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NEW SUBSTITUTED INDOLIZINES BY 1,3-DIPOLAR CYCLOADDITION REACTIONS. Part 2. 7-CYANOINDOLIZINES

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

INTRODUCTION

The field of synthesis of pyrroloazines, although a relativly old one, has also proven to be one of the most versatile and lucrative. This is due to the increasing interest for novel fluorophores in the past decades for 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. Some of the most versatile scaffolds are indolizine[1-8] and azaindolizine[3, 9-12] derivatives. By attaching 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 obtaining indolizines substituted at the 7 position, novel uses may arrise, such and highly selective chemosensors by attaching them to a cyclodextrin moiety, respectively.[13, 14]

One of the most versatile synthetic methods for obtaining the indolizine scaffold are 1,3-dipolar cycloadditions between pyridinium *N*-ylides and activated (electron deficient) alkynes or alkene in the presence of an oxidant reagent, offering both high yields and regioselectivity.[15-23]

Herein we present the synthesis of new indolizines, containing a cyano 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 cyano 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.

RESULTS AND DISCUSSION

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

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 or in DMSO-d_6 for compound **3b**, the signal for the methylenic protons appears in the range δ = 6.56-6.76 ppm as a sharp singlet. The protons H-2 and H-6 from the pyridine moiety are strongly deshielded (δ = 9.06-

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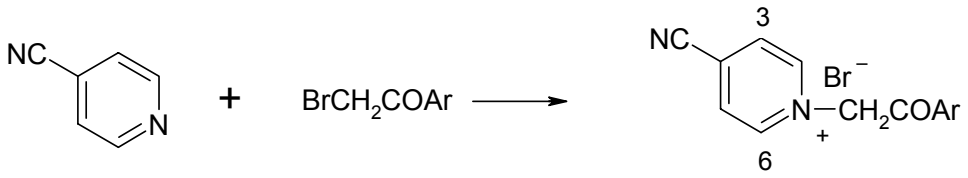
9.43 ppm) in respect with H-3 and H-5 protons from the beta position (δ = 8.35-8.83 ppm), due to the vicinity of the quaternary nitrogen atom.

^{13}C-NMR spectra show all the expected signals. The carbon atoms in the α position (δ = 147.8-148.0 ppm) in respect to the quaternary nitrogen atom of the pyridinium ring are strongly deshielded when compared to the carbon atoms in the β positions (δ = 130.5-130.8 ppm). Even though C-4 (δ = 127.9-129.4 ppm) is in γ position in respect to the nitrogen atom, its low chemical shift can be explained by strong shielding effect of cyano group. The chemical shifts of the carbonyl groups are in the range 187.4-188.8 ppm.

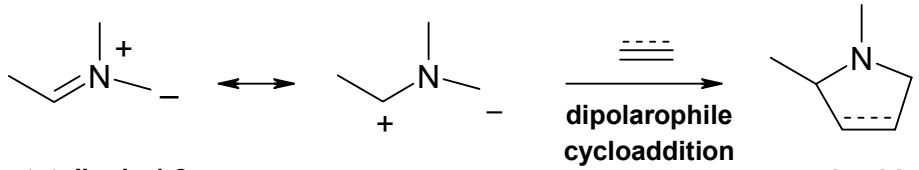


1 **2a-e** **3a-e**

Ar: a = C_6H_5; b = 4-FC_6H_4; c = 4-ClC_6H_4; d = 4-BrC_6H_4; e = 4-$MeOC_6H_4$

Scheme 1

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 five-membered ring which are difficult or impossible to be obtained by other methods, making them very useful synthetic tools.



