New N-bridgehead heterocyclic compounds. II.[1] Carbamoyl-substituted azaindolizines

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Dedicated to Professor Alain Krief on the occasion of his 65th anniversary

Abstract

New carbamoyl-substituted azaindolizines were easily obtained by the reactions of diazines with bromoacetanilides, followed by the reactions of the corresponding *N*-phenylcarbamoylmethyl diazinium quaternary salts with ethyl propiolate in the presence of an epoxide as dehydrohalogenation agent and reaction solvent. Molecular orbital calculations, using AM1approximation, have been used to explain the regioselectivity in the 1,3-dipolar cycloaddition reactions of diazinium *N*-carbamoylmethylides to ethyl propiolate.

Keywords: 1,3-dipolar cycloadditions, pyrrolo[1,2-*b*]pyridazine, pyrrolo[1,2-*c*]pyrimidine, pyrrolo[1,2-*a*]-pyrimidine, theoretical calculation

Introduction

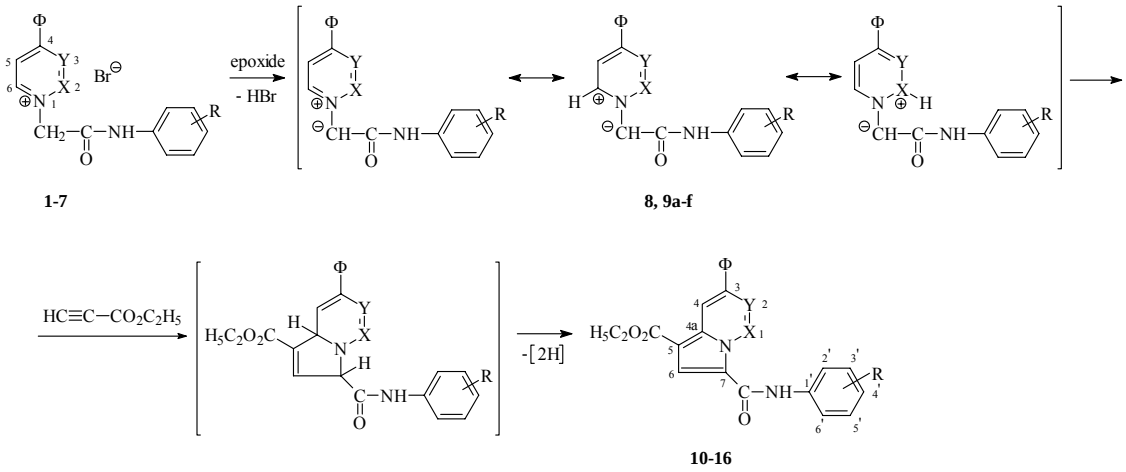
Indolizines and their aza analogues have interesting chemical and biological properties and their utility has been demonstrated in the chemistry of natural products, in materials science and in pharmaceutical chemistry. [2,3] 1,3-Dipolar cycloaddition reactions, by virtue of their atom economy character, are efficient approaches for the synthesis of new indolizines and azaindolizines, otherwise difficulty obtainable. In a previous paper[1] we have presented new carbamoyl substituted indolizines and benzoindolizines obtained via 1,3-dipolar cycloadditions of the corresponding pyridinium and benzopyridinium *N*-carbamoylmethylides to alkynes and alkenes.

Now, we report new carbamoyl-substituted azaindolizines obtained *via* 1,3-dipolar cycloaddition reactions of pyridazinium and pyrimidinium *N*-carbamoylmethylides with ethyl

propiolate. Molecular modelling methods were applied in order to explain the regioselectivity in 1,3-dipolar cycloaddition reactions of the corresponding diazinium *N*-carbamoylmethylides to an unsymmetrical alkyne such as ethyl propiolate.

Results and Discussion

1,3-Dipolar cycloaddition reactions of diazinium *N*-carbamoylmethylides with ethyl propiolate, conducted in a sequential manner, were considered for the synthesis of carbamoyl-substituted N-bridgehead heterocyclic compounds.[4,5] Intermediate diazinium *N*-carbamoylmethylides were obtained by the dehydrohalogenation of the corresponding *N*-phenylcarbamoylmethyl diazinium quaternary salts. By the direct reactions of the pyridazine and 4-substituted pyrimidines with bromo acetanilides the corresponding *N*-phenylcarbamoylmethyl quaternary salts **1-7** were obtained (Scheme 1, Table 1). The structures of quaternary salts **1-7** were confirmed by chemical and spectral analysis.



Scheme 1. The synthetic route.

Table 1. *N*-Methylcarbamoyl diazinium salts

Compound	X	Y	Φ	R	m.p. (°C)	Yield (%)
1	N	CH	H	H	193-194	70.0
2	CH	N	3-ClC_6H_4	3-CF_3	168-169.5	77.0
3	CH	N	2-thienyl	3-CF_3	262-265	68.5
4	CH	N	2-thienyl	H	183-186	81.0
5	CH	N	2-furyl	3-CF_3	222-225	67.0
6	CH	N	2-furyl	H	203-206	68.0
7	CH	N	2-$CH_3OC_6H_4$	3-CF_3	219-220	74.0

Treatment of the 1-methylcarbamoyl pyridazinium bromide **1,** respectively 1-methylcarbamoyl pyrimidinium bromides **2-7,** with ethyl propiolate, in the presence of an epoxide as acid acceptor and reaction solvent, afforded new 7-carbamoyl-pyrrolo[1,2-*b*]-pyridazine **10**, respectively new 7-carbamoyl-pyrrolo[1,2-*c*]pyrimidines **11-16**. The reaction occurs *via* pyridazinium-*N*-carbamoylmethylide **8**, respectively pyrimidinium-*N*-carbamoylmethylides **9a-f**, obtained *in situ* by α-deprotonation of the corresponding quaternary salts **1-7**, followed by 1,3-dipolar cycloaddition reactions of these ylides with ethyl propiolate. Propylene oxide or 1,2-epoxybutane was used as acid acceptor and reaction solvent. In the presence of other acid acceptor such as triethylamine in chloroform an important amount of dipyrimidopyrazine dimers as inactivation compounds of pyrimidinium-1-carbamoylmethylides are obtained among the cycloaddition compounds.[7,8]

Newly synthesised carbamoyl-substituted azaindolizines **10-16** are presented in Table 2.

