Heterocyclic Letters
Vol. 8| No.3|647-656|May-July|2018
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

FREE SOLVENT MICROWAVE-ASSISTED SYNTHESIS OF (1,2,3)-TRIAZOLINES

Amina Chenni, Mohammed Hamadouche*and Douniazed El Abed

Laboratoire de Chimie Fine, Département de Chimie, Faculté des Sciences Exactes et Appliquées, Université Oran1 Ahmed Ben Bella, BP 1524 El M'naouar, Oran, Algérie.
** hamadouchemed@yahoo.fr*

Abstract
The triazoline and its derivatives are a class of heterocyclic that attracted much attention because their pharmaceuticals activities such as antibacterial, antitumor and antifungal. In this paper, we present syntheses of some new 1-aryl-5-morpholino (1,2,3)-triazolines by 1,3-dipolar cycloaddition from arylazides and β-amino methacrylic esters and nitriles where it is shown that microwave-assisted synthesis of triazolines proceeds very rapidly under solvent-free conditions and provides better yields. The products were obtained in good to high yields within few minutes. The newly synthesized compounds were characterized by spectral data (IR, ^{13}C NMR, ^{1}H NMR and MS).

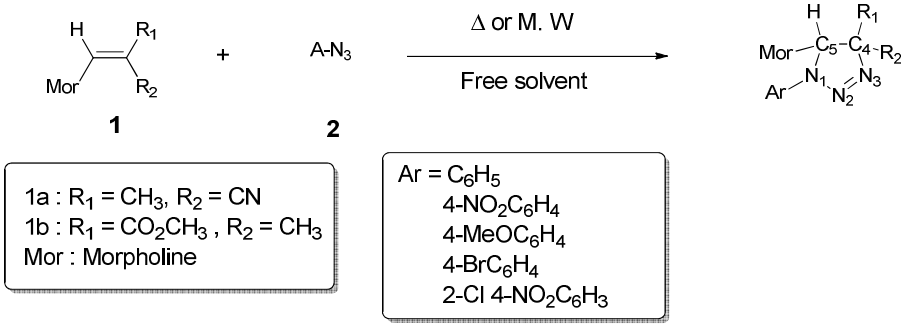
Keywords: enamines ; organic azides ; 1,3-dipolar cycloaddition ; triazolines ; microwave-assisted.

Introduction

Heterocycles constitute the majority of molecules used in industry (dyes, agricultural products, polymers and drugs) and are the subject of active research worldwide [i]. It is noted that two-thirds of the organic compounds known in the literature are heterocycles. The triazoline or triazole units, tri-nitrogen pentagonal heterocycles, incorporated in other structures form a class of compounds with very interesting properties including antidiabetic, [ii] antitubercular, [iii] anti-inflammatory, [iv] antifungal, [v] antiviral [vi] and antibacterial [vii]. As a result, heterocyclic chemistry has become the focus of interest for a large community of chemists.
The "click" chemistry is an extremely interesting method of synthesis for the preparation of heterocycles because it combines a reaction set whose main characteristics and advantages are to be fast, simple to implement and give high yields. Moreover, the "click" chemistry reactions do not require purification and are tolerated by numerous functional groups [viii]. The most studied and most representative "click" chemistry reaction is 1,3-dipolar cycloaddition, it belongs to a fairly widespread category of reactions and on which numerous studies have been carried out, notably by Huisgen in 1963 [ix], which has exhaustive study of possible reactions between dipoles (azide, diazoalkane, nitrile, etc.) and dipolarophils (alkyne, alkene) to yield a wide variety of five-membered heterocycles [x].

Microwave chemistry is a technique increasingly used in the field of chemistry "click" simple to implement, fast and selective, it has many interests. 1,3-cycloaddition reactions by click chemistry can be coupled with microwave activation. While leading to similar yields, this approach reduces reaction times from hours to minutes [xi].

