SYNTHESIS AND CHARACTERISATION OF SOME 1-ARYL-5-MORPHOLINO Δ^2-1,2,3-TRIAZOLINES WITH BIOLOGICAL POTENTIAL

M. Hamadouche, D. El Abed

Laboratory of Applied Synthesis Organic, Department of Chemistry, Faculty of Sciences, University of Oran Es-Sénia, BP 1524, El M'naouer, 31100 Oran, Algeria

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ABSTRACT : The addition of arylazides to β-aminomethacrylic esters and nitriles led to 1-aryl-5-morpholino Δ^2-1,2,3-triazolines with good yields. The structure of these heterocycles with promising biological profile was determined by usual spectroscopic methods : IR, NMR and conforted by mass spectrometry.

Keywords : Arylazides, Enamines, 1,3 Dipolar Cycloaddition, Triazolines, Spectroscopic Analysis.

RESUME : L'addition d'arylazides aux esters et nitriles β-aminométhacryliques conduit aux 1-aryl-5-morpholino Δ^2-1,2,3-triazolines avec de bons rendements. La structure de ces hétérocycles triazotés à 5 chaînons, composés à activité biologique potentielle, a été déterminée par spectroscopie IR, de RMN du ^1H et du ^{13}C et par spectrométrie de masse.

Mots clés : Arylazides, Enamines, Cycloaddition Dipolaire-1,3, Triazolines, Analyse Spectroscopique.

INTRODUCTION

The different synthetic methods of Δ^2-1,2,3-triazolines are : cyclisation of triazenes and isomerisation of nitrogen containing heterocycles[1], 1,3-dipolar cycloaddition of either diazocompounds to imines[2] or azides to alkenes[3].

1,2,3-triazolines and their derivatives represent an important group of compounds used in organic chemistry not only for their application in organic synthesis but also for their biological activities[4]. They are a structural unit appearing in many biologically active natural products[5].

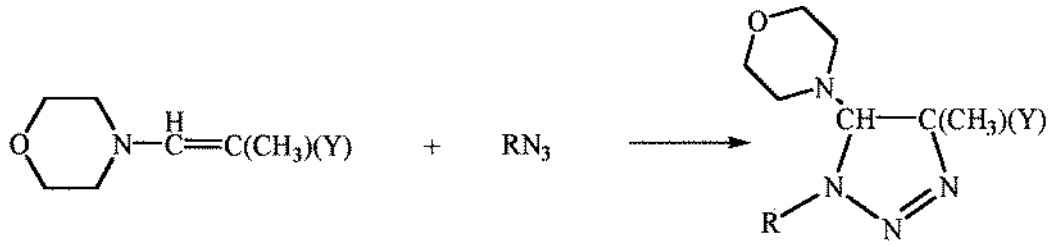
The interesting results obtained in our laboratory about the synthesis and biological activity of 1,2,3-triazolines have incited us to extend this study to other azides in order to examine the influence of the substituents of the phenyl group of azide on biological activity. The results of the biological tests are published elsewhere[6].

In this communication, we report herein the synthesis of some 1-aryl-5-morpholino Δ^2-1,2,3-triazolines **3** by 1,3-dipolar cycloaddition (scheme 1).

RESULTS AND DISCUSSION

1,3-dipolar cycloaddition of arylazides with enaminoesters (Y= CO_2CH_3) and nitriles (Y= CN) have been studied in some details[7].

In our case we have found that arylazides **2** reacted with enamines **1** affording triazolines **3** with good yields in stereo-and regioselective fashion (scheme 1). In each case, only one regiosomer was formed in agreement with the molecular-orbital approach and with previously reported results of the reaction between arylazides and electron rich olefins, such as enamines[3c,8,9]. Thus triazolines **3** should bear the morpholino group at 5-position and nitrile or carboxylate group at 4-position[10].



1 **2** **3**

1 { enamine Z (Y = CN)
enamine E (Y = CO_2CH_3)

2 = R = *m*nitroC_6H_4, *p*nitroC_6H_4, (2,4)-dichloroC_6H_3, *p*$CH_3C_6H_4SO_2$

Scheme 1 : Reactions of arylazides **2** with enamines **1**.

Futhermore, the reaction is stereospecific, to that effect it is known that the addition of arylazides to enamines (Z) affords cis-triazolines whereas the (E) isomer lead to the trans cycloadduct[11].

The assignment of the triazoline structures was based on the analysis of the ^1H, ^{13}C and DEPT NMR spectra.

Further examination of the ^1H and ^{13}C NMR spectra is consistent with triazoline structures. In the ^1H NMR spectra, the proton fixed on the carbon C5 resonates around 5 ppm (singlet), and it is shifted to a lower field when it is an position cis in relation to electron withdrawing substituent [7a].