Table 2. Carbamoyl-substituted azaindolizines

Comp.	X	Y	Φ	R	m.p. (°C)	Yield (%)
10	N	CH	H	H	132-134	28.5*
11	CH	N	3-ClC_6H_4	3-CF_3	183-185	31.0*
12	CH	N	2-thienyl	3-CF_3	184-186	27.0**
13	CH	N	2-thienyl	H	185-187	29.0**
14	CH	N	2-furyl	3-CF_3	180-182	24.0**
15	CH	N	2-furyl	H	227-229	25.5**
16	CH	N	2-$CH_3OC_6H_4$	3-CF_3	104-106	29.0*

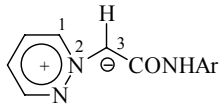
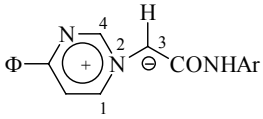
*Experimental procedure A. **Experimental procedure B.

The structures of new compounds **10-16** were attributed on the basis of spectral analysis. The IR spectra of these compounds exhibit the characteristic NH absorption bands at about 3300 cm^{-1} and 3100 cm^{-1}, the characteristic carbonyl absorption bands at about 1680-1700 cm^{-1} (C=O from carbethoxy group) and 1655-1685 cm^{-1} (C=O from carbamoyl group). The ^{1}H-NMR spectra of these compounds reveal characteristic NH signals in the range of δ 8.71-10.80 and the signals of H-2 protons from pyrrolo ring at δ 7.17-8.51. The signals for the ethyl protons of the carbethoxy group appear at δ 4.37-4.46 (q) and δ 1.41-1.49 (t), a normal chemical shift for an α-unsubstituted ethyl ester; not shielded by the nearby carbamoyl group. The ^{1}H-NMR spectra of carbamoyl-substituted pyrrolo[1,2-*c*]pyrimidines **11-16** exhibit the signal of pyrimidine ring H-1, respectively H-2, at δ 10.33-10.88, respectively at δ 8.32-8.69, as characteristic doublets with small coupling constants $J_{1\text{-}4} \approx 1.5$ Hz. The ^{13}C-NMR spectra of **10** and **11-16** show characteristic signals for the carbonyl carbon at δ 159-161 (carbamoyl group) and δ~164 (carbethoxy group). In each of these reactions only one regioisomer was obtained.

In our previous works [7-12] many similar 1,3-dipolar cycloaddition reactions were described. In all cases only pyrrolo[1,2-*c*]pyrimidines are formed. All our reactions were done using epoxides as solvent and hydrobromic acid scavenger. We did not observe selectivity changes when the reactions were done at room temperature in propeneoxide during up to two weeks or in 1,2-epoxybutane at reflux 20 hours followed by 2-3 days at room temperature. If the reactions are done in non-epoxide solvents using amines or alkali carbonates as acid scavengers[13,14] the selectivity and the regioselectivity of the reaction would be both affected, mixtures containing one or both 1,3-dipolar addition products to the dipolarophile triple bond together with ylide dimers beeing generated. The selectivity of the reaction can be increased by adding very slowly the acid scavenger[13], but the formation of the dimers of the 1,3-dipoles could not be avoided. The stability and nucleofilicity of the ylides was analysed in correlation with their structure using semiempirical quantum calculations showing their ability to react as 1,3-dipole or nucleophiles[14] but no thorough evaluation was done on the reagents structure - regioselectivity relation beyond FMO level.

The regioselective control of these cycloaddition reactions has been analysed using the General Theory of Perturbation of the Molecular Frontier Orbitals.[15,16]. Molecular orbital calculations were performed by AM1 method,[17] using HyperChem and MOPAC programs.[18] Atomic charges, energies and molecular frontier orbitals for all the reactive centers involved in these reactions are presented in Table 3.

Table 3. Atomic charges, energies and frontier molecular orbitals for all reagents

Compound*	FMO	OE (eV)	Total charges (C)		
			C-1	C-3	C-4
	HOMO	- 8.0274	0.4182	- 0.6252	
	LUMO	- 0.8785	0.1863	0.4023	
8: Ar=C_6H_5	Q		- 0.2330	- 0.3470	
	HOMO	- 8.150	- 0.3372	0.6585	- 0.3410
	LUMO	- 1.405	- 0.2665	- 0.3506	- 0.2034
9a: Φ=3-ClC_6H_4 Ar=3-$CF_3C_6H_4$	Q		- 0.1606	- 0.4157	- 0.0877
9b: Φ=2-thienyl Ar=3-$CF_3C_6H_4$	HOMO	- 7.966	- 0.3133	0.6486	- 0.3232
	LUMO	- 1.438	- 0.2570	- 0.3303	- 0.1767
	Q		- 0.1508	- 0.4251	- 0.0748
9c: Φ=2-thienyl Ar=C_6H_5	HOMO	- 7.777	- 0.3213	0.6349	- 0.3244
	LUMO	- 1.265	- 0.2457	- 0.3460	- 0.1659
	Q		- 0.1625	- 0.4166	- 0.0798
9d: Φ=2-furyl Ar=3-$CF_3C_6H_4$	HOMO	- 8.001	- 0.3157	0.6299	- 0.3208
	LUMO	- 1.443	- 0.2514	- 0.3552	- 0.1982
	Q		- 0.1605	- 0.4129	- 0.0839
9e: Φ=2-furyl Ar=C_6H_5	HOMO	- 7.840	- 0.3229	0.6176	- 0.3232
	LUMO	- 1.293	- 0.2409	- 0.3730	- 0.1889
	Q		- 0.1705	- 0.4031	- 0.0903
9f: Φ=2-$CH_3OC_6H_4$ Ar=3-$CF_3C_6H_4$	HOMO	- 7.953	- 0.1789	0.3632	- 0.1984
	LUMO	- 1.060	- 0.1633	- 0.1833	- 0.1245
	Q		- 0.1561	- 0.4242	- 0.0899
			C-1	C-2	
HC≡C-CO_2Et 1 2 3	HOMO	-11.3750	0.0498	0.0544	
	LUMO	0.1456	0.3876	- 0.5657	
	Q		- 0.1830	- 0.0960	

* atom numbering included only for calculation purposes.

