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-butyne-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-methyldie, 1,3-dipolar cycloaddition

Substituted Indolizines by 1,3-Dipolar Cycloaddition Reactions

IV. 7-Benzyl-indolizines

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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 cycloextrin moiety, respectively [15, 16].

One of the most versatile synthetic methods for obtaining the indolizine derivatives are 1,3-dipolar cycloadditions between pyridinium N-ylides and activated (electron deficient) alkenes 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 dipolarophiles, ethyl propiolate and butyne-3-one. By introducing the benzyl substituent on the pyridine ring and by varying the 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 cycloextrin moiety, respectively [15, 16].

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 1H and 75 MHz for 13C. Supplementary evidence was obtained by HETCOR and COSY experiments.

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

10 Mmol 4-benzyl-pyridine and 10 mmol phenacyle bromide in 30 mL of methanol were refluxed for 2 h and then were kept at room temperature until the next day.

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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 259-261°C were obtained; Yield 50 %. Anal. Calcld. C 25H20ClNO3: C 71.85; H 4.82; Br 17.60; N 3.31. Found C 71.78; H 4.82; Br 17.60; N 3.31.

4-Benzyl-1-[2-(4-methoxyphenyl)-2-oxoethyl]-pyridinium bromide (3e). The product was recrystallized from methanol and pale yellow crystals with mp 240-2°C were obtained; Yield 37 %. Anal. Calcld. C 25H20FNO3: C 78.26; H 5.61; F 7.39; N 3.39. Found C 78.16; H 5.59; F 7.36; N 3.42.

4-Benzyl-1-[2-(4-nitrophenyl)-2-oxoethyl]-pyridinium bromide (3f). The product was recrystallized from methanol and pale yellow crystals with mp 283-5°C were obtained; Yield 50 %. Anal. Calcld. C 27H20BrNO3: C 78.62; H 5.81; Br 17.28; N 3.03. Found C 78.69; H 5.83; Br 17.28; N 3.03.

4-Benzyl-1-[2-(4-acetoxyphenyl)-2-oxoethyl]-pyridinium bromide (3g). The product was recrystallized from methanol and colorless crystals with mp 180-1°C were obtained; Yield 36 %. Anal. Calcld. C 25H20ClNO3: C 71.85; H 4.82; Cl 17.60; N 3.31. Found C 71.84; H 4.81; Cl 17.60; N 3.30.
Yellow crystals with mp 177-9 oC were obtained; Yield 46 %. Anal. Calcld. 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. 1H-NMR (300 MHz, CDCl_3) δ: 2.50 (s, 3H, MeCO); 3.91 (MeO); 4.11 (s, 2H, CH-PH); 6.93 (dd, 1H, J = 7.2, 1.9 Hz, H-6); 7.03 (dd, 2H, J = 8.8, H-3', H-5'); 7.23-7.29 (m, 3H, H-2', H-2'', H-6''); 7.31-7.36 (m, 2H, H-3', H-5'''); 7.67 (s, 1H, H-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). 13C-NMR (75 MHz, CDCl_3) δ: 27.7 (MeCO); 41.7 (CH-PH); 114.1 (C-1); 117.5 (C-5); 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'); 130.1 (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'); COMe). 13C-NMR spectra show all the expected signals. The carbon atoms in the 2-substituted group appear in the range δ ~ 128 ppm. Carbon C-4 owes its high chemical shift (δ ~ 163 ppm) to its in proximity with the quaternary nitrogen atom.

**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) alkenes. 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 1H-NMR, recorded in mixture of CDCl_3 with trifluoroacetic, the signal for the methylenic protons appear in the range δ = 6.35-6.43 ppm as a sharp singlet. The methylene 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.

The carbon atoms in the α 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 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 alkenes 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.
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 salt by the base.

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.
The appearance of the three protons grafted on the pyridine ring is as doublet of doublets, with the coupling constants of $J_5^6 = 7.2$ Hz, $J_6^7 = 1.9$ Hz and $J_7^8 = 1.0$ Hz. The multiplicity of 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 ($\delta = 9.78-9.86$ ppm). This is due to its vicinity to the nitrogen atom and also due to its spatial proximity to the carboxylic moiety from the phenacyl group. H-8 is also significantly deshielded 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, respectively.

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 to the other atoms from the pyridine system, as they are in $\alpha$ and $\gamma$ 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 ($\delta_C = 142.2-144.7$ 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 $\delta_C = 105.7-106.7$ ppm in the case of carboethoxy substituted derivatives 6 to $\delta_C = 114.1-115.1$ 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.

References


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