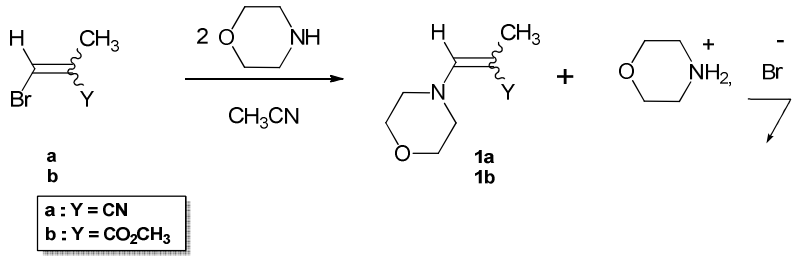
Our study concerns the synthesis of triazolines formed by 1,3-dipolar cycloaddition reaction involving enamines as dipolarophiles and organic azides as dipoles. Microwave heating has taken an indisputable place in the field of organic synthesis as a very efficient and non-polluting activation method [xii]. In our opinion, little work on the synthesis of triazolines activated by microwaves has been carried out. It seemed interesting to activate the reaction of enamines **1** with organic azides **2** by microwaves (reaction which requires a continuous heat supply by conventional heating), without using organic solvents (solvents which are expensive, toxic, not recyclable and therefore pollution generators) **Scheme 1**. The heterocycles obtained during this study will be subjected to *in vitro* antifungal tests in the course of our work.



Scheme1. Formation of 1,2,3-Triazolines by Microwave-Assisted 1,3-Dipolar Cycloaddition of enamines **1** with azido compounds **2**

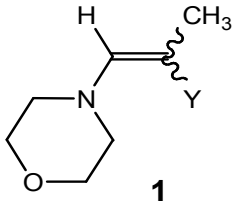
Results and discussion

Preparation of starting product : The addition of *morpholine* at room temperature to the *β bromide* derivatives [xiii] in solution in acetonitrile leads to the *enamines* **1** [xiv]. In all cases, the products are purified by recrystallization from *ethyl alcohol* at 95 ° (**Scheme 2**), the physical characteristics of the *enamines* **1** as well as the procedures employed are summarized in **Table 1**.



Scheme2. Synthesis of enamines **1**

Table1. Physical characteristics and yields of obtained enamines **1**

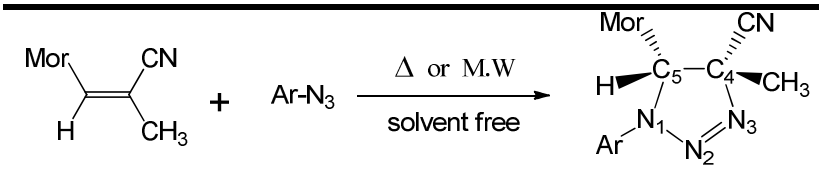


1

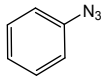
Entry	Geometry	Reaction Solvent	Time (Days)	Yield (%)	mp (°C)	IR (ν cm $^{-1}$)		
						CN	CO	C=C
1a	Z	CH_3CN	40	97	60-62	2177	-	1628
1b	E	CH_3CN	40	99	58-59	-	1720	1605

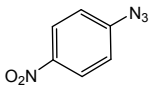
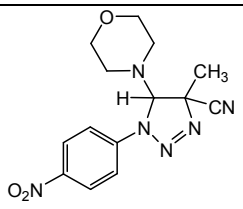
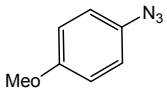
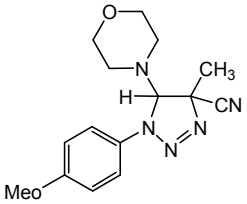
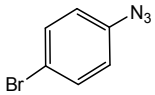
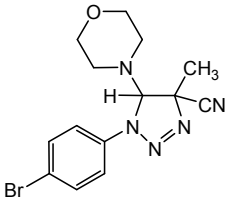
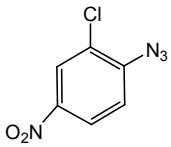
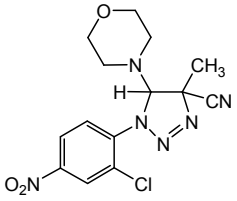
Reaction of *Z- 3-morpholinomethacrylonitrile* **1a** with *para-nitrophenylazide* without solvent and under microwave irradiation gave the desired *4-methyl-5-morpholino-1-(4-nitrophenyl)-4,5-dihydro-1H-1,2,3-triazole-4-carbonitrile* **3a** in high yield and in short reaction time compared to thermal heating (**Table 2, Entry1**). The crude product was obtained with a high purity without the need of any purification steps. Identification of **3a** was done by IR and NMR. The IR spectrum of **3a** showed a sharp absorption band at 2240 cm^{-1} for (C≡N) group. 1H NMR spectrum of compound **3a** showed a singlet in 4.86 ppm for H in position 4 of the triazoline ring and one singlet at 1.64 ppm for methyl hydrogenes in position 5 to ring nitrogen. Two resonances by (75,4 and 81,8ppm), indicate displacement of carbon atom attached to 4 and 5-position of the triazoline ring. With this encouraging result in hands we performed reaction of some *bromo* and *methoxy* and *chloro nitro aromatic azide* with *enamine* under microwave irradiation (**Table 2**).
Similarly, the reaction of *Z-3-morpholinomethacrylonitrile* with *2-chloro 4-nitro phenylazide* gave the desired *1-(2-chloro-4-nitrophenyl)-4-methyl-5-morpholino-4,5-dihydro-1H-1,2,3-triazole-4-carbonitrile* **3e** in a good yield.