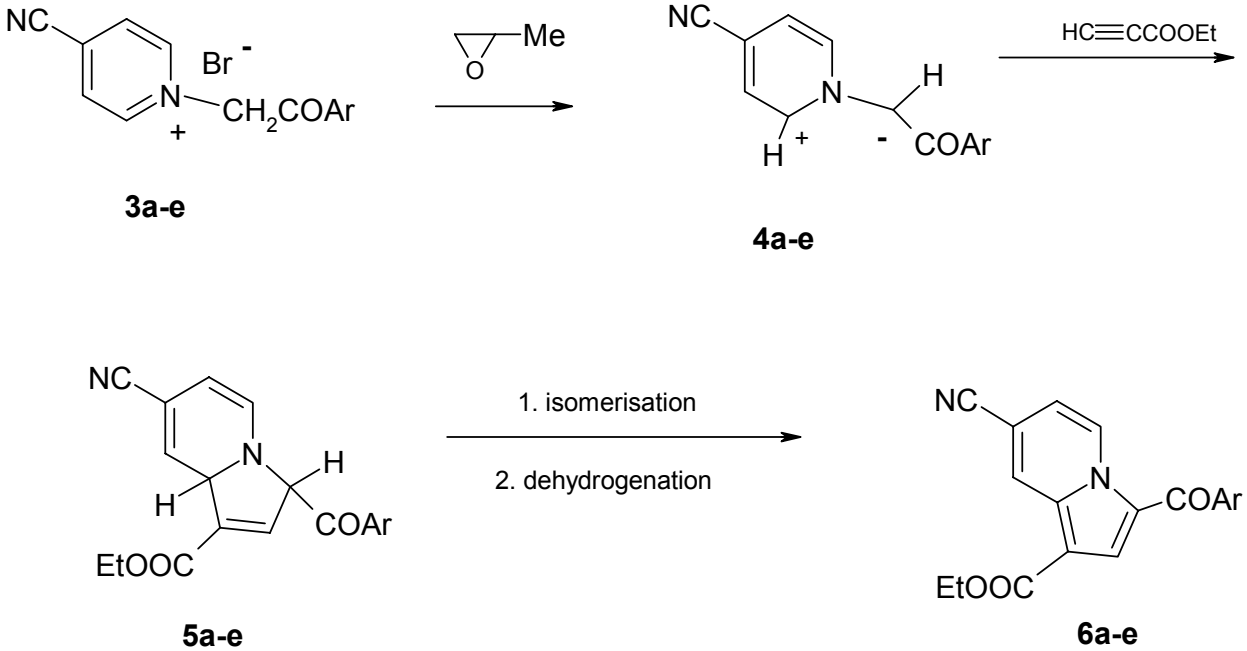
octet dipole 1,2 **sextet dipole 1,3** **cycloadduct**

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 with an aqueous solution of inorganic base, or by using epoxides 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 indirect epoxide method has the advange of using it as an one-pot, multi-step sequences of reactions, with the salt formation occuring 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 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-e** 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.

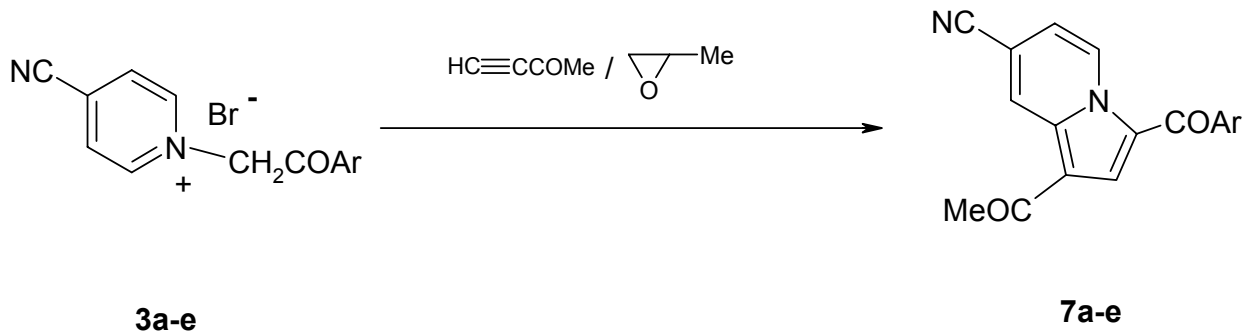
The formation of compounds **6** and **7** implies in the first step the generation of *N*-ylides **4** from bromides **3** by action 1,2-epoxypropane. Subsequently, the 1,3-dipolar cycloaddition between *N*-ylide dipole **4** and ethyl propiolate gave the primary cycloadducts **5a-e** and the corresponding 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).