On the basis of the data from Table 3, the ΔE of interaction $HOMO_{ylide}$-$LUMO_{ethyl\ propiolate}$ and $HOMO_{ethyl\ propiolate}$-$LUMO_{ylide}$ were calculated. The $HOMO_{ylide}$-$LUMO_{ethyl\ propiolate}$ interactions show a smaller energy gaps than the opposite $HOMO_{ethyl\ propiolate}$-$LUMO_{ylide}$ interactions, which

is consistent with ylide-HOMO controlled reactions.[19] In accordance with FMO postulates,[16] once the HOMO/LUMO pair closer in energy has been identified, the new bonds will be formed between centers with atomic orbital coefficients with the same sign, the relative sizes of the possible pairs of coefficients predicting the regioselectivity.

In 1,3-dipolar cycloaddition reaction of pyridazinium-1-carbamoylmethylide **8** with ethyl propiolate, the new bonds will be formed between the ylidic carbon and the unsubstituted C-1 carbon atom from the triple bond of ethyl propiolate, respectively between α-carbon of the pyridazine ring and C-2 carbon from the triple bond of the ethyl propiolate, as predicted by the calculations.

According with the FMO predicted behaviour, for the pyrimidinium-1-carbamoylmethylides **9a-f** the new bonds should be formed between the ylidic carbon atom and the unsubstituted carbon atom C-1 from the triple bond of the ethyl propiolate and between C-2 atom of the pyrimidine nucleus and the C-2 atom from the triple bond of the ethyl propiolate leading to pyrrolo[1,2-*a*]pyrimidines (Figure 1).

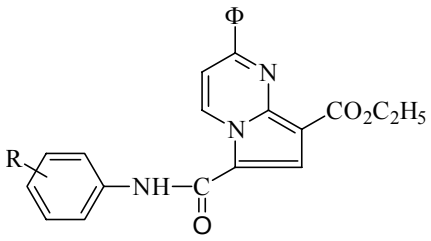


Figure 1. Pyrrolo[1,2-*a*]pyrimidine.

In fact, the second new bond is formed between C-6 atom of the pyrimidine nucleus and the C-2 atom from the triple bond of the ethyl propiolate, affording pyrrolo[1,2-*c*]pyrimidine derivatives **10-16** in disagreement with the FMO predicted behaviour. In order to rationalise these data we made a more thorough analysis. Looking at the MO's of ethyl propiolate one can see that only LUMO is located on the acetylene triple bond, the HOMO being located mainly on the ethyl fragment practically with no contribution of the p_z orbitals of the acetylene fragment. Charge on C1 and C2 are both negatives -0.095 and respectively -0.183. This is in agreement with the ylide-HOMO control of the reaction (Figure 2).

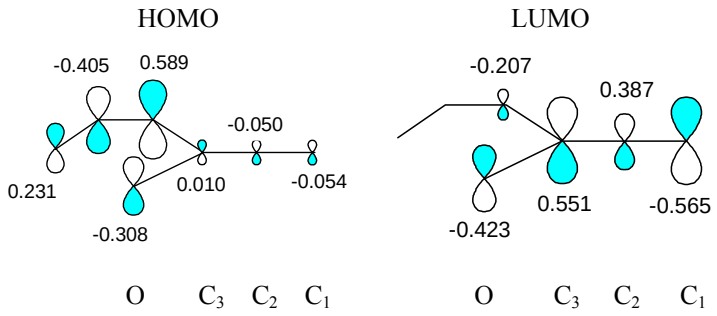


Figure 2. Ethyl propiolate FMO's significant p_z coefficients.

If we look again to the data in Table 3 then it is clear that differences between p_z atomic orbital coefficients for C-1 and C-4 in the ylides **9d-9e** are too small to discriminate reaction regioselectivity. On the other hand the negative charge on C-1 is always approximately the double of the charge on C-4, but the values are quite small and again we think this is not enough to discriminate between the two possible pathways.

In order to get a clearer picture of the interactions during the approach of the two reacting molecules we evaluated an energy hypersurface considering the two molecules at a distance of 3 Å and rotating the propiolate molecule with respect to the axes represented in Figure 3.

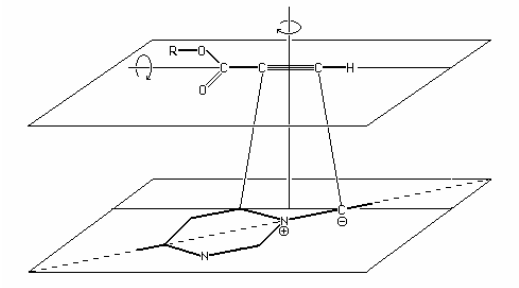


Figure 3. Ylide - propiolate interaction scheme.

A similar interaction scheme and corresponding energy hypersurface has been build for the case when C-1 and C-3 carbons from the ylide react with the propiolate molecule. The obtained hypersurfaces are represented in Figure 4 together with the lowest energy interaction geometry.