Table 2. Triazolines **3** prepared from Z- 3-morpholinomethacrylonitrile[a]



1a **2(a-e)** **3(a-e)**

Entry	Azide	Product	Yield (%) (Time/h)[b]	Yield (%) (Time/min)[c]
1	 **2a**	-	-	-

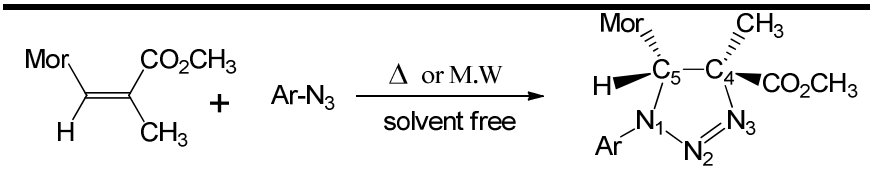
2	 **2b**	 **3b**	91(24)	99(1)
3	 **2c**	 **3c**	50(20)	82(4)
4	 **2d**	 **3d**	19(24)	80(2)
5	 **2e**	 **3e**	86(8)	91(1)

[a] Reaction conditions : Z- 3-morpholinomethacrylonitrile **1** (0,30 mmol, 1 equiv.), organic azide **2** (0,30 mmol, 1 equiv.). [b] Conventional heating at 60°C. [c] Under microwave irradiation.

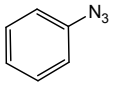
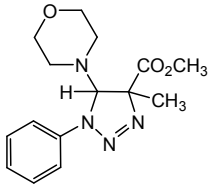
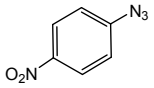
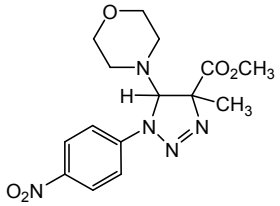
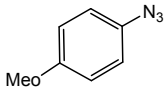
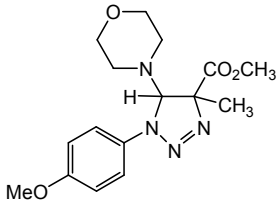
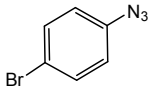
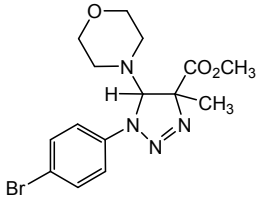
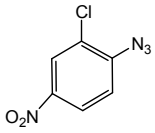
As exemplified in **Table 2**, the reactions proceeded smoothly to completion, and the products were isolated in excellent yields and high purity. The *para-methoxyphenyl* and *para-bromophenyl* derivatives **2c** and **2d** were found to be less reactive than the others. However, the reactions were finished in 4 min and 2 min, and products **3c** and **3d** were isolated in 82% and 80% yields, respectively. In addition, the reaction of *phenylazide* **2a** with the same *enamine* **1a** under above conditions did not give the expected product due to the low reactivity of the phenyl group.

In order to assess the scope of the reaction, we next examined the variety of *azides* **(2a-e)** under the same conditions as the first reaction (conventional heating at 60°C and microwave irradiation without solvent), this set *azides* was examined due to commercial availability and chemical functionality. Reaction of organic *azide*s **2** with *α-carbomethoxy, β-morpholino-methacrylic* **1b** were carried out, and the results are collected in **Table 3**.

