Dedicated to Prof. Sorin Rosca on the occasion of his 70th birthday

New Substituted Indolizines by 1,3-Dipolar Cycloaddition Reactions

I. 7-*tert*-Butylindolizines

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*The new indolizine derivatives **6a-h** containing a tert-butyl group grafted on the pyridinic ring were obtained by reaction of N-phenacylpyridinium bromides **3** with ethyl propiolate as acetylenic dipolarophile in medium of 1,2-epoxybutane at reflux. Structural proof for the compounds was provided by elemental analysis and NMR spectroscopy, including COSY and HETCOR experiments.*

Keywords: pyridinium N-ylides, ethyl propiolate, 1,3-dipolar cycloaddition, indolizine

Interest for novel fluorophores has been on the rise in the past decades due to their 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. One of the most versatile scaffolds are indolizine [1-8] and azaindolizine [3, 9-11] derivatives. By grafting different substituents on this relatively simple system, one can increase the bio-availability and/or alter the quantum yield and the fluorescence spectra. Furthermore, by attaching an indolizine to a cyclodextrin, one obtains highly selective chemosensors [12, 13].

One of the most versatile synthetic methods for obtaining the indolizine scaffold is 1,3-dipolar cycloaddition, offering both high yields and regioselectivity [14-23].

Herein we present the synthesis of new indolizine derivatives, containing a *tert*-butyl group grafted on the pyridine ring, through 1,3-dipolar cycloaddition reactions of pyridinium *N*-ylides with activated alkynes". By introducing such a substituent, 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-tert-butyl-pyridinium bromides 3

10 Mmol 4-*tert*-butyl-pyridine and 10 mmol phenacyl bromide in 50 mL of chloroform were heated at reflux for 8 h and then kept at room temperature until the next day. The pyridinium bromides **3** obtained were collected on the filter and washed with chloroform.

1-(2-Phenyl-2-oxoethyl)-4-tert-butyl-pyridinium bromide (3a). The product was recrystallized from methanol/diethyl ether and colorless crystals with mp 246-9°C were obtained; Yield 90 %. Anal. Calcd. $C_{17}H_{20}BrNO$: N 4.19. Found N 4.41. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 1.45 (s, 9H, *t*-Bu); 6.38 (s, 2H, CH_2); 7.51-7.56 (m, 2H, H-3', H-5'); 7.68-7.73 (m, 1H, H-4'); 8.01-8.06 (m, 4H, H-3, H-5, H-2', H-6'); 8.65 (d, 2H, *J* = 6.3 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 30.1 (3C, C**Me**$_3$); 37.2 (**C**Me$_3$); 66.3 (CH_2); 125.5 (C-3, C-5); 128.9, 129.7 (C-2', C-3', C-5', C-6'); 133.0 (C-1'); 136.0 (C-4'); 145.6 (C-2, C-6); 173.4 (C-4); 190.3 (COAr).

1-[2-(4-Methylphenyl)-2-oxoethyl]-4-tert-butyl-pyridinium bromide (3b). The product was recrystallized from methanol/diethyl ether and colorless crystals with mp 266-9°C were obtained; Yield 91%. Anal. Calcd. $C_{18}H_{22}BrNO$: N 4.02. Found N 4.29. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 1.44 (s, 9H, *t*-Bu); 2.42 (s, 3H, 4'-Me); 6.38 (s, 2H, CH_2); 7.32 (d, 2H, *J* = 8.2 Hz, H-3', H-5'); 7.93 (d, 2H, *J* = 8.2 Hz, H-2', H-6'); 8.00 (d, 2H, *J* = 6.3 Hz, H-3, H-5); 8.67 (d, 2H, *J* = 6.3 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 22.1 (4'-Me); 30.1 (3C, C**Me**$_3$); 37.2 (**C**Me$_3$); 66.2 (CH_2); 125.4 (C-3, C-5); 129.1, 130.3 (C-2', C-3', C-5', C-6'); 130.6 (C-1'); 145.6 (C-2, C-6); 147.6 (C-4'); 173.2 (C-4); 189.8 (COAr).

1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-tert-butyl-pyridinium bromide (3c).