3a-e **4a-e** **5a-e** **6a-e**

Ar: a = C_6H_5; b = 4-FC_6H_4; c = 4-ClC_6H_4; d = 4-BrC_6H_4; e = 4-$MeOC_6H_4$

Scheme 2



3a-e **7a-e**

Ar: a = C_6H_5; b = 4-FC_6H_4; c = 4-ClC_6H_4; d = 4-BrC_6H_4; e = 4-$MeOC_6H_4$

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 values 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 $^3J_{5,6}$ = 7.3 Hz, $^4J_{6,8}$ = 1.9 Hz and $^5J_{5,8}$ = 1.0 Hz. The unusual multiplicity of proton H-8 is caused by a long range coupling with H-5 having the value of 1.0 Hz. By replacing of carboethoxy group (indolizines **6**) with acetyl (indolizines **7**), the magnitude of the long range coupling constant between H-5 and H-8 was decreased to 0.8 Hz, as observed in dilute solution.

In the ^{1}H-NMR spectra of cycloadducts **6** and **7** the most deshielded proton is H-5. 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 8.80 ppm due to its proximity to the pyrrole-grafted carboethoxy or acetyl groups. Also, it was observed that the chemical shifts for H-8 in the series **7** (acetyl) are higher by about 0.2 ppm in regard with those observed in series **6** (carboethoxy).

Proton H-2 grafted on the pyrrole ring appears at around 7.80 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 and 1-acetyl moieties, respectively.

^{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 indolizine **6** 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 cyano group in the 7 position of indolizine moiety has a strong shielding effect at position 7 (δ_{C-7} = 117.0-117.3 ppm). Also, the presence of the cyano moiety changes the overall conjugation of the indolizine scaffold, in comparison with other 7-substituted indolizines. This effect can be observed in the chemical shifts of C-1 and C-8, which are deshielded in respect to those from other indolizines with 4 ppm and a significant 11 ppm, respectivly.[19,20]

The chemical shift of C-1 is increases from 110 ppm in the case of carboethoxy substituted derivatives **6** to 117 ppm in the case of the acetyl substituted indolizines **7**. The shielding observed for C-5 is a consequence of its relative β positions to the pyrrole nitrogen.

EXPERIMENTAL

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-cyano-pyridinium bromides 3

10 Mmol 4-cyano-pyridine and 10 mmol phenacyl bromide in 50 mL of methanol were 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-cyano-pyridinium bromide (**3a**). The product was recrystallized from methanol/diethyl ether and pale yellow crystals with mp 233-5 ºC were obtained; Yield 90 %. Anal. Calcd. $C_{14}H_{11}BrN_2O$: N 9.24. Found N 9.41. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 6.57 (s, 2H, CH_2); 7.58-7.61 (m, 2H, H-3', H-5'); 7.74-7.80 (m, 1H, H-4'); 8.02-8.04 (m, 2H, H-2', H-6'); 8.39 (d, *J* = 6.7 Hz, H-3, H-5) 9.07 (d, 2H, *J* = 6.7 Hz, H-2, H-6). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 67.9 (CH_2); 112.8 (CN); 128.8 (C-4); 128.6, 129.4 (C-2', C-3', C-5', C-6'); 130.5 (C-3, C-5); 132.0 (C-1'); 136.4 (C-4'); 147.8 (C-2, C-6); 188.8 (COAr).

1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-cyano-pyridinium bromide (**3b**). The product was recrystallized from methanol/diethylether and beige crystals with mp 212-5 ºC were obtained; Yield 98 %. Anal. Calcd. $C_{14}H_{10}BrFN_2O$: N 8.72. Found N 8.91. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.76 (s, 2H, CH_2); 7.44 (t, 2H, *J* = 8.7 Hz, H-3', H-5'); 8.15 (dd, 2H, *J* = 8.7, 5.4 Hz, H-2', H-6'); 8.83 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 9.43 (d, 2H, *J* = 6.7 Hz, H-2, H-6). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 67.1 (CH_2); 114.8 (CN); 116.4 (d, *J* = 22.2 Hz, C-3', C-5'); 127.9 (C-4); 130.8 (C-3, C-5); 130.3 (d, *J* = 3.1 Hz, C-1'); 131.6 (d, *J* = 10.0 Hz, C-2', C-6'); 147.8 (C-2, C-6); 166.0 (d, *J* = 258.7 Hz, C-4'); 188.7 (COAr).