Table 3. Triazolines **4** prepared from E- 3-morpholinomethylmethacrylate [a]

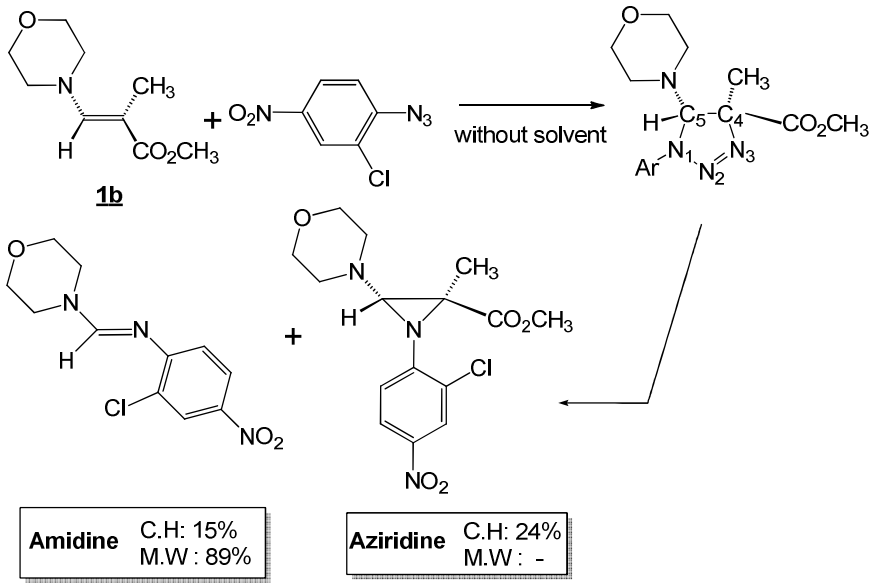


1b **2(a-e)** **4(a-e)**

Entry	Azide	Product	Yield (%) (Time/h)[b]	Yield (%) (Time/min)[c]
1	 **2a**	 **4a**	50(96)	46(1)
2	 **2b**	 **4b**	98(24)	99(1)
3	 **2c**	 **4c**	20(20)	82(4)
4	 **2d**	 **4e**	28(24)	80(2)
5	 **2e**	-	-	-

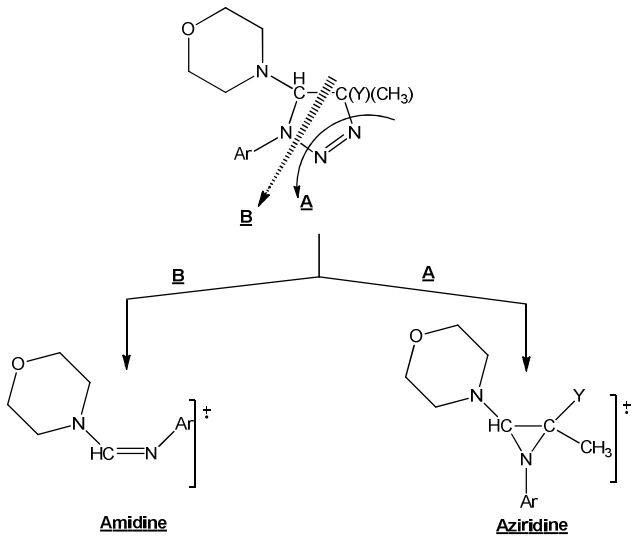
[a] Reaction conditions : E- 3-morpholinomethylmethacrylate **1b** (0,30 mmol, 1 equiv.), organic azide **2** (0,30 mmol, 1 equiv.).
[b] Conventional heating at 60°C. [c] Under microwave irradiation.

The *phenylazide* **2a** reacts also with *E-3-morpholino methylmethacrylate* **1b** in equimolar amount (0,30 mmol; 0,30 mmol) and placed without solvent under microwave irradiation to give *the methyl 4-methyl-5-morpholino-1-phenyl-4,5-dihydro-1H-1,2,3-triazole-4-carboxylate* **4a** with a low yield compared to other products because of their low reactivity. IR spectrum of compound **4a** revealed absorption bands ν_{max} =1724 cm^{-1} assignable to the C=O of the ester groups. The 1H NMR spectrum of **4a** revealed signals as expected. The reaction of *4-nitrophenylazide* **2b**, *4-methoxyphenylazide* **2c**, *4-bromophenylazide* **2d** with *E-3-morpholino methylmethacrylate* **1b** under above conditions led to the corresponding triazolines respectively **4b**, **4c** and **4d** with an excellent yield. Their 1H NMR spectrum are reflected, in particular, by the presence of a singlet between δ= 5.28 ppm and δ= 5.37 ppm relative to the carbon-bound proton in position 5 of triazoline ring. In the 13C NMR spectrum of the isolated triazolines, one pic corresponding to the carbon of the ester group is observed between 170.3 ppm and 171.4 ppm. The reaction of *2-chloro, 4-nitrophenylazide* with *enamine* **1b** does not lead to the expected triazoline, but to a mixture of *amidine* **4e** and *aziridine* **4f** in conventional heating, and only to the *amidine* by microwave (**Scheme 3**).