The product was recrystallized from methanol/diethylether and colorless crystals with mp 154-6°C were obtained; Yield 94 %. Anal. Calcd. $C_{17}H_{19}BrFNO$: N 3.98. Found N 4.23. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 1.43 (s, 9H, *t*-Bu); 6.46 (s, 2H, CH_2); 7.17(t, 2H, *J* = 8.6 Hz, H-3', H-5'); 8.00 (d, 2H, *J* = 6.4 Hz, H-3, H-5); 8.11 (dd, 2H, *J* = 8.6, 5.2 Hz, H-2', H-6'); 8.73 (d, 2H, *J* = 6.3 Hz, H-2, H-6). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 30.1 (3C, C**Me**$_3$); 37.2 (**C**Me$_3$); 66.1 (CH_2); 116.8 (d, *J* = 22.2 Hz, C-3', C-5'); 125.4 (C-3, C-5); 129.7 (d, *J* = 3.1 Hz, C-1'); 132.0 (d, *J* = 10.0 Hz, C-2', C-6'); 145.7 (C-2, C-6); 167.3 (d, *J* = 258.7 Hz, C-4'); 173.1 (C-4); 188.6 (COAr).

1-[2-(4-Chlorophenyl)-2-oxoethyl]-4-tert-butyl-pyridinium bromide (3d). The product was recrystallized from methanol and colorless crystals with mp 157-9°C were obtained; Yield 96 %. Anal. Calcd. $C_{17}H_{19}BrClNO$: N 3.80. Found N 4.03. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 1.43 (s, 9H, *t*-Bu); 6.47 (s, 2H, CH_2); 7.47 (d, 2H, *J* = 8.6 Hz, H-3', H-5'); 7.99 (d, 2H, *J* = 6.3 Hz, H-3, H-5); 8.01 (d, 2H, *J* = 8.6 Hz,

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H-2', H-6'); 8.67 (d, 2H, *J* = 6.3 Hz, H-2, H-6). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 30.1 (3C, C**Me**$_3$); 37.2 (**C**Me$_3$); 66.2 (CH_2); 125.4 (C-3, C-5); 129.9, 130.4 (C-2', C-3', C-5', C-6'); 131.6 (C-1'); 142.3 (C-4'); 145.7 (C-2, C-6); 173.1 (C-4); 189.1 (COAr).

1-[2-(4-Bromophenyl)-2-oxoethyl]-4-tert-butyl-pyridinium bromide (3e). The product was recrystallized from methanol and colorless crystals with mp 263-6°C were obtained; Yield 94 %. Anal. Calcd. $C_{17}H_{19}Br_2NO$: N 3.39. Found N 3.57. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 1.45 (s, 9H, *t*-Bu); 6.37 (s, 2H, CH_2); 7.68, 7.92 (2d, 4H, *J* = 8.5 Hz, H-2', H-3', H-5', H-6'); 8.02 (d, 2H, *J* = 6.3 Hz, H-3, H-5); 8.66 (d, 2H, *J* = 6.3 Hz, H-2, H-6). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 30.0 (3C, C**Me**$_3$); 37.2 (**C**Me$_3$); 66.1 (CH_2); 125.5 (C-3, C-5); 130.3, 133.0 (C-2', C-3', C-5', C-6'); 131.6, 131.8 (C-1', C-4'); 145.6 (C-2, C-6); 173.6 (C-4); 189.4 (COAr).

1-[2-(3-Nitrophenyl)-2-oxoethyl]-4-tert-butyl-pyridinium bromide (3f). The product was recrystallized from methanol and colorless crystals with mp 212-3°C were obtained; Yield 99 %. Anal. Calcd. $C_{17}H_{19}BrN_2O_3$: N 7.39. Found N 7.58. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 1.45 (s, 9H, *t*-Bu); 6.58 (s, 2H, CH_2); 7.75 (t, 1H, *J* = 8.0 Hz, H-5'); 8.05 (d, 2H, *J* = 6.3 Hz, H-3, H-5); 8.41-8.48 (m, 2H, H-4', H-6'); 8.75 (d, 2H, *J* = 6.3 Hz, H-2, H-6); 8.86 (bs, 1H, H-2'). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 30.1 (3C, C**Me**$_3$); 37.3 (**C**Me$_3$); 66.4 (CH_2); 123.9 (C-2'); 125.6 (C-3, C-5); 129.4, 134.7 (C-4', C-6'); 131.0 (C-5'); 134.6 (C-1'); 145.6 (C-2, C-6); 148.7 C-3'); 173.6 (C-4); 188.6 (COAr).

