HETEROCYCLISATION OF AZACYANINE WITH AMINES. SYNTHESIS OF NEW FUSED TRIAZINES AND PYRIMIDINES RINGS

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ABSTRACT : Some novel triazine and pyrimidine derivatives were synthetized by reaction of 1,3-bis (dimethylamino)-1,3-dichloro-2-azapropenylium chloride (azacyanine) with heterocyclic compounds substituted by an amino group.

Key words : heterocyclisation; azacyanine ; triazine ; pyrimidine ; amine.

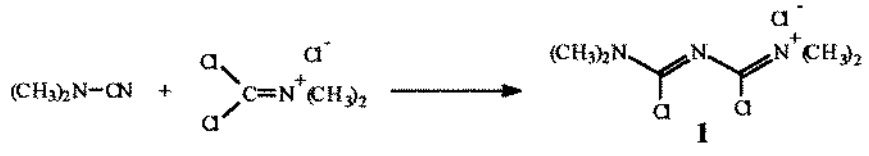
RÉSUMÉ : De nouveaux dérivés de triazines et de pyrimidines ont pu être obtenus par condensation du chlorure de 1,3-bis (diméthylamino)-1,3-dichloro-2-azapropénylium avec des composés hétérocycliques substitués par un groupement amino.

Mots clés : hétérocyclisation ; azacyanine ; triazine ; pyrimidine ; amine.

Compounds containing a fused 1,3,5-triazine or pyrimidine ring exhibit antitumor [1-3], fungicidal [4] and biological [5-7] activities.

Here we would like to report a new access to triazolotriazines, benzimidazolotriazine, quinazoline, pyrazolopyrimidine and isoxazolopyrimidine by using 1,3-bis (diméthylamino)-1,3-dichloro-2-azapropenylium chloride (azacyanine) **1**.

Azacyanine **1** is a versatile bis-electrophilic reagent, particularly useful in the synthesis of heterocyclic compounds such as 1,2,4-triazoles [8], oxadiazoles [9] and 1,3-oxazin-6-ones [10]. This azacyanine was prepared by treatment of (dichloromethylene) dimethylammonium chloride (phosgene iminium chloride) with N,N-dimethylcyanamide [8] (Scheme 1).



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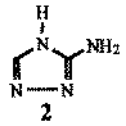
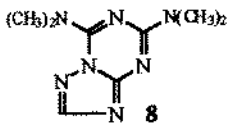
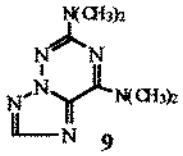
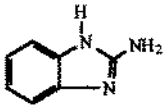
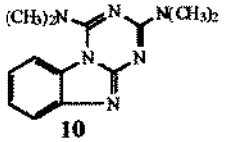
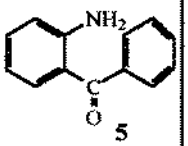
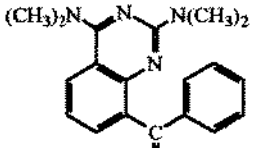
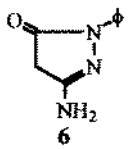
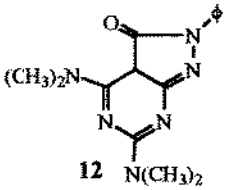
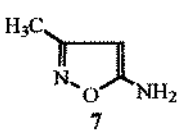
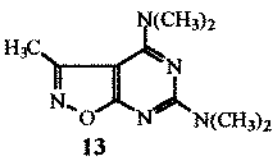
Scheme 1

Condensation of azacyanine **1** with 3-amino [1,2,4]triazole **2**, 4-amino[1,2,4] triazole **3**, 2-amino benzimidazole **4** in refluxing xylene led respectively, after treatment with sodium hydroxide, to the corresponding 1,2,4-triazolo [1,5-a] 1,3,5-triazine **8**, 1,2,4-triazolo [1,5-f] 1,2,4-triazine **9** and 1,3,5-triazino [1,2-a] benzimidazole **10** in good yields. Furthermore, when azacyanine **1** was refluxed in xylene with 2-aminobenzophenone **5**, 3-amino-1-phenylpyrazolin-5-one **6** and 5-amino-3-methylisoxazole **7** , quinozoline **11**, pyrazolo [4,3-d] pyrimidine **12** and isoxazolo [5,4-d] pyrimidine **13** were respectively isolated. These latter compounds were obtained in good to moderate yields (24 % < yield < 98 %) (Table I).

