SYNTHESIS OF NEW TRIAZOLOTRIAZINONES AND TRIAZOLOTHIATRIAZINONES FROM 5-AMINO 3-ALKYL-1-PHENYL-1,2,4-TRIAZOLES

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Abstract : A variety of triazolothiatriazinones 3 has been prepared by reaction of 5-amino-3-alkyl-1-phenyl-1,2,4-triazoles 1 with isocyanate of chlorosulfonyle. The condensation of substrates 1 with ethyl chloroformiate followed by that of cyanamide leads to new triazolotriazinones 6, whose structures were confirmed by IR, RMN and mass spectroscopy.

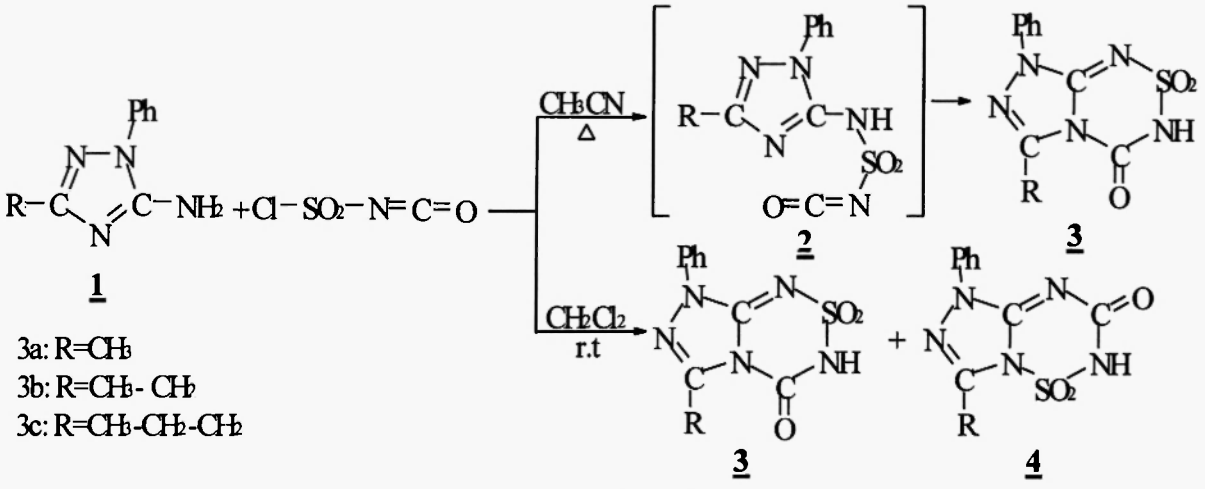
Introduction

A number of studies have been carried out on the reaction of aminotriazoles with bielectrophiles compounds (1-7), which can exhibit various biological activities (8-12). Previously we have shown that 5-amino-3-alkyl-1-phenyl-1,2,4-triazoles 1 are useful binucleophile agents in position 1,3. They react with α-bromoesters, oxalyl chloride (13), imidates *N*- fonctinnalized (14) and enols ethers (15). Most of the reactions lead to the formation of polycondensed heterocyclic compounds. As an extension of our efforts directed toward the study of the reactivity of 5-amino-3-alkyl -1-phenyl-1,2,4-triazoles, in this article we report on the synthesis of new families of triazolothiatriazinones 3 and triazolotriazinones 6 obtained respectively by action of 5-amino-1-phenyl-1,2,4-triazoles with isocyanate of chlorosulfonyle (CSI) and by condensation of substrates 1 with ethyl chloroformiate followed by that of cyanamide.

Result and Discussion

Action of 5-amino N^1 -phenyl-1,2,4-triazoles with isocyanate of chlorosulfonyle

The behaviour of 1 toward some bieleophilic reagents was discussed. Thus, at elevated temperature (16) the treatment of 5-amino-3-alkyl-1-phenyl-1,2,4-triazoles with isocyanate of chlorosulfonyle in reflexing acetonitrile affords a new class of triazolothiatriazinones 3. The formation of the products seems to be obtained by a nucleophilic addition of the extracyclic amine group to sulphur of the sulfonyl chloride group (Scheme-1). The triazolothiatriazinones probably passes by the intermediate 2 which is readily cyclized by the attack of the carbonyl group. At ordinary temperature, the reaction of aminotriazole with isocyanate of chlorosulfonyle in methylene chloride yields the melange of 3 and 4. This reaction is quite analogous to those of 2-aminobenzophenones with CSI (17).