1-[2-(4-Chlorophenyl)-2-oxoethyl]-4-cyano-pyridinium bromide (**3c**). The product was recrystallized from methanol/diethylether and beige crystals with mp 259-262 ºC were obtained; Yield 78 %. Anal. Calcd. $C_{14}H_{10}BrClN_2O$: N 8.30. Found N 8.56. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 6.60 (s, 2H, CH_2); 7.55 (d, 2H, *J* = 8.6 Hz, H-3', H-5'); 8.01 (d, 2H, *J* = 8.6 Hz, H-2', H-6'); 8.37 (d, 2H, *J* = 6.7 Hz, H-3, H-5); 9.07 (d, 2H, *J* = 6.7 Hz, H-2, H-6). ^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 67.8 (CH_2); 113.2 (CN); 129.8, 130.0 (C-2', C-3', C-5', C-6'); 130.7 (C-3, C-5); 130.1, 142.3 (C-1', C-4'); 130.8 (C-4); 148.0 (C-2, C-6); 187.4 (COAr).

1-[2-(4-Bromophenyl)-2-oxoethyl]-4-cyano-pyridinium bromide (**3d**). The product was recrystallized from methanol/diethylether and colorless crystals with mp 275-8 ºC were obtained; Yield 85 %. Anal. Calcd. $C_{14}H_{10}Br_2N_2O$: N 7.33. Found N 7.54. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 6.59 (s, 2H, CH_2); 7.74, 7.92 (2d, 4H, *J* = 8.5 Hz, H-2', H-3', H-5', H-6'); 8.38 (d, *J* = 6.8 Hz, H-3, H-5); 9.06 (d, 2H, *J* = 6.8 Hz, H-2, H-6).

1-[2-(4-Methoxyphenyl)-2-oxoethyl]-4-cyano-pyridinium bromide (**3e**). The product was recrystallized from methanol/diethylether and colorless crystals with mp 242-4 ºC were obtained; Yield 84 %. Anal. Calcd. $C_{15}H_{13}BrN_2O_2$: N 8.41. Found N 8.70. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA) δ: 3.90 (s, 3H, MeO); 6.56 (s, 2H, CH_2); 7.00 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 8.00 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 8.35 (d, *J* = 6.7 Hz, H-3, H-5); 9.12 (d, 2H, *J* = 6.7 Hz, H-2, H-6).

^{13}C-NMR (75 MHz, $CDCl_3$+TFA) δ: 55.7 (OMe); 67.5 (CH_2); 114.8 (C-3', C-5'); 113.8 (CN); 125.1 (C-1'); 129.1 (C-4); 130.3 (C-3, C-5); 131.4 (C-2', C-6'); 147.9 (C-2, C-6); 165.8 (C-4'); 186.6 (COAr).

General procedure for synthesis of 7-cyano-indolizines 6 and 7

5 Mmol of 4-cyano-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 temperature for 20 days (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.

3-Benzoyl-1-carboethoxy-7-cyano-indolizine (**6a**). Pale yellow crystals with mp 140-2 ºC were obtained; Yield 52 %. Anal. Calcd. $C_{19}H_{14}N_2O_3$: C 71.69; H 4.43; N 8.80. Found C 71.98; H 4.81; N 9.02. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.42 (t, 3H, *J* = 7.1 Hz, Me); 4.42 (q, 2H, *J* = 7.1 Hz, CH_2); 7.17 (dd, 1H, *J* = 7.3, 1.9 Hz, H-6); 7.52-7.58 (m, 2H, H-3', H-5'); 7.63-7.67 (m, 1H, H-4'); 7.82-7.85 (m, 2H, H-2', H-6'); 7.91 (s, 1H, H-2); 8.78 (dd, 1H, *J* = 1.9, 1.0, Hz, H-8); 9.97 (dd, *J* = 7.3, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 60.9 (CH_2); 109.4, 109.7 (C-1, CN); 114.8 (C-6); 117.3 (C-7); 124.2 (C-3); 125.7 (C-8); 128.6, 129.0 (C-2', C-3', C-5', (C-6'); 128.7 (C-2); 129.3 (C-5); 132.3 (C-4'); 136.9 (C-8a); 138.9 (C-1'); 163.2 (COO); 186.1 (COAr).