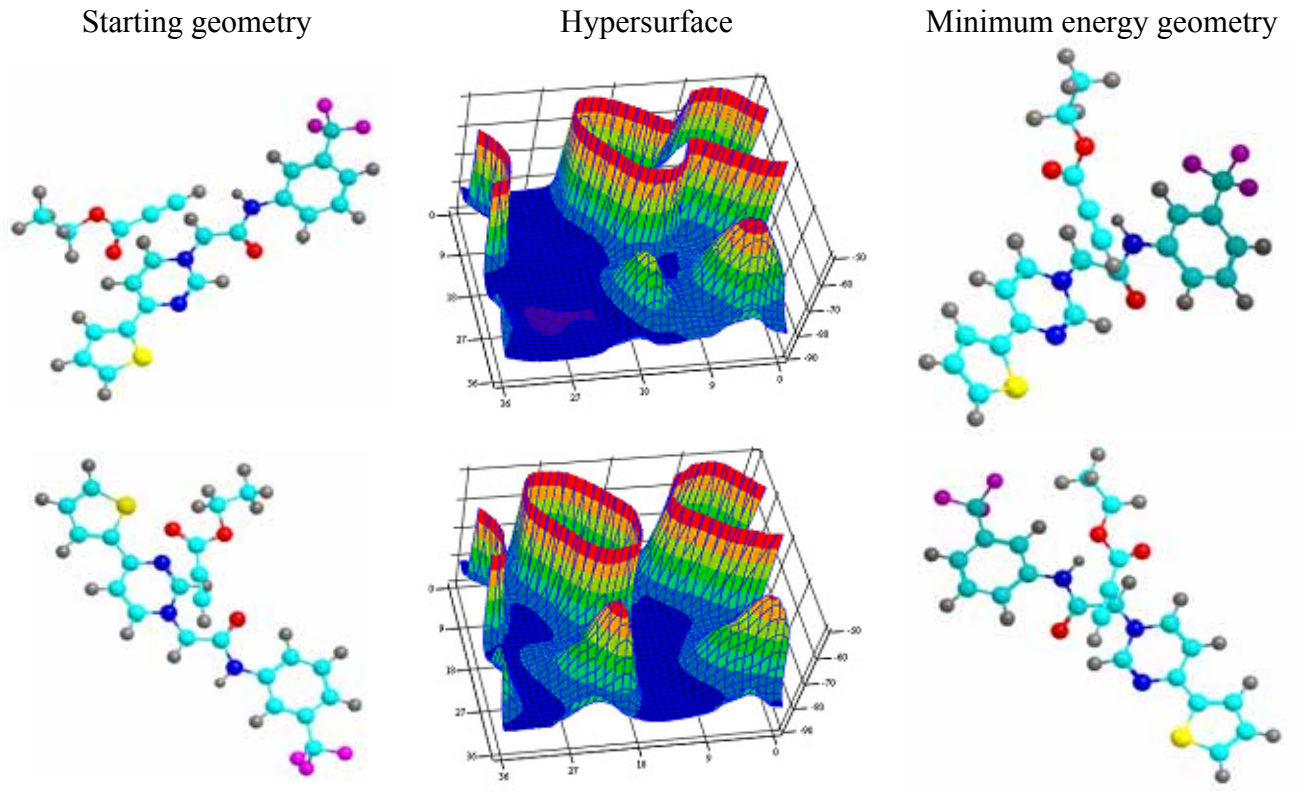


Figure 4. Energy hypersurfaces and optimal interaction geometry's for ylide **8c** and ethyl propiolate.

In the case of cycloaddition to C-1 and C-3 carbons of the ylide the energetically favoured geometry does not correspond to the standard antarafacial interaction expected for this reaction and the rotation of the propiolate molecule is strongly influencing the energy of the system generating a quite narrow energy minimum while in the case of C-4 and C-3 carbons the favoured geometry is the standard antarafacial interaction and also the energy minimum is wide being not so sensitive to the rotation of the propiolate molecule. The second minimum is favoured by approximately 8 Kcal/mol, at AM1 level, with respect to the first.

We can conclude that the formation of pyrrolo[1,2-c]pyrimidines **10-16** is favoured at least by three factors: charge distribution in the ylide molecule, minimal energy interaction geometry and sterically favoured antarafacial approach. These results still do not explain why the selectivity is affected by the reaction conditions namely changing the solvent and the acid scavenger. Also substituent effects observed in the additions of *para* substituted benzoyl 4-methypyrimidinium ylides[13] are not explained by our analysis. Further theoretical investigations will try to rationalise these experimental data.

Experimental Section

General Procedures. Melting points were determined on a Boetius apparatus and are uncorrected. The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets. The ^{1}H- and ^{13}C-NMR spectra were registered with a Varian Gemini 300BB instrument at ambient temperature using TMS as internal standard; for unambiguous assignment ^{1}H-decoupling COSY (^{1}H-^{1}H) and COSY (^{1}H-^{13}C) were used. The solvent used was $CDCl_3$ for the compounds **10**, **14, 15** and **16**, or a mixture of 10:1 molar ratio $CDCl_3$:TFA for the compounds **1**, **2-7**, **11**, **12** and **13**. Satisfactory microanalyses for all new compounds were obtained. Pyridazine was a commercially available product (Aldrich). 4-Substituted pyrimidines were obtained according a previously described procedure[7,20,21] by heating formamide with dimethylsulphate and treating the intermediate triformylaminomethane with 3-chloroacetophenone, 2-acetyl thiophene, 2-acetyl furane, respectvely 2-methoxyacetophenone, in the presence of *p*-toluenesulfonic acid. Bromoacetanilides were obtained from the corresponding aromatic amines and bromoacetyl bromide.

General procedure for N-methylcarbamoyl diazinium salts

A mixture of a diazine (20 mmol) and the corresponding bromoacetanilide (20 mmol) in chloroform (50 mL) was heated at reflux for 20 hours. The mixture was cooled and left overnight at the room temperature. The solid product was filtered, washed with a mixture of methylene dichloride-diethyl ether (30 mL) and recrystallised from methanol or methanol/diethyl ether.

The yields and m. p. are shown in Table 1. The spectral data are given below.

1-(*N*-Phenylcarbamoylmethyl)pyridazinium bromide (1). IR (ν_{max}, cm^{-1}): 3188, 3069, 1700, 1551. ^{1}H-NMR (δ, ppm, *J*, Hz): 9.91 (bd, 1H, H-3, *J* = 5.9); 9.67 (s, 1H, NH); 9.38 (dd, 1H, H-6, *J* = 5.9, 1.5); 8.59 (ddd, 1H, H-4, *J* = 1.5, 5.9, 8.3); 8.41 (ddd, 1H, H-5, *J* = 1.5, 5.9, 8.3); 7.47 (dd, 2H, H-2'+6', *J* = 8.3, 1.3); 7.33 (dd, 2H, H-3'+5', *J* = 8.3, 7.4); 7.21 (tt, 1H, H-4', *J* = 7.4, 1.3); 6.17 (s, 2H, CH_2). ^{13}C-NMR (δ, ppm): 162.65 (*C*=O); 159.03 (C-6); 151.71 (C-3); 136.77 (C-4/5); 135.85 (C-5/4); 132.26 (C_q-1'); 129.34 (C-3'+5'); 126.85 (C-4'); 121.47 (C-2'+6'); 67.25 (CH_2). Anal. calcd. for $C_{12}H_{12}BrN_3O$ (294.15): C, 49.00; H, 4.11; N, 14.28%. Found: C, 49.27; H, 3.98; N, 14.50%.

