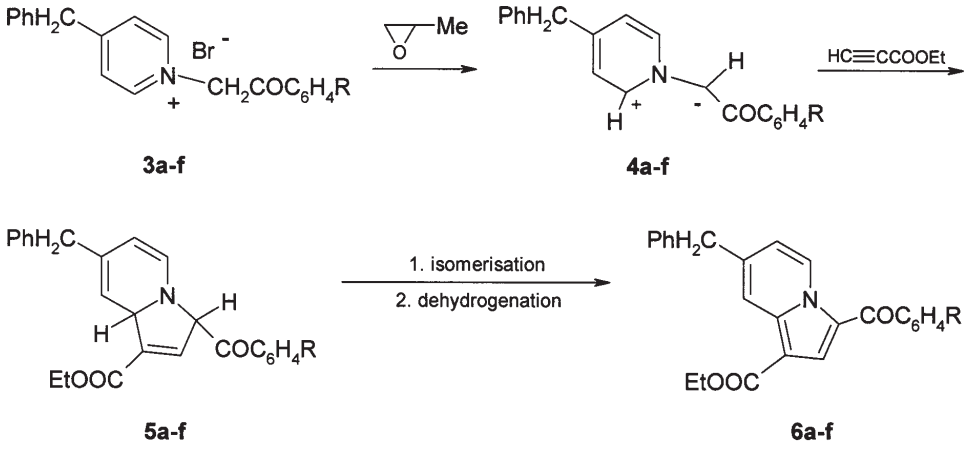

Carbanion monosubstituted pyridinium *N*-ylides are generally unstable compounds, and thus are generated *in situ*. This can be performed by treatment of pyridinium salts with a base, such as triethylamine in organic solvents or an aqueous solution of inorganic base, or by using epoxides as the reaction medium [26-30]. In the first case, the *N*-ylide generation mechanism is direct, consisting of the deprotonation of the pyridinium salt by the base. However, when the reaction is performed in epoxides, the bromide ion attacks the oxirane ring, which is subsequently followed by the ring opening and the formation of the corresponding alkoxide. This, in turn, performs the actual deprotonation of the pyridinium salts, thus generating the *N*-ylide. The indirect epoxide method has the advange of using it as an one-pot, multi-step sequences of reactions, with the salt formation occurring in the same pot as the *N*-ylide generation and the subsequent 1,3-dipolar cycloaddition.

The cycloaddition reaction was performed in 1,2-epoxypropane at room temperature with magnetic stirring in 20 days. The reaction mixture was concentrated by vacuum distillation and then ca. 10 mL methanol were added and it was left over night, after which the precipitate was filtered and recrystallized from a chloroform/ether mixture.

As resulted from NMR data, the cycloaddition between *N*-ylides **4a-f** and the non-symmetrical alkynes, is completely regioselective, as only the formation of the regioisomer substituted at the 1 position of the pyrrolopyridine moiety was observed.

The formation of compounds **6** and **7** implies in the first step the generation of *N*-ylides **4** from bromides **3** by action 1,2-epoxypropane. Subsequently, the 1,3-dipolar cycloaddition between *N*-ylide dipole **4** and ethyl propiolate gave the primary cycloadducts **5a-f** and the corresponding ones for cycloadducts with butyne-3-one**,** which undergo an isomerization reaction followed by dehydrogenation to the aromatic compounds **6** and **7**, respectively (scheme 2 and scheme 3).