Scheme 3. Reaction of obtaining of amidine **4e** and aziridine **4f**

The *aziridine* **4f** has a resonance signal to 3.5 ppm corresponding to the aziridine proton, the latter is shielded from the triazolinic proton (4.7 < δ< 6.0 ppm). IR spectrum of compound **4e** revealed absorption bands ν_{max} = 1614 cm^{-1} assignable to the (C=N).In order to confirm the structure of the heterocycles obtained from *β-morpholinomethacryl esters* **1b**, we recorded and studied their mass spectra. We were able to identify a general cut-off scheme for triazolines; the way **B** leads by 1,3-dipolar retrocycloaddition to *amidine* **4e**, and the way **A** leads to *aziridine* **4f** by nitrogen loss as shown in **Scheme 4**.



Scheme 4. General fragmentation of triazolines by mass spectra

From the point of view of the stereospecificity of the 1,3-dipolar cycloaddition reaction, the results set out above show that the reaction leads to a single triazoline unless otherwise indicated, so it is well established that this reaction is stereospecific. Given the existence of a single orientation of the addition and previously developed arguments, we attributed the same sequence to all the compounds obtained (carbon bearing the ester or nitrile group bound to the unsubstituted nitrogen).

Experimental Section

General procedure for the preparation of enamine 1

A solution of 2.1 mL (24 mmol) of morpholine dissolved in 5 mL of anhydrous acetonitrile was added slowly to 12 mmol of bromide derivative dissolved in 5 mL of anhydrous acetonitrile, the resulting solution was then left at room temperature. After 40 days of reaction, the solution was filtered, The solvent was removed, and the isolated enamines **1** were recrystallized from ethanol at 96 ° to gave a pure product for the next reaction.

Enamine 1a was obtained as a beige solid in 97% yield; m.p 60-62°C; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.80 (d, *J*=0.9 3H), 3.42 (t, *J* = 4.9 4H), 3,69 (t, *J* = 4.9 4H), 6.14 (s, 1H); ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 18.7, 49.3, 50.1, 66.4, 66.7, 69.9, 122.0, 148.5; IR (ATR): 1628, 2177 cm^{-1}.

Enamine 1b was obtained as a white solid in 99% yield; m.p 58-59°C; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.92 (d, *J*=0.9 3H), 3.39 (t, *J*=4.9 4H), 3.67 (s, 3H), 3.69 (t, *J* = 4.9 4H), 7.22 (s, 1H); ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 12.5, 49.4, 50.0, 52.3, 66.5, 66.8, 86.3, 147.6, 165.0. IR (ATR): 1605, 1720 cm^{-1}.

General procedure for the synthesis of 1,2,3-triazolines 3 and 4 :

The organic azide **2 (**0,30 mmol) and enamine **1 (**46 mg,0.30 mmol) were mixed in equimolar amount and placed, without solvent: a) In an oil bath thermostated at 60 ° C. The duration of the reaction varies from 4 hours to several days; b) In a CEM Discover microwaves in Open Vessel mode with cooling (110 watt) and heated at 60 °C for a period ranging from 1 min to 10 x 1 min. When the product was mass, it is recrystallized in a minimum of ethanol 96%. Otherwise it is purified on a silica column in a mixture of petroleum ether / ethyl acetate (4/1).

The chemical shift values of different triazolines are in good agreement with the proposed structure.