1-[2-(4-Nitrophenyl)-2-oxoethyl]-4-tert-butyl-pyridinium bromide (3g). The product was recrystallized from methanol and colorless crystals with mp 231-4°C were obtained; Yield 98 %. Anal. Calcd. $C_{17}H_{19}BrN_2O_3$: N 7.39. Found N 7.61. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 1.45 (s, 9H, *t*-Bu); 6.51 (s, 2H, CH_2); 8.02 (d, 2H, *J* = 6.3 Hz, H-3, H-5); 8.26, 8.32 (2d, 4H, *J* = 8.8 Hz, H-2', H-3', H-5', H-6'); 8.71 (d, 2H, *J* = 6.3 Hz, H-2, H-6). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 30.0 (3C, C**Me**$_3$); 37.3 (**C**Me$_3$); 66.5 (CH_2); 124.6 (C-3', C-5'); 125.6 (C-3, C-5); 130.3 (C-2', C-6'); 137.7(C-1'); 145.6 (C-2, C-6); 151.6 C-4'); 173.6 (C-4); 189.0 (COAr).

1-[2-(4-Methoxyphenyl)-2-oxoethyl]-4-tert-butyl-pyridinium bromide (3h). The product was recrystallized from methanol/diethylether and colorless crystals with mp 223-6°C were obtained; Yield 86%. Anal. Calcd. $C_{18}H_{22}BrNO_2$: N 3.84. Found N 4.09. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 1.44 (s, 9H, *t*-Bu); 3.90 (s, 3H, MeO); 6.31 (s, 2H, CH_2); 7.01 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 8.02-8.05 (m, 4H, H-3, H-5, H-2', H-6'); 8.61 (d, 2H, *J* = 6.3 Hz, H-2, H-6). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 30.0 (3C, C**Me**$_3$); 37.2 (**C**Me$_3$); 56.0 (OMe); 66.0 (CH_2); 115.1 (C-3', C-5'); 125.4 (C-3, C-5); 125.7 (C-1'); 131.7 (C-2', C-6'); 145.5 (C-2, C-6); 166.1 C-4'); 173.5 (C-4); 189.0 (COAr).

General procedure for synthesis of 7-tert-butyl-indolizines 6

5 Mmol of 4-*tert*butyl-pyridinium bromide **1** were suspended in 50 mL 1,2-epoxybutane, 7 mmol of ethyl propiolate were added and the mixture was heated at reflux temperature for 30 h (with protection against moisture). The solvent was partly removed under reduced pressure then 5-10 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 (2:1) and recrystallized from chloroform/diethyl ether.

7-tert-Butyl-1-carbethoxy-3-benzoyl-indolizine (6a). Yellow crystals with mp 121-3°C were obtained; Yield 48 %. Anal. Calcd. $C_{22}H_{23}NO_3$: C 75.62; H 6.63; N 4.01. Found C 75.90; H 6.91; N 4.27. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, 3H, *J* = 7.1 Hz, Me); 1.33 (s, 9H, *t*-Bu); 4.28 (q, 2H, *J* = 7.1 Hz, CH_2); 7.08 (dd, 1H, *J* = 7.4, 2.1 Hz, H-6); 7.38-7.48 (m, 3H, H-3', H-4', H-5'); 7.70 (s, 1H, H-2); 7.72-7.73 (m, 2H, H-2', H-6'); 8.28 (dd, 1H, *J* = 2.1, 1.0, Hz, H-8); 9.79 (dd, *J* = 7.4, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 30.4 (3C, 3Me, *t*-Bu); 35.2 (**C**Me$_3$); 59.9 (CH_2); 105.6 (C-1); 114.3 (C-8); 114.4 (C-6); 122.0 (C-3); 128.3 (C-3', C-5'); 128.7 (C-5); 129.0 (C-2', C-6'); 129.2 (C-2); 131.3 (C-4'); 139.9 (C-1'); 140.4 (C-8a); 152.3 (C-7); 164.4 (COO); 185.2 (COAr).