1-[*N*-(3-Trifluoromethylphenyl)carbamoylmethyl]-4-(3-chlorophenyl)pyrimidinium bromide (2). IR (ν_{max}, cm^{-1}): 3144, 3093, 1685, 1554. ^{1}H-NMR (δ, ppm, *J*, Hz): 9.91 (s, 1H, NH), 9.48 (dd, 1H, H-2, *J* = 0.9, 1.9), 9.19 (dd, 1H, H-6, *J* = 1.9, 6.9), 8.40 (dd, 1H, H-5, *J* = 0.9, 6.9), 8.35 (t, 1H, H-2", *J* = 1.9), 8.20 (ddd, 1H, H-6", *J* = 1.1, 1.9, 7.8), 7.85 (bs, 1H, H-2'), 7.76 (ddd, 1H, H-4", *J* = 1.1, 1.9, 7.8), 7.64 (m, 1H, H-5'), 7.62 (t, 1H, H-5", *J* = 7.8), 7.48 (m, 2H, H-4'+6'), 5.92 (s, 2H, CH_2). ^{13}C-NMR (δ, ppm): 170.50 (C_q), 162.94 (*C*=O), 153.44 (C-2), 152.27 (C-6), 136.76 (C_q), 136.18 (C_q), 136.03 (C-4"), 133.86 (C_q), 132.03 (C_q-3', 33.7), 131.33 (C-5"), 130.01 (C-6'), 129.54 (C-5), 127.65 (C-6"), 124.21 (C-5'), 123.54 (q, CF_3, 272.4 Hz),

123.20 (q, C-4', 3.7 Hz), 118.05 (C-2"), 117.98 (C-2'), 59.33 (*C*H_2). Anal. calcd. for $C_{19}H_{14}BrClF_3N_3$ (472.69): C, 48.28, H, 2.98, N, 8.89%. Found: C, 48.19, H, 2.77, N, 8.96%.

1-[*N*-(3-Trifluoromethylphenyl)carbamoylmethyl]-4-(2-thienyl)pyrimidinium bromide (3). IR ($\nu_{max.}$): 3200, 3054, 1685, 1550. ^{1}H-NMR (δ, ppm, *J*, Hz): 10.46 (s, 1H, NH), 9.20 (dd, 1H, H-2, *J* = 1.0, 1.9), 8.95 (dd, 1H, H-6, *J* = 1.9, 7.0), 8.22 (dd, 1H, H-5, *J* = 1.0, 7.0), 8.20 (dd, 1H, H-3", *J* = 1.1, 4.0), 8.07 (dd, 1H, H-5", *J* = 1.1, 4.9), 7.90 (bs, 1H, H-2'), 7.67 (m, 1H, H-4'), 7.45 (m, 2H, H-5'+6'), 7.39 (dd, 1H, H-4", *J* = 4.0, 4.9), 5.83 (s, 2H, CH_2). ^{13}C-NMR (δ, ppm): 164.91 (*C*=O), 163.17 (C_q), 153.21 (C-2), 150.47 (C-6), 140.77 (C-5"), 136.38 (C_q), 136.11 (C-3"), 131.71 (q, C_q-3', 32.9 Hz), 131.05 (C-4"), 129.86 (C-5'), 123.95 (C-6'), 123.51 (q, *C*F_3, 272.7 Hz), 122.82 (q, C-4', 3.6 Hz), 117.70 (q, C-2', 3.8 Hz), 115.54 (C-5), 58.83 (*C*H_2). Anal. calcd. for $C_{17}H_{13}BrF_3N_3OS$ (444.27): C, 45.96, H, 2.95, N, 9.46%. Found: C, 46.07, H, 2.80, N, 9.55%.

1-(*N*-Phenylcarbamoylmethyl)-4-(2-thienyl)pyrimidinium bromide (4). IR (ν_{max}, cm^{-1}): 3178, 3023, 1693, 1549. ^{1}H-NMR (δ, ppm, *J*, Hz): 9.92 (s, 1H, NH), 9.19 (dd, 1H, H-2, *J* = 1.0, 1.9), 8.99 (dd, 1H, H-6, *J* = 1.9, 7.0), 8.22 (dd, 1H, H-5, *J* = 1.0, 7.0), 8.18 (dd, 1H, H-3", *J* = 1.1, 4.0), 8.03 (dd, 1H, H-5", *J* = 1.1, 4.9), 7.51 (dd, 2H, H-2'+6', *J* = 1.5, 8.1), 7.37 (dd, 1H, H-4", *J* = 4.0, 4.9), 7.32 (dd, 2H, H-3'+5', *J* = 7.5, 8.1), 7.19 (tt, 1H, H-4', *J* = 1.5, 7.5), 5.81 (s, 2H, CH_2). ^{13}C-NMR (δ, ppm): 164.77 (*C*=O), 163.02 (C_q), 153.27 (C-2), 150.55 (C-6), 140.48 (C-5"), 138.43 (C_q), 135.96 (CH-3"), 135.56 (C_q), 130.96 (C-4"), 129.26 (C-3'+5'), 126.51 (C-4'), 121.19 (C-2'+6'), 115.56 (C-5), 58.80 (*C*H_2). Anal. calcd. for $C_{16}H_{14}BrN_3OS$ (376.27): C, 51.07, H, 3.75, N, 11.17%. Found: C, 51.01, H, 3.69, N, 11.29%.

1-[*N*-(3-Trifluoromethylphenyl)carbamoylmethyl]-4-(2-furyl)pyrimidinium bromide (5). IR (ν_{max}, cm^{-1}): 3197, 3051, 1686, 1574. ^{1}H-NMR (δ, ppm, *J*, Hz): 10.03 (s, 1H, NH), 9.23 (dd, 1H, H-2, *J* = 1.0, 1.9), 8.97 (dd, 1H, H-6, *J* = 1.9, 7.0), 8.07 (dd, 1H, H-5, *J* = 1.0, 7.0), 7.97 (dd, 1H, H-3", *J* = 0.8, 1.8), 7.93 (bs, 1H, H-2'), 7.91 (dd, 1H, H-5", *J* = 0.8, 3.8), 7.68 (m, 1H, H-4'), 7.45 (m, 2H, H-5'+6'), 6.87 (dd, 1H, H-4", *J* = 1.8, 3.8), 5.85 (s, 2H, CH_2). ^{13}C-NMR (δ, ppm): 163.38 (*C*=O), 159.72 (C_q), 153.67 (C-2), 152.30 (C-6), 151.19 (CH), 149.35 (C_q), 136.41 (C_q), 131.79 (C_q-3', 31.1 Hz), 129.95 (CH), 124.43 (CH), 124.13 (CH), 123.60 (q, *C*F_3, 272.4 Hz), 122.93 (q, C-4', 3.9 Hz), 117.85 (q, C-2', 3.4 Hz), 115.84 (CH), 114.93 (CH), 59.05 (*C*H_2). Anal. calcd. for $C_{17}H_{13}BrF_3N_3O_2$ (428.21): C, 47.68, H, 3.06, N, 9.81%. Found: C, 47.55, H, 2.84, N, 9.89%.