4-methyl-5-morpholino-1-(4-nitrophenyl)-4,5-dihydro-1H-1,2,3-triazole-4-carbonitrile(3b). (R_f = 0.42) yellow solid; m.p 151-153°C; Yield by (C.H) 91%, by (M.W) 99%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.64 (s, 3H), 2.60-2.71 (m, 4H), 3.55-3.58 (m, 4H), 4.86 (s, 1H), 7.51 (d, *J*= 9.2Hz 2H), 8.28 (d, *J*= 9.2Hz 2H); ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 16.1, 44.1, 66.5, 75.4, 81.8, 115.6, 116.6, 125.7, 142.1, 144.7; IR (ATR) : 2240 cm^{-1}; elemental analysis calculated for $C_{14}H_{16}N_6O_3$: C 53.16%, H 5.10%, N 26.57%, found: C 53.58%, H 5.17%, N 26.49%; SM : m/z (%): 339,2 (43, [M + K^+]), 288 (19), 152 (100).

4-methyl-5-morpholino-1-(4-methoxyphenyl)-4,5-dihydro-1H-1,2,3-triazol-4-carbonitril(3c)

(R_f = 0.38) yellow solid; m.p 126-128°C; Yield by (C.H) 50%, by (M.W) 82%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm: 1.60 (s, 3H), 2.49-2.57 (m, 4H), 3.55-3.59 (m, 4H), 3.82 (s, 3H), 4.76 (s, 1H), 6.91 (d, *J*= 9.0 2H), 7.31 (d, *J*= 9.0 2H); ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm: 49.2, 55.5, 66.6, 74.5, 83.4, 114.7, 115.6, 120.0, 133.2, 157.3; IR (ATR) : 2240 cm^{-1}.

1-(4-bromophenyl)-4-methyl-5-morpholino-4,5-dihydro-1H-1,2,3-triazol-4-carbonitril(3d). (R_f = 0.40) as yellow solid; m.p 121-122°C; Yield by (C.H) 19%, by (M.W) 80%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm:1.60 (s, 3H), 2.57-2.64 (m, 4H), 3.52-3.65 (m, 4H), 4.79 (s, 1H), 7.28 (d, *J*= 8,9 2H), 7.49(d, *J*= 8,9 2H); ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm: 22.8, 48.8, 66.5, 74.9, 82.4, 115.9, 117.8, 119.2, 132.6, 138.8; IR (ATR) : 2230 cm^{-1}; elemental analysis calculated for $C_{14}H_{17}BrN_5O$: C 47.88%, H 4.88%, N 19.94%, found: C 49.20%, H 4.71%, N 20.47%.

1-(2-chloro-4-nitrophenyl)-4-methyl-5-morpholino-4,5-dihydro-1H-1,2,3-triazol-4-carbonitril (3e).Column chromatography (Petroleum Ether / Ethyl Acetate: 4/1; R_f = 0.69) afforded the triazoline **3e** as orang solid; m.p 131-132°C; Yield by (C.H) 86%, by (M.W) 91%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm: 1.64 (s, 3H), 2.36-2.43(m, 2H), 2.51-2.60 (m, 2H), 3.55 (t, *J*= 4,6 4H), 5.44 (s, 1H), 8.02 (d Large, *J*= 8,9 1H), 8.25 (dd Large, *J*= 6,4, *J*= 2,5 1H), 8.36 (d, *J*= 2,4 1H); ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm: 18.7, 49.3, 66.3, 76.4, 83.3, 115.3, 123.7, 124.8, 125.8, 126.5, 143.7, 148.5; IR (ATR) : 2340, 1510, 1019 cm^{-1}; elemental analysis calculated for $C_{14}H_{15}ClN_6O_3$: C 47.94%, H 4.31%, N 23.96%, found: C 48.67%, H 4.39%, N 24.58%; SM : m/z (%): 373,2 (81, [M + Na^+]).

methyl 4-methyl-5-morpholino-1-phenyl-4,5-dihydro-1H-1,2,3-triazol-4-carboxylat (4a). Column chromatography (Petroleum Ether / Ethyl Acetate: 4/1; R_f = 0.35) afforded the triazoline **4a** as orang oil; yield by (C.H) 50%, by (M.W) 46%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm: 1.73 (s, 3H), 2.51-2.64 (m, 4H), 3.49-3.54 (m, 4H), 3.73 (s, 3H), 5.35 (s, 1H), 7.09-7.14 (m, 2H), 7.33-7.38 (m, 2H), 7.42-7.46 (m, 2H); ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 16.2, 53.6, 51.0, 67.2, 79.9, 85.4, 117.8, 124.5, 129.8, 141.1, 171.8; IR (ATR) : 1724 cm^{-1}; elemental analysis calculated for $C_{15}H_{20}N_4O_3$: C 59.20%, H 6.62%, N 18.41%, found: C 59.41%, H 6.87%, N 17.22%.