1-Carboethoxy-7-cyano-3-(4-fluorobenzoyl)-indolizine (**6b**). Pale yellow crystals with mp 143-5 ºC were obtained; Yield 49 %. Anal. Calcd. $C_{19}H_{13}FN_2O_3$: N 8.33. Found N 8.59. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.43 (t, 3H, *J* = 7.1 Hz, Me); 4.43 (q, 2H, *J* = 7.1 Hz, CH_2); 7.17 (dd, 1H, *J* = 7.3, 1.9 Hz, H-6); 7.24 (t, 2H, *J* = 8.8 Hz, H-3', H-5'); 7.87 (s, 1H, H-2); 7.88 (dd, 2H, *J* = 8.8; 5.4 Hz, H-2', H-6'); 8.79 (dd, 1H, *J* = 1.9, 1.0, Hz, H-8); 9.92 (dd, 1H, *J* = 7.3, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 60.9 (CH_2); 109.5, 109.8 (C-1, CN); 114.9 (C-6); 115.9 (d, *J* = 21.9 Hz, C-3', C-5'); 117.3 (C-7); 123.9 (C-3); 125.7 (C-8); 128.7 (C-2); 129.3 (C-5); 131.6 (d, *J* = 9.0 Hz, C-2', C-6'); 135.1 (d, *J* = 3.0 Hz, C-1'); 136.9 (C-8a); 163.1 (COO); 165.0 (d, *J* = 253.5 Hz, C-4'); 184.5 (COAr).

1-Carboethoxy-3-(4-chlorobenzoyl)-7-cyano-indolizine (**6c**). Pale yellow crystals with mp 150-2 ºC were obtained; Yield 60 %. Anal. Calcd. $C_{19}H_{13}ClN_2O_3$: C 64.69; H 3.71; Cl 10.05; N 7.94. Found C 65.01; H 3.98; Cl 10.39; N 8.22. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.43 (t, 3H, *J* = 7.1 Hz, Me); 4.43 (q, 2H, *J* = 7.1 Hz, CH_2); 7.17 (dd, 1H, *J* = 7.3, 1.9 Hz, H-6); 7.53 (d, 2H, *J* = 8.5 Hz, H-3', H-5'); 7.90 (s, 1H, H-2); 7.88 (d, 2H, *J* = 8.5 Hz, H-2', H-6'); 8.79 (dd, 1H, *J* = 1.9, 1.0, Hz, H-8); 9.93 (dd, 1H, *J* = 7.3, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 60.09 (CH_2); 109.6, 110.0 (C-1, CN); 114.9 (C-6); 115.0 (C-6); 117.2 (C-7); 123.6 (C-3); 125.7 (C-8); 128.7 (C-2); 129.0; 130.5 (C-2', C-3', C-5', C-6'); 129.3 (C-5); 137.0 (C-8a); 137.2, 138.8 (C-1', C-4'); 163.1 (COO); 184.7 (COAr).