1-(*N*-Phenylcarbamoylmethyl)-4-(2-furyl)pyrimidinium bromide (6). IR ($\nu_{max.}$, cm^{-1}): 3122, 3050, 1697, 1593. ^{1}H-NMR (δ, ppm, *J*, Hz): 9.72 (s, 1H, NH), 9.28 (dd, 1H, H-2, *J* = 1.0, 1,8), 8.95 (dd, 1H, H-6, *J* = 1.8, 7.0), 8.08 (dd, 1H, H-5, *J* = 1.0, 7.0), 7.97 (dd, 1H, H-3", *J* = 1.0, 1.7), 7.91 (dd, 1H, H-5", *J* = 3.7), 7.45 (dd, 2H, H-2'+6', *J* = 1.5, 8.1), 7.36 (dd, 2H, H-3'+5', *J* = 7.3, 8.1), 7.27 (tt, 1H, H-4', *J* = 1.5, 7.3), 6.87 (dd, 1H, H-4", *J* = 1.7, 3.8), 5.79 (s, 2H, CH_2). ^{13}C-NMR (δ, ppm): 163.55 (*C*=O), 159.28 (C_q), 153.64 (C-2), 152.32 (CH-6), 151.03 (C-3"), 149.08 (C_q), 134.90 (C_q), 129.31 (C-3'+5'), 127.02 (C-5"), 124.48 (C-4'), 121.66 (C-2'+6'), 115.74 (C-5), 114.94 (C-4"), 58.81 (*C*H_2). Anal. calcd. for $C_{16}H_{14}BrN_3O_2$ (360.21): C, 53.35, H, 3.92, N, 11.66%. Found: C, 53.66, H, 3.72, N, 11.79%.

1-[N-(3-Trifluoromethylphenyl)carbamoylmethyl]-4-(2-methoxyphenyl)-pyrimidinium bromide (7). IR (ν_{max}, cm^{-1}): **3144, 3093, 1685, 1554.** ^{1}H-NMR (δ ppm, *J* Hz): 9.91 (s, 1H, NH), 9.42 (dd, 1H, H-2, *J* = 0.9, 1.9), 9.01 (dd, 1H, H-6, *J* = 1.9, 7.0), 8.91 (dd, 1H, H-5, *J* = 0.9, 7.0), 8.46 (dd, 1H, H-6", *J* = 1.9, 8.1), 7.88 (bs, 1H, H-2'), 7.74 (ddd, 1H, H-4", *J* = 1.9, 8.1, 8.4), 7.67 (m, 1H, H-6'), 7.49 (m, 2H, H-4'+5'), 7.23 (ddd, 1H, H-5", *J* = 0.8, 8.1, 8.4), 7.16 (dd, 1H, H-3", *J* = 0.8, 8.4), 5.90 (s, 2H, CH_2), 4.06 (s, 3H, OCH_3). ^{13}C-NMR (δ, ppm): 170.09 (C_q), 163.61 (*C*=O), 161.31 (CH), 152.19 (CH), 150.47 (CH), 138.06 (CH), 136.09 (C_q), 133.11 (CH), 131.90 (C_q-3', 33.0 Hz), 129.98 (CH), 124.35 (CH), 124.29 (q, *C*F_3, 273 Hz), 123.21 (q, C-4', 4.0 Hz), 122.09 (CH), 121.30 (C_q), 118.09 (q, C-2', 4.1 Hz), 112.41 (CH), 58.88 (*C*H_2), 55.95 (O*C*H_3). Anal. calcd. for $C_{20}H_{17}BrF_3N_3O_2$ (468.27): C, 51.3, H, 3.66, N, 8.98%. Found: C, 51.49, H, 3.50, N, 9.12%.

Carbamoyl-substituted azaindolizines

General procedure A

A mixture of diazinium N-methylcarbamoyl quaternary salt (10 mmol) and ethyl propiolate (1.14 mL, 11 mmol) in propenoxid (50 mL) was stirred at room temperature for 10-12 days and then was concentrated under reduced pressure. The residue was treated with methanol (10 mL) and kept refrigerated overnight. The solid was filtered and washed with cold methanol and then with diethyl ether. All crude products were recrystallised from chloroform/methanol.

General procedure B

To a suspension of diazinium N-methylcarbamoyl quaternary salt (10 mmol) in 1,2-epoxybutane (30 mL) 11 mmol of ethyl propiolate (1.14 mL, 11mmol) was added at room temperature The reaction mixture was refluxed for 18-20 hours and allowed at the room temperature for 2-3 days. Then, the solvent was evaporated *in vacuum* and the residue was treated with methanol (10-15 mL) when carbamoyl-substituted azaindolizines were precipitated. The solid mass was filtered off, washed with ether and recrystallised from chloroform-methanol.

The yields and m. p. for carbamoyl-substituted azaindolizines 9-15 are shown in Table 2. The spectral data are given below.