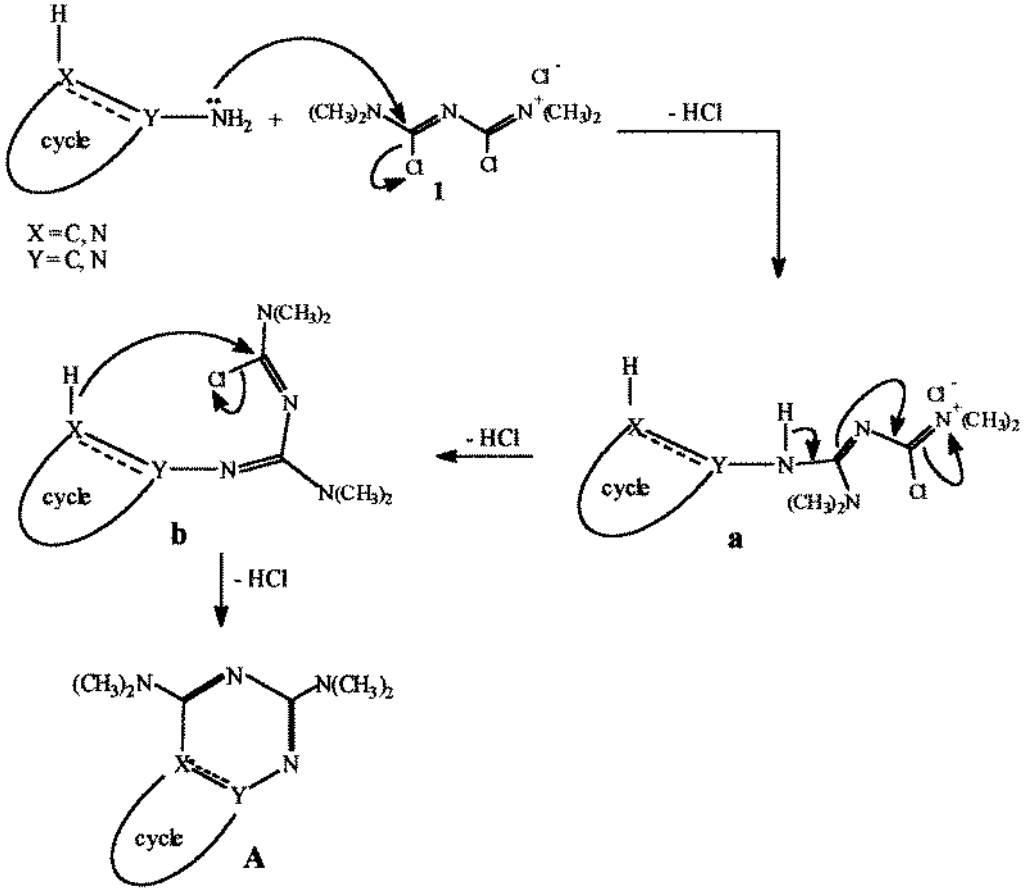
Table I : Formation of heterocyclic compounds from azacyanine **1**

Starting material	Time*	Product	Yield %
 **2**	25 h	 **8**	46
 **3**	40 h	 **9**	61
 **4**	24 h	 **10**	53
 **5**	35 h	 **11**	49
 **6**	40 h	 **12**	24
 **7**	38 h	 **13**	98