3-(4-Bromobenzoyl)-1-carboethoxy-7-cyano-indolizine (**6d**). Pale yellow crystals with mp 174-6 ºC were obtained; Yield 54 %. Anal. Calcd. $C_{19}H_{13}BrN_2O_3$: C 57.45; H 3.30; Br 20.12; N 7.05. Found C 57.76; H 3.55; Br 20.51; N 7.28. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.43 (t, 3H, *J* = 7.1 Hz, Me); 4.42 (q, 2H, *J* = 7.1 Hz, CH_2); 7.17 (dd, 1H, *J* = 7.3, 1.9 Hz, H-6); 7.70 (s, 4H, H-2', H-3', H-5', H-6'); 7.87 (s, 1H, H-2); 8.79 (dd, 1H, *J* = 1.9, 1.0, Hz, H-8); 9.93 (dd, 1H, *J* = 7.3, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.5 (Me); 60.9 (CH_2); 109.6, 110.0 (C-1, CN); 114.9 (C-8); 115.0 (C-6); 117.2 (C-7); 123.7 (C-3); 125.7 (C-8); 128.8 (C-2) 129.3 (C-5); 127.3 (C-4'); 130.6; 132.0 (C-2', C-3', C-5', C-6'); 137.1 (C-8a); 137.6 (C-1'); 163.1 (COO); 184.8 (COAr).

1-Carboethoxy-7-cyano-3-(4-methoxybenzoyl)-indolizine (**6e**). Pale yellow crystals with mp 157-9 ºC were obtained; Yield 47 %. Anal. Calcd. $C_{20}H_{16}N_2O_4$: C 68.96; H 4.63; N 8.04. Found 69.26; H 4.91; N 8.29. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.43 (t, 3H, *J* = 7.1 Hz, Me); 3.92 (s, 3H, MeO); 4.42 (q, 2H, *J* = 7.1 Hz, CH_2); 7.04 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 7.17 (dd, 1H, *J* = 7.3, 1.9 Hz, H-6); 7.86 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 7.90 (s, 1H, H-2); 8.74 (dd, 1H, *J* = 1.0, 1.0, Hz, H-8); 9.92 (dd, 1H, *J* = 7.3, 1.0 Hz, H-5).

1-Acetyl-3-Benzoyl-7-cyano-indolizine (**7a**). Pale yellow crystals with mp 188-190 ºC were obtained; Yield 41 %. Anal. Calcd. $C_{18}H_{12}N_2O_2$: C 74.99; H 4.20; N 9.72. Found C 75.31; H 4.49; N 9.95. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.57 (s, 3H, Me);); 7.22 (dd, 1H, *J* = 7.3, 1.9 Hz, H-6); 7.55-7.60 (m, 2H, H-3', H-5'); 7.64-7.67 (m, 1H, H-4'); 7.79 (s, 1H, H-2); 7.83-7.86 (m, 2H, H-2', H-6'); 9.03 (dd, 1H, *J* = 1.9, 0.8, Hz, H-8); 9.97 (dd, *J* = 7.3, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 28.0 (Me); 110.8 (CN); 115.7 (C-6); 116.8, 117.0 (C-1, C-7); 123.5 (C-3); 126.3 (C-8); 128.2 (C-2); 128.7, 128.9 (C-2', C-3', C-5', (C-6'); 129.0 (C-5); 132.3 (C-4'); 136.5 (C-8a);138.8 (C-1'); 185.9 (COAr); 193.0 (CO).

1-Acetyl-7-cyano-3-(4-fluorobenzoyl)-indolizine (**7b**). Pale yellow crystals with mp 210-2 ºC were obtained; Yield 40 %. Anal. Calcd. $C_{18}H_{11}FN_2O_2$: N 9.15. Found N 9.39. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.58 (s, 3H, Me); 7.21 (m, 3H, H-6, H-3', H-5'); 7.79 (s, 1H, H-2); 7.89 (dd, 2H, *J* = 8.8; 5.4 Hz, H-2', H-6'); 9.03 (dd, 1H, *J* = 1.8, 0.8, Hz, H-8); 9.92 (dd, 1H, *J* = 7.3, 0.8 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 28.0 (Me); 110.9 (CN); 115.7 (d, *J* = 21.9 Hz, C-3', C-5'); 115.9 (C-6); 116.8, 117.0 (C-1, C-7); 123.6 (C-3); 126.4 (C-8); 128.1 (C-2); 129.0 (C-5)**;** 131.4 (d, *J* = 9.0 Hz, C-2', C-6'); 135.0 (d, *J* = 3.0 Hz, C-1'); 136.6 (C-8a); 165.2 (d, 2C, *J* = 252.5 Hz, C-4'); 184.4 (COAr); 193.0 (CO).