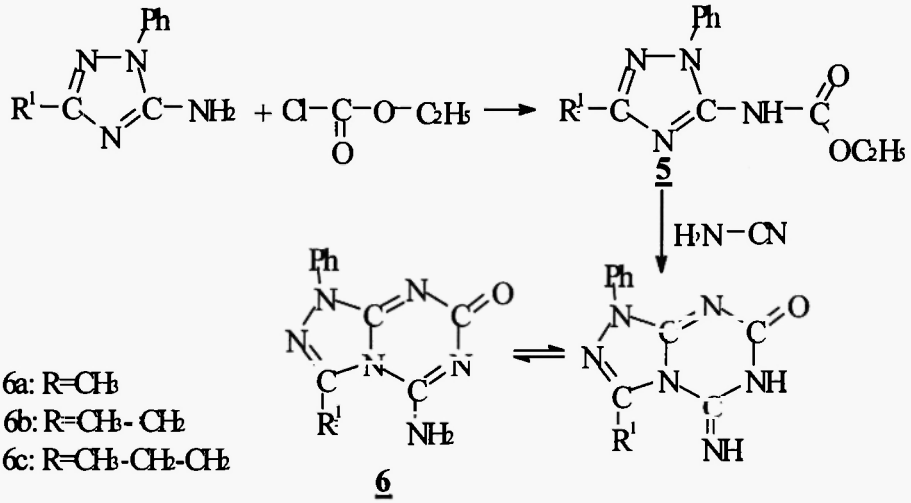


Scheme-1

The structure of compounds 3 is deduced from their IR, mass spectra, ^{1}H and ^{13}C NMR. Indeed, IR spectra of these compounds showed two bands at 3320 cm^{-1} and 1690 cm^{-1} corresponding respectively to NH and C=O groups. ^{1}H NMR spectrum clearly showed the presence of a large singulet at 11ppm assigned to NH proton. ^{13}C confirms without ambiguity the structure of the obtained product. In particular we observe the appearance of the signal of C=O carbon at 159 ppm.

Action of the 5-amino N^{1} -phenyl-1,2,4-triazoles with ethyl chloroformiates followed by that of cyanamide

The reactivity of 5-amino-3-alkyl N^{1}phenyl-1,2,4-triazoles toward electrophilic compounds as ethyl chloroformiate was investigated and furnished amidotriazole 5. On reflexing compound 5 with cyanamide in acetonitrile afforded biheterocyclic compounds 6 of the family of triazolotriazinones (scheme 2).



5a, 6a: R=CH_3
5b, 6b: R=CH_3-CH_2
5c, 6c: R=CH_3-CH_2-CH_2

6

Scheme-2

The structure of all compounds 5 and 6 have been assigned from their analytical data IR, ^{1}H NMR, ^{13}C NMR and mass spectrum. In fact, the ^{1}H NMR spectra of product 5 showed the presence of the signals corresponding to $O-CH_2-CH_3$ group. The IR spectrum revealed the presence of absorption bands at 1700 cm^{-1} and 3280 cm^{-1} assigned for C=O and N-H groups respectively. The ^{1}H NMR spectrum of triazolotriazines 6 indicates the disappearance of all signals corresponding to the $O-CH_2-CH_3$ groups.