The methyl group appeared between 1.65 and 2.43 ppm, the others signals are attributable to skeleton morpholino, aryls and ester function methyl (3.74 – 3.77 ppm), while the ^{13}C NMR shows signals at 115.7 ppm and 117.6 ppm assignable to the carbon bonded to the nitrile group and at 170.3 ppm relative to the carbon of the ester group.

The infrared spectra of the triazolines **3** showed a strong band at 2240-2360 cm^{-1} region due to $\nu_{(C\equiv N)}$ for **3a**, **3c**, **3d** and **3e**. In the cases of triazolines **3b**, **3'b** and **3f**, the IR spectra exhibit a new band in the 1735 cm^{-1}range, attributed to the $\nu_{(C=O)}$ of the ester group ($COOCH_3$).

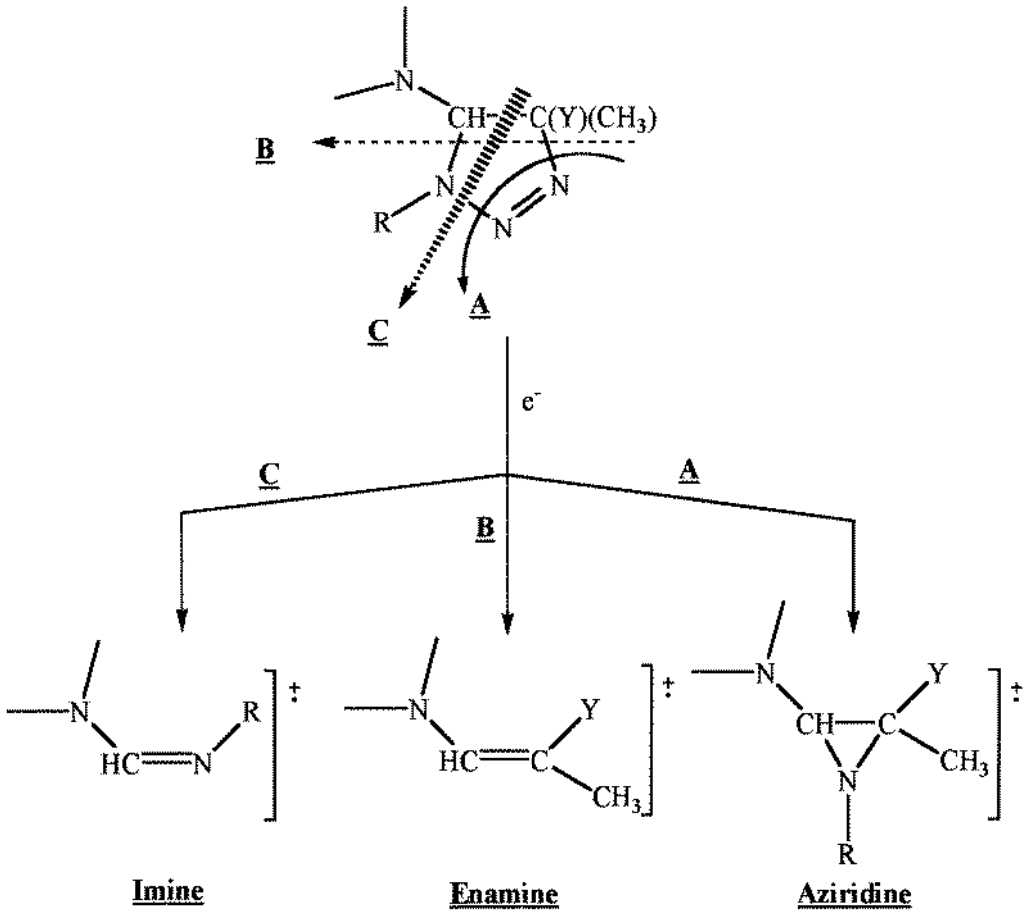
All data were in complete agreement with the mass spectra of **3a**, **3b**, **3'b** and **3c**.

The direct introduction in the source was made at temperatures close to their melting points (140°C). The mass spectra of the triazolines are similar.

The main fragments observed on the mass spectra and their relative abundances are listed in experimental section. The obtained fragments allow us to disengage a general scheme of the rupture (scheme 2).

The put in evidence of the fragments which correspond to the rupture according to A, B, and C seems to confirm the regiochemistry of the cycloaddition.

It was ohserved that the peaks corresponding to an inverse orientation are pratically absent on the mass spectra.



Scheme 2

This study indicates that the mass spectrum of the triazolines is the superposition of the mass spectra corresponding to aziridines, enamines and imines.