1-Acetyl-3-(4-chlorobenzoyl)-7-cyano-indolizine (**7c**). Pale yellow crystals with mp 206-8 ºC were obtained; Yield 42 %. Anal. Calcd. $C_{18}H_{11}ClN_2O_2$: C 66.99; H 3.44; Cl 10.98; N 8.68. Found C 67.31; H 3.76; Cl 11.36; N 8.91. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.58 (s, 3H, Me); 7.23 (dd, 1H, *J* = 7.3, 1.9 Hz, H-6); 7.54 (d, 2H, *J* = 8.5 Hz, H-3', H-5'); 7.76 (s, 1H, H-2); 7.79 (d, 2H, *J* = 8.5 Hz, H-2', H-6'); 9.03 (dd, 1H, *J* = 1.9, 0.8, Hz, H-8); 9.93 (dd, 1H, *J* = 7.4, 1.0 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 28.0 (Me); 111.1 (CN); 115.9 (C-6); 116.9, 117.0 (C-1, C-7); 123.5 (C-3); 126.4 (C-8); 128.5 (C-2); 129.0 (C-5); 129.1; 130.3 (C-2', C-3', C-5', C-6'); 136.6 (C-8a); 137.2, 138.8 (C-1', C-4'); 184.6 (COAr); 192.9 (CO).

1-Acetyl-3-(4-bromobenzoyl)-7-cyano-indolizine (**7d**). Pale yellow crystals with mp 231-3 ºC were obtained; Yield 46 %. Anal. Calcd. $C_{18}H_{11}BrN_2O_2$: C 58.88; H 3.02; Br 21.76; N 7.63. Found C 58.88; H 3.02; Br 21.76; N 7.63. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.57 (s, 3H, Me); 7.23 (dd, 1H, *J* = 7.3, 1.9 Hz, H-6); 7.71 (s, 4H, H-2', H-3', H-5', H-6'); 7.74 (s, 1H, H-2); 9.04 (dd, 1H, *J* = 1.8, 0.8, Hz, H-8); 9.94 (dd, 1H, *J* = 7.3, 0.8 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 28.0 (Me); 111.1 (CN); 116.0 (C-6); 116.9, 117.0 (C-1, C-7); 123.5 (C-3); 127.3 (C-4'); 126.4 (C-8); 128.5 (C-2); 129.0 (C-5); 130.6, 132.0 (C-2', C-3', C-5', C-6'); 136.7 (C-8a); 137.6 (C-1'); 184.7 (COAr); 192.9 (CO).

1-Acetyl-7-cyano-3-(4-methoxybenzoyl)-indolizine (**7e**). Pale yellow crystals with mp 229-231 ºC were obtained; Yield 55 %. Anal. Calcd. $C_{19}H_{14}N_2O_3$: C 71.69; H 4.43; N 8.80. Found C 71.87; H 4.75; N 9.07. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.58 (s, 3H, Me); 3.93 (s, 3H, MeO); 7.06 (d, 2H, *J* = 8.8 Hz, H-3', H-5'); 7.19 (dd, 1H, *J* = 7.3, 1.9 Hz, H-6); 7.78 (s, 1H, H-2); 7.87 (d, 2H, *J* = 8.8 Hz, H-2', H-6'); 9.03 (dd, 1H, *J* = 1.9, 0.8, Hz, H-8); 9.87 (dd, 1H, *J* = 7.3, 0.8 Hz, H-5). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 28.0 (Me); 55.5 (OMe); 110.4 (CN); 115.5 (C-6); 116.6, 117.2 (C-1, C-7); 124.1 (C-3); 126.4 (C-8); 127.7 (C-2); 128.9 (C-5); 113.9 (C-8, C-3', C-5'); 131.3 (C-2', C-6'); 131.3, 132.5 (C-1', C-4'); 136.2 (C-8a); 184.8 (COAr); 193.0 (CO).

CONCLUSIONS

Ten 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. Structural assignment was provided by NMR spectroscopy. The influence of the 7-cyano group on the conjugation of the indolizine scaffold was observed in the ^{13}C-NMR spectra.

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