7-tert-Butyl-1-carbethoxy-3-(4-methylbenzoyl)-indolizine (6b). Yellow crystals with mp 145-7°C were obtained; Yield 49 %. Anal. Calcd. $C_{23}H_{25}NO_3$: C 76.01; H 6.93; N 3.85. Found C 76.90; H 7.18; N 4.11. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.40 (t, 3H, *J* = 7.1 Hz, Me); 1.41 (s, 9H, *t*-Bu); 2.45 (s, 3H, 4'-Me); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 7.14 (dd, 1H, *J* = 7.4, 2.1 Hz, H-6); 7.31 (d, 1H, *J* = 8.1 Hz, H-3', H-5'); 7.73 (d, 1H, *J* = 8.1 Hz, H-2', H-6'); 7.78 (s, 1H, H-2); 8.35 (dd, 2H, *J* = 2.1, 1.0, Hz, H-8); 9.85 (dd, 1H, *J* = 7.4, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 21.5 (4'Me); 30.4 (3C, 3Me, *t*-Bu); 35.2 (**C**Me$_3$); 59.9 (CH_2); 105.5 (C-1); 114.3 (2C, C-8, C-6); 122.0 (C-3); 128.7 (C-5); 129.0, 129.1 (C-2', C-3', C-5', C-6'); 129.3 (C-2); 137.3 (C-1'); 140.4 (C-8a); 141.9 (C-4'); 152.1 (C-7); 164.2 (COO); 185.1 (COAr).

*7-tert-Butyl-1-carbethoxy-3-(4-fluorobenzoyl)-indolizine (6c).*Yellow crystals with mp 138-141°C were obtained; Yield 51 %. Anal. Calcd. $C_{22}H_{22}FNO_3$: N 3.81. Found N 4.04. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.40 (s, 9H, *t*-Bu); 1.41(t, 3H, *J* = 7.1 Hz, Me); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 7.16 (dd, *J* = 7.4, 2.1 Hz, H-6); 7.18 (t, *J* = 8.8 Hz, H-3', H-5'); 7.74 (s, 1H, H-2); 7.83 (dd, *J* = 8.8; 5.4 Hz, H-2', H-6'); 8.35 (dd, *J* = 2.1, 1.0, Hz, H-8); 9.82 (dd, *J* = 7.4, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 30.4 (3C, 3Me, *t*-Bu); 35.2 (**C**Me$_3$); 60.0 (CH_2); 105.7 (C-1); 114.3 (C-8); 114.5 (C-6); 115.3 (d, *J* = 21.9 Hz, C-3', C-5'); 121.8 (C-3); 128.7 (C-5); 129.0 (C-2); 131.2 (d, *J* = 9.0 Hz, C-2', C-6'); 136.1 (d, *J* = 3.0 Hz, C-1'); 140.4 (C-8a); 152.4 (C-7); 164.2 (COO); 163.6 (d, *J* = 253.5 Hz, C-4'); 183.7 (COAr).

7-tert-Butyl-1-carbethoxy-3-(4-chlorobenzoyl)-indolizine (6d). Yellow crystals with mp 151-3°C were obtained; Yield 53 %. Anal. Calcd. $C_{22}H_{22}ClNO_3$: C 68.84; H 5.78; Cl 9.24; N 3.65. Found C 69.10; H 5.93; Cl 9.61; N 3.80. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (s, 9H, *t*-Bu); 1.33 (t, 3H, *J* = 7.1 Hz, Me); 4.29 (q, 2H, *J* = 7.1 Hz, CH_2); 7.09 (dd, 1H, *J* = 7.4, 2.1 Hz, H-6); 7.40 (d, 2H, *J* = 8.5 Hz, H-3', H-5'); 7.66 (s, 1H, H-2); 7.68 (d, 2H, *J* = 8.5 Hz, H-2', H-6'); 8.28 (dd, 1H, *J* = 2.1, 1.0, Hz, H-8); 9.76 (dd, 1H, *J* = 7.4, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 30.4 (3C, 3Me, *t*-Bu); 35.2 (**C**Me$_3$); 60.0 (CH_2); 105.9 (C-1); 114.4 (C-8); 114.6 (C-6); 121.3 (C-3); 128.5 (C-5); 128.6; 130.3 (C-2', C-3', C-5', C-6'); 129.0 (C-2); 137.6 (C-1'); 138.3 C-4'); 140.5 (C-8a); 152.6 (C-7); 164.2 (COO); 183.7 (COAr).