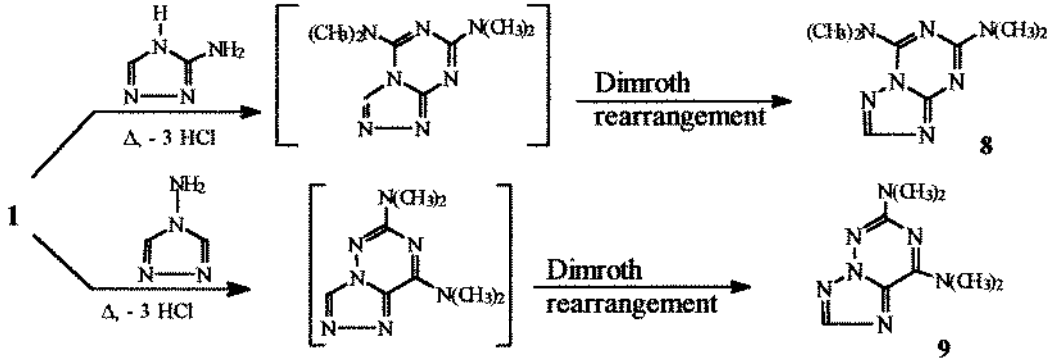
*Refluxing xylene

The formation of **10-13** can be explained according to Scheme 2. When azacyanine **1** was treated

with heterocyclic compounds substituted with an amino group, the amino group can attack **1** to afford intermediate **a**. By losing HCl, intermediate **a** can be transformed into intermediate **b** which can be attacked intramolecularly by the heterocyclic ring to form a C-C or C-N bond producing fused triazine and pyrimidine compounds of type **A** (Scheme 2). It is worthnoting that treatment of azacyanine **1** with **2** and **3**, probably affords intermediates 1,2,4-triazolo [4,3-a] 1,3,5-triazine and 1,2,4-triazolo [3,4-f] 1,2,4-triazine which in refluxing xylene isomerised respectively to **8** and **9** according to a Dimroth rearrangement [1, 11-15] (Scheme 3).



Scheme 2



Scheme 3

In conclusion, we have shown that a one step heterocyclization reaction can take place and allows the formation of C-C and/or C-N bonds when azacyanine **1** was condensed with heterocyclic compounds substitued by an amino group. This simple methodology leads to new heterocyclic compounds with moderate to good yields and is synthetically useful. The biological properties of these compounds is currently being evaluated

EXPERIMENTAL PART

The amines and (dichloromethylene) dimethylammonium chloride were purchased from commercial suppliers and used without further purification. Melting points were taken on a Reichert-Heizbank apparatus and are incorrected. IR were recorded on a Perkin-Elmer 298. Mass Spectra were obtained by GC/MS with electron impact ionization using a 5971 Hewlett Packard instrument at 70 eV. ^{1}H and ^{13}C spectrum were recorded on a Bruker AC 300 Spectrometer (300 MHz and 75 MHz for ^{1}H and ^{13}C respectively). Chemical shifts are expressed in ppm relative to TMS.

A mixture of azacyanine [8] (1.3 g, 5.10^{-3} mol) and amine (5.10^{-3} mol) was refluxed in xylene (25 ml) under dry and inert atmosphere for 24-40 h until disapprarance of starting material (checked by TLC).

The solvent was then removed under reduced pressure and the residue was treated by NaOH (10 %) and extracted by CH_2Cl_2. The organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by chromatography on silicagel with hexane/ethyl acetate as the eluent.

5,7-Bis (dimethylamino) 1,2,4-triazolo-[1, 5-a] 1,3,5-triazine 8

Column chromatography eluant: hexane/ethyl acetate (1:9); yield 46 % ; mp 156 °C (literature [15]: mp 157-158 °C) ; IR (KBr) : 1559, 1582, 1635 (C=N), 2925 and 3082 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.15 (6H, s, $N(CH_3)_2$) , 3.5 (6H, s, $N(CH_3)_2$) , 7.9 (1H, s, CH), ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 36.91 , 39.56, 4C, 2 $N(CH_3)_2$; 149.50, C9 ; 153.51, C2 ; 160.13 , 161.30, 2C, C5 and C7; MS 207 ($M^{+\cdot}$), 192, 178,164,149 ,138, 109, 96.

6,8-Bis (dimethylamino) 1,2,4-triazolo-[1,5-f] 1,2,4-triazine 9

Column chromatography eluant: hexane/ethyl acetate (1:1); yield 61 % ; mp 183 °C ; IR (KBr) : 1534, 1558, 1635 (C=N), 2925 and 3088 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.10 (6H, s, N $(CH_3)_2$) , 3.30 (3H, s, N $(CH_3)_2$) , 3.90 (3H, s, N $(CH_3)_2$) 8.65 (1H, s, CH) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 36.97 , 37.58, 40.08, 4C, 2 N $(CH_3)_2$) ; 135.88, C5; 138.24, C3; 149.98, C6; 157.77,

C8; MS 207 ($M^{+\cdot}$), 192, 178, 163, 149, 137, 109, 95.