EXPERIMENTAL SECTION

Melting points were determined with Kofler hot and Buchi 530. The IR spectra were recorded on a Perkin Elmer 298 infrared spectrometer. The samples are analyzed in solution. A Varian EM 360 spectrometer was employed for ^{1}H NMR spectra. ^{13}C NMR spectra were obtained with a Bruker AC 200 (50,3 Hz). The degree of substitution of the C atoms was determined by DEPT methods. All NMR spectra were obtained using $CDCl_3$ as solvant and with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet) or m (multiplet).

Mass spectra were recorded at 70 eV electron energy with Varian Mat 311 instrument with GC linkage. Intensity of emission current is 300 μA and acceleration voltage of the ions is 2,3 kV. Data are reported in the form m/e (intensity relative to base = 100).

Preparation of products

Azides

The nitrosubstituted arylazides derivatives were obtained according to the Noelting and Michel method[12]. Tosylazide was prepared by reacting sodium azide and the corresponding halogenated derivative[13].

Arylazides are generally characterized by a band IR in the 2100 - 2150 cm^{-1} region, due to ν (N_3)[14].

β-Aminomethacrylic esters and nitriles

These olefines were obtained through a nucleophilic substitution of vinylic halogenide of a β-bromo-methacrylic ester and nitrile, according to the described method in the literature[15].

1,2,3-Triazolines

A solvent less equimolar mixture of arylazide **2** and enamine **1** was heated on an oil bath at 62°C, over a period of time varying 3 - 8 hours, depending to the substrates used. The solid product was recrystallized in a minimum of ethanol.

4-Cyano-4-methyl-5-morpholin-4-yl-1-(4-nitro-phenyl)-Δ^2-1,2,3-triazoline **(3a)** formed yellow crystals ; m.p. 149 °C; yield 51%. ^{1}H NMR ($CDCl_3$) : δ (ppm) = 1.65 (s, 3H, Me), 3.62 - 3.64 (m, $8H_{amin}$), 4.88 (s, 1H), 7.58 - 8.33 (m, $4H_{arom.}$). ^{13}C NMR ($CDCl_3$) : δ (ppm) = 75.47 (C-4), 81.80 (C-5), 115.75 (C≡N), 116.62-144.72(C_{arom}). IR : $\nu_{C\equiv N}$ = 2360-2240 cm^{-1}, $\nu_{N=N}$ = 1500-1400 cm^{-1}. MS (EI) *m/z* (relative intensity) : 316 [$M^{+\cdot}$], m/z : 288 ($M^{+\cdot}$-$N_2^{+\cdot}$), 261 ($M^{+\cdot}$-$N_2^{+\cdot}$-$HCN^{+\cdot}$), 152 ($M^{+\cdot}$-$RN_3^{+\cdot}$).

4-Carbomethoxy-4-methyl-5-morpholin-4-yl-1-(4-nitro-phenyl)-Δ^2-1,2,3-triazoline **(3b)** formed yellow crystals ; m.p. 118 °C; yield 41%. ^{1}H NMR ($CDCl_3$) : δ (ppm) = 1.78 (s, 3H, Me), 3.52 - 3.54 (m, $8H_{amin}$), 3.74 (s, 3H, OMe), 5.36 (s, 1H), 7.54 - 8.23 (m, $4H_{arom}$). ^{13}C NMR ($CDCl_3$): δ (ppm) =78.70 (C-4), 86.77 (C-5), 115.71-145.51 (C_{arom}), 170.25 (C_{ester}). IR : $\nu_{C=O}$ = 1735.3 cm^{-1}, $\nu_{N=N}$ = 1596.8-1517.4 cm^{-1}. MS (EI) *m/z* (relative intensity) : 349 [$M^{+\cdot}$], m/z : 321 ($M^{+\cdot}$-$N_2^{+\cdot}$), 320 ($M^{+\cdot}$-$N_2^{+\cdot}$-$H^{+\cdot}$), 185 ($M^{+\cdot}$-$RN_3^{+\cdot}$).

4-Carbomethoxy-4-methyl-5-morpholin-4-yl-1-(3-nitro-phenyl)-Δ^2-1,2,3-triazoline **(3'b)** formed yellow crystals ; m.p. 126 °C; yield 38%. ^{1}H NMR ($CDCl_3$) : δ (ppm) = 1.79 (s, 3H, Me), 3.53 - 3.55 (m, $8H_{amin}$), 3.74 (s, 3H, OMe), 5.41 (s, 1H), 7.55 - 8.22 (m, $4H_{arom.}$). ^{13}C NMR ($CDCl_3$) : δ (ppm) = 76.03 (C-5), 79.59 (C-4), 110.39-148.84 (C_{arom}), 170.20 (C_{ester}). IR : $\nu_{C=O}$ = 1730 cm^{-1}, $\nu_{N=N}$ = 1500-1400 cm^{-1}. MS (EI) *m/z* (relative intensity) : 349 [$M^{+\cdot}$], m/z : 321 ($M^{+\cdot}$-$N_2^{+\cdot}$), 320 ($M^{+\cdot}$-$N_2^{+\cdot}$-$H^{+\cdot}$), 185 ($M^{+\cdot}$-$RN_3^{+\cdot}$).