7-tert-Butyl-1-carbethoxy-(4-bromobenzoyl)-indolizine (6e). Orange crystals with mp 146-8°C were obtained; Yield 52 %. Anal. Calcd. $C_{22}H_{22}BrNO_3$: C 61.69; H 5.18; Br 18.65; N 3.27. Found C 61.87; H 5.44; Br 19.02; N 3.51. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.39 (t, 3H, *J* = 7.1 Hz, Me); 1.40 (s, 9H, *t*-Bu); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 7.17 (dd, 1H, *J* = 7.4, 2.1 Hz, H-6); 7.64, 7.66 (2d, 4H, *J* = 8.5 Hz, H-2', H-3', H-5', H-6'); 7.73 (s, 1H, H-2); 8.35 (dd, 1H, *J* = 2.1, 1.0, Hz, H-8); 9.84 (dd, 1H, *J* = 7.4, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.6 (Me); 30.5 (3C, 3Me, *t*-Bu); 35.3 (**C**Me$_3$); 60.1 (CH_2); 106.0 (C-1); 114.4 (C-8); 114.7 (C-6); 121.7 (C-3); 126.1 (C-4'); 128.7 (C-5); 129.1 (C-2); 130.5; 131.6 (C-2', C-3', C-5', C-6'); 138.8 (C-1'); 140.6 (C-8a); 152.6 (C-7); 164.2 (COO); 183.9 (COAr).

7-tert-Butyl-1-carbethoxy-3-(3-nitrobenzoyl)-indolizine (6f). Cream crystals with mp 143-5°C were obtained; Yield 49 %. Anal. Calcd. $C_{22}H_{23}N_2O_5$: C 66.99; H 5.62; N 7.10. Found

C 70.09; H 5.88; N 7.37. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.40 (t, 3H, *J* = 7.1 Hz, Me); 1.41 (s, 9H, *t*-Bu); 4.37 (q, 2H, *J* = 7.1 Hz, CH_2); 7.22 (dd, 1H, *J* = 7.4, 2.1 Hz, H-6); 7.71 (s, 1H, H-2); 7.72 (t, 1H, *J* = 7.8 Hz, H-5'); 8.10-8.14 (m, 1H, H-6'); 8.38-8.44 (m, 2H, H-8, H-4'); 8.63 (t, 1H, *J* = 1.9 Hz, H-2') 9.86 (dd, 1H, *J* = 7.4, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 30.5 (3C, 3Me, *t*-Bu); 35.4 (**C**Me_3); 60.2 (CH_2); 106.7 (C-1); 114.6 (C-8); 115.1 (C-6); 121.3 (C-3); 123.7 (C-2'); 125.7 (C-4'); 128.8 (C-5); 129.3 (C-2); 129.6 (C-5'); 134.4 (C-6'); 140.9 (C-8a); 141.5 (C-1'); 148.3 (C-3'); 153.3 (C-7); 164.0 (COO); 182.0 (COAr).

7-tert-Butyl-1-carbethoxy-(4-nitrobenzoyl)-indolizine (6g). Mustard color crystals with mp 153-5°C were obtained; Yield 54 %. Anal. Calcd. $C_{22}H_{23}N_2O_5$: C 66.99; H 5.62; N 7.10. Found C 70.27; H 5.94; N 7.41. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, 3H, *J* = 7.1 Hz, Me); 1.33 (s, 9H, *t*-Bu); 4.29 (q, 2H, *J* = 7.1 Hz, CH_2); 7.14 (dd, 1H, *J* = 7.4, 2.1 Hz, H-6); 7.61 (s, 1H, H-2); 7.86 (d, 2H, *J* = 8.9 Hz, H-3', H-5'); 8.27 (d, 2H, *J* = 8.9 Hz, H-2', H-6'); 8.32 (dd, 1H, *J* = 2.1, 1.0, Hz, H-8); 9.80 (dd, 1H, *J* = 7.4, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.6 (Me); 30.4 (3C, 3Me, *t*-Bu); 35.3 (**C**Me_3); 60.1 (CH_2); 106.6 (C-1); 114.6 (C-8); 115.0 (C-6); 121.4 (C-3); 123.6 (C-3', C-5'); 128.9 (C-5); 129.4 (C-2); 129.6 (C-2', C-6'); 140.8 (C-8a); 145.5 (C-1'); 149.3 (C-4'); 153.3 (C-7); 163.8 (COO); 182.4 (COAr).