5-Carbethoxy-7-(*N*-phenylcarbamoyl)pyrrolo[1,2-*b*]pyridazine (10). IR ($\nu_{max.}$, cm^{-1}): 3290, 3038, 1703, 1664, 1552. ^{1}H-RMN (δ, ppm, *J*, Hz): 10.80 (s, 1H, NH), 8.71 (dd, 1H, H-4, *J* = 1.7, 9.2), 8.47 (dd, 1H, H-2, *J* = 1.7, 4.5), 8.23 (s, 1H, H-6), 7.75 (dd, 2H, H-2'+6', *J* = 1.0, 7.4), 7.38 (t, 2H, H-3'+5', *J* = 7.4), 7.14 (tt, 1H, H-4', *J* = 1.0, 7.4), 7.09 (dd, 1H, H-3, *J* = 4.5, 9.2), 4.40 (q, *J* = 7.1, CH_2 from CO_2Et), 1.42 (t, *J* = 7.1, CH_3 from CO_2Et). ^{13}C-RMN (δ, ppm): 163.49 (*C*OO), 156.99 (*C*=O), 142.80 (CH-2), 137.96 (C_q-1'), 131.69 (C_q-7), 129.34 (CH-4), 129.00 (CH-3'+5'), 124.29 (CH-4'), 123.26 (C_q-4a), 121.92 (CH-6), 120.47 (CH-2'+6'), 114.98 (CH-3), 106.06 (C_q-5), 60.37 (*C*H_2 from CO_2Et), 14.40 (*C*H_3 from CO_2Et). Anal. calcd. for $C_{17}H_{15}N_3O_3$ (309.32): C, 66.01, H, 4.89, N, 13.58%. Found: C, 65.98, H, 4.70, N, 13.71%.

3-(3-Chlorophenyl)-5-carbethoxy-7-[*N*-(3-trifluoromethylphenyl)carbamoyl]pyrrolo-[1,2-*c*]pyrimidine (11). IR (ν_{max}, cm^{-1}): 3323, 3112, 1669, 1656, 1529. ^{1}H-RMN (δ, ppm, *J*, Hz): 11.24 (d, 1H, H-1, *J* = 1.1), 8.99 (s, 1H, NH), 8.63 (d, 1H, H-4, *J* = 1.1), 8.51 (s, 1H, H-6), 7.83 (t, 1H, H-2", *J* = 1.9), 7.75 (bs, 1H, H-2'), 7.75-7.50 (m, 6H, H-4'-6', 4"-6"), 4.56 (q, *J* = 7.1, CH_2 from CO_2Et), 1.51 (t, *J* = 7.1, CH_3 from CO_2Et). ^{13}C-NMR (δ, ppm): 164.00 (*C*OO), 158.79 (*C*=O), 144.00 (CH-1), 137.40 (C_q), 136.46 (C_q), 135.78 (C_q), 132.37 (CH), 131.82 (C_q), 131.32 (CH), 130.58 (q, C_q-3', 31.4), 130.24 (CH), 127.22 (CH), 126.39 (CH), 125.16 (CH), 125.03 (CH), 123.73 (q, *C*F_3, 269.8), 123.44 (q, CH, 3.4), 120.13 (C_q), 118.75 (q, CH, 3.4), 112.62 (CH), 110.12 (Cq), 3.30 (*C*H_2 from CO_2Et), 13.94 (*C*H_3 from CO_2Et). Anal. calcd. for $C_{23}H_{17}ClF_3N_3O_3$ (487.86): C, 59.08, H, 3.51, N, 8.61%. Found: C, 58.75, H, 3.60, N, 8.80%.

3-(2-Thienyl)-5-carbethoxy-7-[*N*-(3-trifluoromethylphenyl)carbamoyl]pyrrolo[1,2-*c*]-pyrimidine (12). IR (ν_{max}, cm^{-1}): 3247, 3109, 1684, 1655, 1534. ^{1}H-RMN (δ, ppm, *J*, Hz): 10.88 (d, 1H, H-1, *J* = 1.2), 8.71 (s, 1H, NH), 8.34 (d, 1H, H-4, *J* = 1.2), 8.32 (s, 1H, H-6), 7.81 (dd, 1H, H-3", *J* = 1.1, 3.9), 7.74 (bs, 1H, H-2'), 7.69 (bd, 1H, H-6', *J* = 7.9), 7.62 (dd, 1H, H-5", *J* = 1.1, 5.1), 7.47 (t, 1H, H-5', *J* = 7.9), 7.46 (m, 1H, H-4'), 7.25 (dd, 1H, H-4", *J* = 3.9, 5.1), 4.47 (q, *J* = 7.1, CH_2 from CO_2Et), 1.49 (t, *J* = 7.1, CH_3 from CO_2Et). ^{13}C-RMN (δ, ppm): 164.46 (*C*OO), 158.69 (*C*=O), 142.85 (CH-1), 139.23 (C_q-2"), 138.17 (C_q-3), 136.53 (C_q-4a), 135.91 (C_q-1'), 131.83 (q, C_q-3', 32.7), 130.67 (CH-5"), 129.96 (CH-5'), 129.52 (CH-4"), 128.78 (CH-3"), 124.97 (CH-6), 124.26 (CH-6'), 123.01 (q, CF_3, 272.7), 122.54 (q, CH-4', 3.7), 118.88 (C_q-7), 117.92 (q, CH-2', 3.6), 109.02 (CH-4), 107.66 (C_q-5), 62.62 (*C*H_2 from CO_2Et), 14.00 (*C*H_3 from CO_2Et). Anal. calcd. for $C_{22}H_{16}F_3N_3O_3S$ (459.44): C, 57.51, H, 3.51, N, 9.14%. Found: C, 57.42, H, 3.24, N, 9.32%.

3-(2-Thienyl)-5-carbethoxy-7-[(*N*-phenyl)carbamoyl]pyrrolo[1,2-*c*]pyrimidine (13). IR (ν_{max}, cm^{-1}): 3312, 3069, 1700, 1685, 1523. ^{1}H-RMN (δ, ppm, *J*, Hz): 10.85 (d, 1H, H-1, *J* = 1.2), 8.71 (s, 1H, NH), 8.69 (d, 1H, H-4, *J* = 1.2), 8.17 (s, 1H, H-6), 7.78 (dd, 1H, H-3", *J* = 1.1, 3.9), 7.77-7.72 (m, 2H), 7.62 (dd, 1H, H-5", *J* = 1.1, 5.1), 7.68-7.51 (m, 3H), 7.23 (dd, 1H, H-4", *J* = 3.8, 5.1), 4.45 (q, *J* = 7.1, CH_2 from CO_2Et), 1.49 (t, *J* = 7.1, CH_3 from CO_2Et). ^{13}C-RMN (δ ppm): 164.76 (*C*OO), 162.02 (*C*=O), 142.73 (CH-1), 139.48 (C_q-2"), 138.76 (C_q-3), 138.08 (C_q-1'), 137.01 (C_q-4a), 130.72 (CH-3'+5'), 129.60 (CH-5"), 128.88 (CH-4"), 125.55 (CH-4'), 125.12 (CH-6), 122.02 (CH-2'+6'), 121.60 (CH-3"), 119.09 (C_q-7), 109.15 (CH-4), 108.98 (C_q-5), 61.98 (*C*H_2 from CO_2Et), 14.14 (*C*H_3 from CO_2Et). Anal. calcd. for $C_{21}H_{17}N_3O_3S$ (391.45): C, 64.43, H, 4.38, N, 10.73%. Found: C, 64.19, H, 4.29, N, 10.78%.