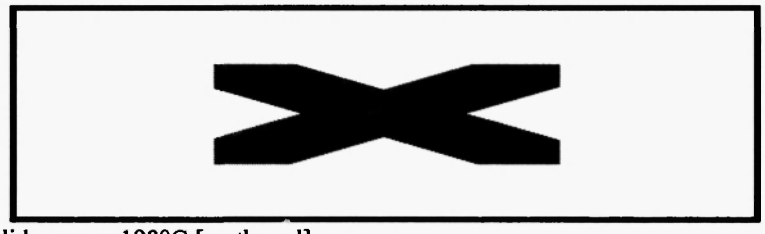
Experimental Part

- I R: Spectra IR were determined for KBr on a JASCO FT-IR-420 spectrometer whose precision is of 2 cm^{-1} covering field 400 - 4000cm^{-1}.
- NMR: The spectra of NMR ^{1} H and NMR ^{13} C were recorded in solution in $CDCl_3$ or in DMSO-d_6 on a spectrometer BRUKER (^{1}H at 300 MHz, ^{13}C at 75 MHz). The chemical shifts are expressed in ppm by using the T.M.S like internal reference. The multiplicities of the signals are indicated by the following abbreviations: S:singulet, D:doublet, T: triplet, Q:quadruplet, m: multiplet and the constants of coupling are expressed in Hz.
- Melting point: The melting points were determined in Electrothermal 9100 apparatus and are not corrected.
- mass Spectrometry: The spectra of mass were carried out on a GC/MS Hewlett-packard 989 A under 70 ev.
- the reactions were monitored by thin layer chromatography (TLC) using aluminium sheets with silica gel 60 F_{254} Merk.
- the 5-amino-3-alkyl-1-phenyl-1,2,4-triazoles 1 are synthesized according to a procedure described in the literature (18).

Synthesis of the Triazolothiatriazinones

Preparation of triazolothiatriazinones 3

To a stirred solution of the appropriate 5-amino-3-methyl-1-phényl-1,2,4-triazoles compound 1.74g (10 mmol) in acetonitrile (25mL) at 82°C is added isocyanate of chlorosulfonyle 0.86 mL (10 mmol) in acetonitrile (5mL) over a period of 20min. Then, triethylamine is added 1.39 mL (10 mmol). The mixture is heated for 3h and the product formed is filtred, washed with water and recristallized from methanol to give triazolothiatriazinones 3.



3a: Yield : 73% white solid. mp = 198°C [methanol].
IR (cm $^{-1}$): $\nu_{C=N}$ = 1685 et 1664, $\nu_{C=O}$ = 1764, ν_{N-H} = 3310.
^{1}H NMR (DMSO-d_6): δ (ppm): 2.55 (s, 3H); 7.37-7.99 (mu, 5H); 11.50 (s, 1H).
^{13}C NMR (DMSO-d_6): δ (ppm): C_1 13.38; C_{arom} 120.48-140.13; C_7 145.32; C_8 151.51; C_9 155.51.
MS: m/e = 279 (M^+); 174 (100); 132 (27); 91 (96); 77 (11); 64 (13).

3b: Yield : 80% white solid: mp = 214°C [methanol].
IR (cm $^{-1}$): $\nu_{C=N}$ = 1690 et 1666, $\nu_{C=O}$ = 1766, ν_{N-H} = 3350.
^{1}H NMR (DMSO-d_6): δ (ppm): 1.28 (t, 3H); 3.01(q, 3H); 7.36-7.98 (mu, 5H); 11.49 (s, 1H).
^{13}C NMR (DMSO-d_6): δ (ppm): C_2 10.52; C_3 20. 69; C_{arom} 120.59-141.22; C_7 145.26; C_8 151.70; C_9 155.47.
MS: m/e = 293 (M^+); 188 (100); 146 (24); 91 (80); 77 (12); 64(10).

3c: Yield : 75% white solid: mp = 248°C [methanol].
IR (cm $^{-1}$): $\nu_{C=N}$ = 1683 et 1662, $\nu_{C=O}$ = 1760, ν_{N-H} = 3320.
^{1}H NMR (DMSO-d_6): δ (ppm): 0.96 (t, 3H); 1.42 (m, 2H); 2.19 (t, 2H); 7.11-7.83 (m, 5H); 10.45 (s, 1H).
^{13}C NMR (DMSO-d_6): δ (ppm): C_4 14.16; C_5 21. 16; C_6 30.24; C_{arom} 118.80-137.76; C_7 148.26; C_8 150.25; C_9 159.55.

Preparation of the Triazolotriazinones

Action of 5-amino-3-alkyl-1-phenyl-1,2,4-triazoles with ethyl chloroformiate
To a solution of the appropriate 5-amino-3-methyl-1-phenyl-1,2,4-triazole 1.74g (10 mmol) in dry chloroform (5 mL) was added pyridine 0.96 mL (12 mmol) at 0°C. After 30min, ethyl chloroformiate 1.33 mL (14 mmol) in chloroform was slowly added. The mixture was stirred for 2h then hydrolysed. The residue is purified by chromatography on column [chloroform/methanol].