7-tert-Butyl-1-carbethoxy-(4-methoxybenzoyl)-indolizine (6h). Yellow crystals with mp 154-5°C were obtained; Yield 49 %. Anal. Calcd. $C_{23}H_{25}NO_4$: C 72.80; H 6.64; N 3.69. Found $C_{23}H_{25}NO_4$: C 73.12; H 6.93; N 3.91. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, 3H, *J* = 7.1 Hz, Me); 1.33 (s, 9H, *t*-Bu); 3.82 (s, 3H, MeO); 4.30 (q, 2H, *J* = 7.1 Hz, CH_2); 6.97 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 7.05 (dd, 1H, *J* = 7.4, 2.1 Hz, H-6); 7.71 (s, 1H, H-2); 7.76 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.26 (dd, 1H, *J* = 2.1, 1.0, Hz, H-8); 9.73 (dd, 1H, *J* = 7.4, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.6 (Me); 30.5 (3C, 3Me, *t*-Bu); 35.2 (**C**Me_3); 55.5 (OMe); 60.1 (CH_2); 105.4 (C-1); 113.7 (C-8, C-3', C-5'); 114.3 (C-6); 121.4 (C-3); 128.5 (C-5); 128.6 (C-2); 131.2 (C-2', C-6'); 131.5, 132.5 (C-4a, C-1'); 140.3 (C-8a); 152.0 (C-7); 162.5 (COO); 184.4 (COAr).

Results and Discussion

The starting materials, pyridinium bromides **3** were prepared by *N*-alkylation of 4-*tert*-butyl-pyridine **1** with the corresponding 2-bromoacetophenones **2** in chloroform at reflux (scheme 1). 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 acid the signal for the methylenic protons appear in the range δ = 6.31-6.38 ppm as a sharp singlet, as well as the protons of *tert*-butyl group. The protons H-2 and H-6 from the pyridine moiety are strongly deshielded (δ = 8.65-8.75 ppm) in respect with H-3 and H-5 protons from the beta position (δ = 7.99-8.05 ppm), due to the vicinity of the quaternary nitrogen atom.

^{13}C-NMR spectra show all the expected signals. The carbon atoms in the α and γ positions with respect to the nitrogen atoms of the pyridinium ring are strongly deshielded when compared to the carbon atoms in the β positions (δ = 125.4-125.6 ppm). The high chemical shift for C-4 is ca. 173 ppm and is explained by supplementary effect of *tert*-butyl group. The chemical shifts of the carbonyl groups are in the range 188.6-190.3 ppm.

Carbanion monosubstituted pyridinium *N*-ylides are generally unstable compounds, and thus are generated *in situ*. This can be done by treatment of pyridinium salts with a base, such as triethylamine in organic solvents or with an aqueous solution of inorganic base, or by using an epoxide as the reaction medium [24-28]. 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 cycloaddition reaction was performed in 1,2-epoxybutane at reflux for 30 h. The reaction mixture was concentrated by vacuum distillation and then 5-10 mL methanol were added and it was left over night.

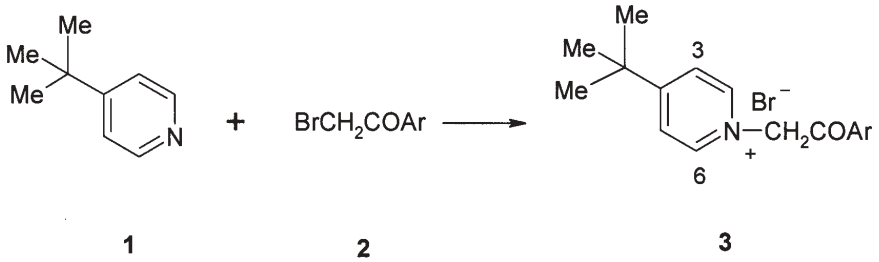
As resulted from NMR data, the cycloaddition between *N*-ylides **4a-h** and non-symmetrical alkyne, ethyl propiolate, is completely regioselective, as only the formation of the regioisomer with the ester grafted in the 1 position of the pyrrolopyridine moiety was observed.

The formation of compounds **6** implies in the first step the generation of *N*-ylides **4** from bromides **3** by action 1,2-epoxybutane. Subsequently, the 1,3-dipolar cycloaddition between *N*-ylide dipole **4** and acetylenic dipolarophile give the primary cycloadducts **5** which undergo an isomerization reaction followed by dehydrogenation to the aromatic compounds **6**.