2,4-Bis (dimethylamino) 1,2,5-triazino-[1,2-a] benzimidazole 10

Column chromatography eluant: hexane/ethyl acetate (8:2); yield 53 % ; mp 210 °C ; IR (KBr) : 1525, 1577, 1596, 1646 (C=N) and 2920 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 3.1 (6H, s, N $(CH_3)_2$) , 3.3 (6H, s, $N(CH_3)_2$), 7.15 (1 H, t, J = 7 Hz), 7.35 (1 H, t, J = 7 Hz), 7.55 (1 H, d, J = 8 Hz), 7.65 (1H, d, J = 7 Hz) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 36.90 , 40.25 , 4C, 2 N $(CH_3)_2$) ; 113.61 , 117.90 , 119.45 , 124.95 , 4 CH arom.; 126.33 , 144.82, 159.59, 3 C quat.; 156,07 , 156.38, 2C, C2 and C4 ; 159.59, C6; MS 256 ($M^{+\cdot}$), 241, 227, 212, 198, 171, 157, 144, 128, 118.

2,4-Bis (dimethylamino) 8-benzoylquinazoline 11

Column chromatography eluant: hexane/ethyl acetate (1:1); yield 49 % ; mp 210 °C ; IR (KBr) : 1528, 1560, 1600, 1654 (C=N) and 1718 cm^{-1} (C=O) ; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 2.8 (6H, s, $N(CH_3)_2$) , 3.25 (6H, s, $N(CH_3)_2$) , 7.05 (1 H, t, J = 7 Hz), 7.35 (2 H, td, J = 2.27 Hz et J' = 3.25 Hz), 7.45 (1 H, t, J = 4 Hz), 7.65 (1 H, d, J = 6 Hz), 7.80 (2 H, d, J = 7 Hz), 7.95 (1 H, d, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 36.13 , 41.58, 4C, 2 N $(CH_3)_2$) ; 116.24, 118.22 , 119.05 , 127.69 , 128.31 , 129.35 , 131.73 , 131.93 , CH arom.; 111.18 , 135.07 , C quat.; 139.29 , C10; 152.92, 154.84, C2 and C4 ; 164.24, C9; 199.05, CO; MS 320 ($M^{+\cdot}$), 320, 305, 291, 277 , 262, 233, 205, 130, 105, 77.

4,6-Bis (dimethylamino) –2-phenyl [2,3-a] dihydro-3H-pyrazolo [3,4-d] pyrimidin-3-one 12

Column chromatography eluant: hexane/ethyl acetate (7:3); yield 24 % ; mp 214 °C ; IR (KBr) : 1489, 1591, 1639 (C=N), 1690 (C=O), 2922 and 3022 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.3 (1H, s, CH) , 2.4 (12H, s, 2 $N(CH_3)_2$) , 7.20 (1 H, t, J = 7 Hz), 7.35 (2 H, t, J = 8 Hz), 7.95 (2 H, d, J = 8 Hz),; ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 36.98 , 4C, 2 N $(CH_3)_2$) ; 83.17 , C9; 119.83 , 123.64 , 128.53 , CH arom.; 139.83 , C8; 154.19 , 154.95, C4 and C6 ; 158.03, C quat.; 158.95 , CO; MS 298 ($M^{+\cdot}$), 283, 269, 254, 240, 206, 163, 149, 93.

3-Methyl-4,6-bis (dimethylamino) isoxazolo-[5,4-d] pyrimidine 13

Column chromatography eluant: hexane/ethyl acetate (1:1); yield 98 % ; mp 152 °C ; IR (KBr) : 1515, 1542, 1570, 1606 (C=N) and 2926 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 2.5 (6H, s, $N(CH_3)_2$) , 3.2 (6H, s, $N(CH_3)_2$) , 3.15 (6H, s) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 15.98 , CH_3; 36.96 , 39.92 , 4C, 2 N $(CH_3)_2$) ; 88.41 , C9; 152.60 , C3; 159.65 ,160.93 , C4 and C6; 178.74, C8; MS 221 ($M^{+\cdot}$), 206, 192, 177, 163, 149 , 137, 96.

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