4-Cyano-4-methyl-5-morpholin-4-yl-1-(toluene-4-sulfonyl)-Δ^2-1,2,3-triazoline **(3c)** formed white crystals ; m.p. 156 °C; yield 54%. ^{1}H NMR ($CDCl_3$) : δ (ppm) = 1.71 (s, 3H, Me), 2.43 (Me_{arom}), 3.71 - 3.80 (m, $8H_{amin}$), 5.60 (s, 1H), 7.28 - 8.21 (m, $4H_{arom.}$).^{13}C NMR ($CDCl_3$) : δ (ppm) = 50.24 (C-4), 81.0 (C-5), 117.57 (C≡N), 129.35-158.95 (C_{arom}). IR : $\nu_{C\equiv N}$ = 2361.1 cm^{-1}, $\nu_{N=N}$ = 1558.1-1444.9 cm^{-1}. MS (EI) *m/z* (relative intensity) : 349 [$M^{+\cdot}$], m/z : 321 ($M^{+\cdot}$-$N_2^{+\cdot}$), 268 ($M^{+\cdot}$-$MeC(CN)N_2^{+\cdot}$), 152 ($M^{+\cdot}$-$RN_3^{+\cdot}$).

4-Cyano-4-methyl-5-morpholin-4-yl-1-(3-nitro-phenyl)-Δ^2-1,2,3-triazoline **(3d)** formed yellow crystals ; m.p. 152 °C; yield 48%. ^{1}H NMR ($CDCl_3$) : δ (ppm) = 1.66 (s, 3H, Me), 3.61 - 3.63 (m, $8H_{amin}$), 4.92 (s, 1H), 7.84 - 8.19 (m, $4H_{arom.}$). ^{13}C NMR ($CDCl_3$) : δ (ppm) = 75.47 (C-5), 79.66 (C-4), 117.57 (C≡N), 110.01-146.03 (C_{arom}). IR : $\nu_{C\equiv N}$ = 2260-2240 cm^{-1}, $\nu_{N=N}$ = 1540-1420 cm^{-1}. MS (EI) *m/z* (relative intensity) : 316 [$M^{+\cdot}$], m/z : 288 ($M^{+\cdot}$-$N_2^{+\cdot}$), 152 ($M^{+\cdot}$-$RN_3^{+\cdot}$).

4-Cyano-4-methyl-5-morpholin-4-yl-1-(2,3-dichloro-phenyl)-Δ^2-1,2,3-triazoline **(3e)** formed brown crystals ; m.p. 154 °C; yield 52%. ^{1}H NMR ($CDCl_3$) : δ (ppm) = 1.69 (s, 3H, Me), 3.52 - 3.56 (m, $8H_{amin}$), 5.29 (s, 1H), 7.32 - 7.74 (m, $3H_{arom.}$). ^{13}C NMR ($CDCl_3$) : δ (ppm) = 55.4 (C-5), 93.9 (C-4), 116.50 (C≡N), 111.43-148.67 (C_{arom}). IR : $\nu_{C\equiv N}$ = 2350-2230 cm^{-1}, $\nu_{N=N}$ = 1500-1430 cm^{-1}. MS (EI) *m/z* (relative intensity) : 321 [$M^{+\cdot}$], m/z : 293 ($M^{+\cdot}$-$N_2^{+\cdot}$), 152 ($M^{+\cdot}$-$RN_3^{+\cdot}$).

4-Carbomethoxy-4-methyl-5-morpholin-4-yl-1-(2-chloro-4-nitro-phenyl)-Δ^2-1,2,3-triazoline **(3f)** formed orange crystals ; m.p. 162 °C; yield 20%. ^{1}H NMR ($CDCl_3$) : δ (ppm) = 1.78 (s, 3H, Me), 3.52-3.54 (m, $8H_{amin}$), 5.30 (s, 1H), 7.55 - 8.23 (m, $3H_{arom.}$). ^{13}C NMR ($CDCl_3$) : δ (ppm) = 69.66 (C-4), 91.30 (C-5), 115.05-144.34 (C_{arom}), 170.50 (C_{ester}). IR : $\nu_{C=O}$ = 1735 cm^{-1}, $\nu_{N=N}$ = 1500-1450 cm^{-1}. MS (EI) *m/z* (relative intensity) : 383 [M^+], m/z : 355 ($M^{+\cdot}$-$N_2^{\cdot+}$), 185 ($M^{+\cdot}$-$RN_3^{\cdot+}$).

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