The structure of cycloadducts **6** 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.

The appearance of the three protons grafted on the pyridine ring is as doublet of doublets, with the coupling constants of $^3J_{5,6}$ = 7.4 Hz, $^4J_{6,8}$ = 2.1 Hz and $^5J_{5,8}$ = 1.0 Hz. The unusual multiplicity of proton H-8 is cause by a long range coupling with H-5 having the value of 1.0 Hz.

In the ^{1}H-NMR spectra of cycloadducts **6a-h**, the most deshielded proton is H-5 at around 9.80 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

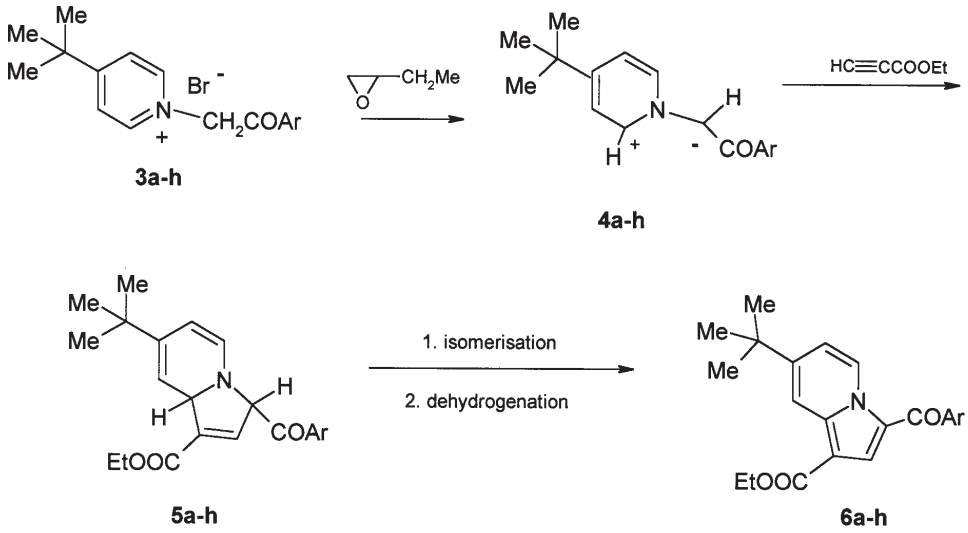


1 **2** **3**

Ar: a = C_6H_5; b = 4-MeC_6H_4; c = 4-FC_6H_4; d = 4-ClC_6H_4; e = 4-BrC_6H_4; f = 3-$O_2NC_6H_4$;

g = 4-$O_2NC_6H_4$; h = 4-$MeOC_6H_4$;

Scheme 1



Scheme 2

Ar: a = C_6H_5; b = 4-MeC_6H_4; c = 4-FC_6H_4; d = 4-ClC_6H_4; e = 4-BrC_6H_4; f = 3-$O_2NC_6H_4$;
g = 4-$O_2NC_6H_4$ h = 4-$MeOC_6H_4$;

due to its proximity to the pyrrole-grafted carboethoxy moiety.

Proton H-2 grafted on the pyrrole ring appears at around 7.70 ppm as a sharp singlet as a result of the combined deshielding effects of the carboethoxy and phenacyl groups.

^{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 **6a-h** were established by HETCOR experiments and by comparison with similar compounds.

The atoms C-5, C-7 and C-8 from the indolizine **6** are highly deshielded in respect with the other atoms from the pyridine system, as they are in α and γ positions with respect to the nitrogen atoms of the pyridine ring. The grafting of a *tert*-butyl group in the 7 position of indolizine moiety has a strong deshielding effect at positions 7 (δ_{C-7} = 152.0-153.7 ppm) by comparison with unsubstituted indolizine. The strong shielding observed for C-5 (δ = 105.6-106.7 ppm) is a consequence of its relative β positions to the pyrrole nitrogen.

Conclusions

Eight new indolizines were synthesized by 1,3-dipolar cycloadditions between pyridinium *N*-ylides and ethyl propyolate as non-symmetrical dipolarophile. The reactions were performed in 1,2-epoxybutane as solvent and bromide scavenger. Structural assignment was provided by NMR spectroscopy and elemental analysis. The regioselectivity of the the cycloaddition was found to be total.

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