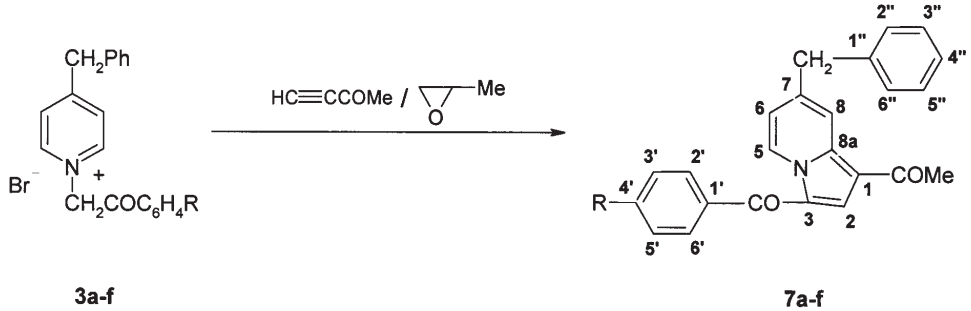
The structure of cycloadducts **6** and **7** was assigned by elemental analysis and NMR spectroscopy. The chemical shifts for hydrogen and carbon atoms were established on the basis of multiplicity, the magnitude of the coupling constants, as well as by two dimensional H/H and H/C experiments.




**3a-f** **4a-f** **5a-f** **6a-f**

R: a = H; b = 4-F; c = 4-Cl; d = 4-Br; e = 4-$NO_2$; f = 4-OMe

Scheme 2




**3a-f** **7a-f**

R: a = H; b = F; c = Cl; d = Br; e = $NO_2$; f = OMe

Scheme 3

The appearance of the three protons grafted on the pyridine ring is as doublet of doublets, with the coupling constants of $^{3}J_{5,6}$ = 7.2 Hz, $^{4}J_{6,8}$ = 1.9 Hz and $^{5}J_{5,8}$ = 1.0 Hz. The multiplicity the proton H-8 is caused by a *para* coupling with H-5 having the value of 1.0 Hz. By replacing the carboethoxy group (indolizines **6**) with acetyl (indolizines **7**), the magnitude of the coupling constant between H-5 and H-8 was decreased to 0.8 Hz due to the electronic effects of the substituents attached at C-1. Also, in dilute solutions of indolizines **7**, a coupling between H-8 and the methylenic protons of the benzyl moiety of 0.8 Hz was observed. However, no such coupling was observed between H-5 and the methylenic protons.

In the $^{1}$H-NMR spectra of cycloadducts **6** and **7** the most deshielded proton is H-5 (δ= 9.78-9.86 ppm). This is due to its vicinity to the nitrogen atom and also due to its spatial proximity to the carbonyl moiety from the phenacyl group. H-8 is also singnificantly deshieded at around 8.20 ppm in the case of **6** and at around 8.50 ppm in the case of **7**, due to its proximity to the pyrrole-grafted carboethoxy or acetyl group, respectivly.

Proton H-2 grafted on the pyrrole ring appears at around 7.70 ppm as a sharp singlet in both compounds **6** and **7** as a result of the combined deshielding effects of the 3-phenacyl groups and the 1-carboethoxy or 1-acetyl moieties.

$^{13}$C-NMR spectra show all the expected signals. The values of the chemical shifts for the carbon atoms of the indolizine moiety in compounds **6** and **7** were established by HETCOR experiments and by comparison with similar compounds.

The atoms C-5, C-7 and C-8 from the indolizines **6** and **7** are highly deshielded in respect with the other atoms from the pyridine system, as they are in α and γ positions in respect to the nitrogen atom of the pyridine ring. The grafting of a benzyl group in the 7 position of indolizine moiety has a strong deshielding effect at position 7 ($\delta_{C-7}$ = 142.2 -144.7 ppm). Also, the presence of the benzyl moiety changes the overall conjugation of the indolizine scaffold, in comparison with other 7-substituted indolizines. The chemical shift of C-1 is increases from $\delta_{C-1}$ = 105.7 -106.7 ppm in the case of carboethoxy substituted derivatives **6** to $\delta_{C-1}$ = 114.1 - 115.1 ppm in the case of the acetyl substituted indolizines **7**.

## Conclusions

Twelve new indolizines were synthesized by 1,3-dipolar cycloadditions between pyridinium *N*-ylides and ethyl propiolate or butyne-3-one as non-symmetrical dipolarophiles. The reactions were performed in 1,2-epoxypropane as solvent and hydrogen bromide scavenger. The new compounds were characterized by mp and elemental analysis and structural assignment was made by NMR spectroscopy.

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Manuscript received: 14.03.2008