3-(2-Furyl)-5-carbethoxy-7-[*N*-(3-trifluoromethylphenyl)carbamoyl]pyrrolo[1,2-*c*]-pyrimidine (14). IR (ν_{max}, cm^{-1}): 3329, 3105, 1679, 1656, 1555. ^{1}H-RMN (δ, ppm, *J*, Hz): 10.33 (d, 1H, H-1, *J* = 1.5), 8.71 (s, 1H, NH), 8.32 (d, 1H, H-4, *J* = 1.5), 7.97 (bs, 1H, H-2'), 7.93 (s, 1H, H-6), 7.90 (bd, 1H, H-6', *J* = 8.0), 7.58 (dd, 1H, H-3", *J* = 0.8, 1.8), 7.50 (t, 1H, H-5', *J* = 8.0), 7.40 (bd, 1H, H-4', *J* = 8.0), 7.17 (dd, 1H, H-5", *J* = 0.8, 3.4), 6.58 (dd, 1H, H-4", *J* = 1.8, 3.4), 4.44 (q, *J* = 7.1, CH_2 from CO_2Et), 1.47 (t, *J* = 7.1, CH_3 from CO_2Et). ^{13}C-RMN (δ ppm, *J* Hz): 164.31 (*C*OO), 159.06 (*C*=O), 151.73 (C_q), 144.16 (CH-3"), 140.57 (CH-1), 139.58 (C_q), 138.61 (C_q), 138.50 (C_q), 131.06 (q, C_q-3', 32.4), 129.28 (CH-5'), 123.84 (q, CF_3, 272.0), 123.33 (CH-6'), 121.67 (CH-6), 120.45 (q, CH-4', 3.9), 117.90 (C_q-1'), 116.94 (q, CH-2', 3.8), 112.38(CH-4"), 110.88 (CH-5"), 105.95 (C-4), 105.66 (C_q), 60.66 (*C*H_2 from CO_2Et), 14.22

(*C*H_3 from CO_2Et). Anal. calcd. for $C_{22}H_{16}F_3N_3O_4$ (443.37): C, 59.59, H, 3.64, N, 9.48%. Found: C, 59.69, H, 3.51, N, 9.59%.

3-(2-Furyl)-5-carbethoxy-7-[(*N*-phenyl)carbamoyl]pyrrolo[1,2-*c*]pyrimidine (15). IR (ν_{max}, cm^{-1}): 3352, 3100, 1686, 1648, 1535. ^{1}H-RMN (δ, ppm, *J*, Hz): 10.38 (d, 1H, H-1, *J* = 1.5), 9.61 (s, 1H, NH), 8.34 (d, 1H, H-4, *J* = 1.5), 8.07 (s, 1H, H-6), 7.68 (dd, 2H, H-3'+5', *J* = 1.4, 8.4), 7.60 (dd, 1H, H-3", *J* = 0.7, 1.8), 7.39 (dd, 2H, H-3'+5', *J* = 7.9, 8.4), 7.17 (dd, 1H, H-5", *J* = 0.7, 3.6), 7.16 (tt, 1H, H-4', *J* = 1.4, 7.9), 6.59 (dd, 1H, H-4", *J* = 1.8, 3.6), 4.46 (q, *J* = 7.1, CH_2 from CO_2Et), 1.49 (t, *J* = 7.1, CH_3 from CO_2Et). ^{13}C-RMN (δ ppm): 164.81 (*C*OO), 159.55 (*C*=O), 152.55 (C_q), 144.49 (CH-3"), 141.11 (CH-1), 139.70 (C_q), 138.80 (C_q), 138.18 (C_q), 129.10 (CH-3'+5'), 124.67 (CH-4'), 121.25 (CH-6), 121.14 (CH-2'+6'), 118.84 (C_q), 112.69(CH-4"), 111.02 (CH-5"), 106.47 (CH-4), 105.98 (C_q), 60.92 (*C*H_2 from CO_2Et), 14.53 (*C*H_3 from CO_2Et). Anal. calcd. for $C_{21}H_{17}N_3O_4$ (375.37): C, 67.19, H, 4.56, N, 11.19%. Found: C, 67.02, H, 4.27, N, 11.28%.

3-(2-Methoxyphenyl)-5-carbethoxy-7-[*N*-(3-trifluoromethylphenyl)carbamoyl]pyrrolo-[1,2-*c*]pyrimidine (16). IR (ν_{max}, cm^{-1}): XX . ^{1}H-RMN (δ, ppm, *J*, Hz): 10.39 (d, 1H, H-1, *J* = 1.5), 8.82 (d, 1H, H-4, *J* = 1.5), 8.14 (dd, 1H, H-6", *J* =1.7, 7.7), 7.98 (bs, 1H, H-2'), 7.96 (s, 1H, H-6), 7.89 (bd, 1H, H-6', *J* = 8.0), 7.51 (td, 1H, H-4", *J* = 7.7, 1.7), 7.31 – 7.43 (m, 2H, H-4'-5'), 7.12 (td, 1H, H-5", *J* = 7.7, 1.0), 7.03 (dd, 1H, H-3", *J* = 1.0, 8.3), 4.38 (q, OCH_2, *J* = 7.1), 3.96 (s, OCH_3), 1.43 (t, CH_3, *J* = 7.1). ^{13}C-RMN (δ ppm, *J* Hz): 164.00 (*C*OO), 158.76 (*C*O), 157.70 (C-2"), 145.76(CH-1), 139.78 (Cq), 139.70 (Cq), 139.09 (Cq), 138.30 (Cq), 125.79 (Cq), 123.48 (q, *C*F3, 269.8), 116.92 (Cq), 105.74 (Cq), Anal. calcd. for $C_{25}H_{20}F_3N_3O_4$ (483.45): C, 62.11, H, 4.17, N, 8.69%. Found: C, 61.8, H, 4.3, N, 8.5%.

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