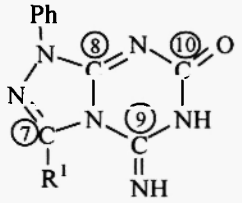
5a: Yield : 95% .
IR (cm $^{-1}$): $\nu_{C=N}$ = 1675, $\nu_{C=O}$ = 1702, ν_{N-H} = 3280.
^{1}H NMR ($CDCl_3$): δ (ppm): 1.01(t, 3H); 2.35(s, 3H); 3.92(q, 2H); 7.26-7.51(mu, 5H); 10.27(s, 1H).
^{13}C NMR ($CDCl_3$): δ (ppm): C_1 10.26; C_7 62.13; C_8 13.99; C_{arom}123.11-139.79; $C_9$145.97; C_{10}153.73; C_{11} 164.66.

5b: Yield : 93% .
IR (cm $^{-1}$): $\nu_{C=N}$ = 1664, $\nu_{C=O}$ = 1711, ν_{N-H} = 3200.
^{1}H NMR ($CDCl_3$): δ (ppm): 0.99(t, 3H); 1.30(t, 3H); 2.72(q, 2H); 3.91(q, 2H); 7.26-7.50; (m, 5H); 10,47(s, 1H).
^{13}C NMR ($CDCl_3$): δ (ppm): C_2 12.36; C_8 14.12; C_3 21.66; C_7 62.08; C_{arom} 122.91-137.89; C_9 146.99; C_{10} 153.47; C_{11} 162.97.

5c: Yield : 90% .
IR (cm $^{-1}$): $\nu_{C=N}$ = 1673, $\nu_{C=O}$ = 1709, ν_{N-H} = 3273.
^{1}H NMR ($CDCl_3$): δ (ppm): 0.98(t, 3H); 1.02(t, 3H); 1.39(m, 2H); 2.17(t, 2H); 3.94(q, 2H); 7.21-7.75 (m, 5H); 10,31(s, 1H).
^{13}C NMR ($CDCl_3$): δ (ppm): C_4 12.86; C_8 14.31; C_5 21. 24; C_6 31.12; C_7 63.19; C_{arom} 121.41-140.19; C_9 148.89; C_{10} 152.77; C_{11} 168.17.

Action of compound 5 with cyanamide

A mixture of compound 5 (10 mmol) and 0.42g (10 mmol) of cyanamide in 25mL of acetonitrile was heated for 3h. The trizolotriazinone 6 that cristallized after cooling at room temperature was filtered and washed with chloroform.



① ② ③ ④ ⑤ ⑥
CH_3-; CH_3-CH_2-; $CH_3-CH_2-CH_2-$

6a: Yield = 82% white solid: mp = 229°C [methanol].
IR (cm^{-1}): $\nu_{C=O}$ = 1707, $\nu_{C=N}$ = 1653, ν_{N-H} = 3384.
^{1}H NMR (DMSO-d): δ (ppm): 2.51(s, 3H); 7.35-8.01(mu, 5H); 6.47(s, 1H); 10.11(s, 1H).
^{13}C NMR (DMSO-d): δ (ppm): C_1 14.28; C_{arom} 120.57-137.47; C_7 142.77; C_8 151.65; C_9 154.60; C_{10} 156.93.

6b: Yield= 85% white solid: mp = 220°C [methanol].
IR (cm^{-1}): $\nu_{C=O}$ =1700, $\nu_{C=N}$ = 1648 , ν_{N-H} =3330.
^{1}H NMR (DMSO-d): δ (ppm): 1.29(t, 3H); 3.13(q, 2H); 7.36-8.01(m, 5H); 6.70(s, 1H); 10.28(s, 1H).
^{13}C NMR (DMSO-d): δ (ppm): C_7 10.79; C_3 21.67; C_7 143.87; C_8 148.63; C_9 151.81; C_{arom} 120.74-136.62; C_{10} 154.53.

6c: Yield = 80% white solid: mp = 210°C [methanol].
IR (cm^{-1}): $\nu_{C=O}$ =1712, $\nu_{C=N}$ = 1634 , ν_{N-H} =3294.
^{1}H NMR (DMSO-d): δ (ppm): 0.99 (t, 3H); 1.37(m, 2H); 2.21 (t, 2H); 7.14-7.89(m, 5H); 6.41(s, 1H); 10.32(s, 1H).
^{13}C NMR (DMSO-d): δ (ppm): C_4 14.16; C_5 21. 16; C_6 30.24; C_{arom} 120.57-137.47; C_7 143.71; C_8 151.65; C_9 154.60; C_{10} 156.93.

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