methyl4-methyl-5-morpholino-1-(4-nitrophenyl)-4,5-dihydro-1H-1,2,3-triazol-4-carboxylat(4b). (R_f = 0.36) yellow ; m.p: 126-128°C; Yield by (C.H) 98%, by (M.W) 99%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm: 1.79 (s, 3H), 2.35-2.80 (m, 4H), 3.43-3.75 (m, 4H), 3.75 (s, 3H), 5.37 (s, 1H),7.52 (d, *J*= 9.1 2H), 8.25 (d, *J*= 9.1 2H); ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm: 15.8, 53.5, 53.6, 66.6, 78.5, 86.8, 116.0, 125.6, 143.2, 145.5,170.3; IR (ATR) : 1732 cm^{-1}; elemental analysis calculated for $C_{15}H_{19}N_5O_5$: C 51.57%, H 5.48%, N 20.05%, found: C 50.99%, H 5.48%, N 19.55%; SM: m/z (%): 28(100), 321(20).

methyl4-methyl-5-morpholino-1-(4-methoxyphenyl)-4,5-dihydro-1H-1,2,3-triazol-4-carboxylat(4c). Column chromatography (Petroleum Ether / Ethyl Acetate: 4/1; R_f = 0.35)

afforded the triazoline **4c** as orang oil; Yield by (C.H) 20%, by (M.W) 82%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm: 1.69 (s, 3H), 2.39-2.58 (m, 4H), 3.46-3.50 (m, 4H), 3.75 (d, *J*=0.6 3H), 3.79 (d, *J*=0.6 3H), 6.86 (d, *J*= 9.0 2H), 7.33 (d, *J*= 9.0 2H); ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm: 15.6, 49.6, 53.1, 55.4, 66.7, 80.2, 84.6, 114.5, 119.4, 134.4, 156.6, 171.4.

1-(4-bromophenyl)Methyl4-methyl-5-morpholino-4,5-dihydro-1H-1,2,3-triazol-4-carboxylat(4d). Column chromatography (Petroleum Ether / Ethyl Acetate: 4/1; R_f = 0.35) afforded the triazoline **4d** as yellow oil. ; Yield by (C.H) 28%, by (M.W) 80%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm: 1.73 (s, 3H), 2.42-2.60 (m, 4H), 3.48-3.53 (m, 4H), 3.73 (s, 3H), 5.30 (s, 1H), 7.30 (d, *J*= 8.7 2H), 8.46 (d, *J*= 8.7 2H);^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm: 15.7, 49.0, 53.2, 66.7, 79.4, 85.5, 116.6, 118.8, 132.4, 139.8, 171,0; IR (ATR) : 1729 cm^{-1}; elemental analysis calculated for $C_{15}H_{20}BrN_4O_3$: C 46.89%, H 5.25%, N 14.58%, found: C 48.25%, H 5.20%, N 13.65%.

(2-chloro-N)-(morpholinomethylene)-4-nitrobenzenamine (4e). Column chromatography (Petroleum Ether / Ethyl Acetate: 4/1; R_f = 0.31) afforded the amidine **4e** as yellow solid. m.p: 88-90°C; Yield by (C.H) 15%, by (M.W) 89%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm: 3.46-3.50 (m, 2H), 3.75-3.81 (m, 6H), 6.90 (d, *J*=8.9 1H), 7.57 (s, 1H), 8.00 (dd, *J*= 7.3 *J*= 2.7 1H), 8.24 (d, *J*= 2.6 1H); ^{13}C NMR (75 MHZ, $CDCl_3$) δ ppm: 43.1, 49.3, 66.1, 67.0, 119.7, 123.1, 125.5, 128.3, 142.6, 152.3, 157.6; IR (ATR) : 1614, 1554, 1103 cm^{-1}; elemental analysis calculated for $C_{11}H_{12}ClN_3O_3$: C 48.99%, H 4.49%, N 15.58%, found: C 49.78%, H 4.73%, N 15.53%.

methyl 1-(2-chloro-4-nitropheny)-2-methyl-3-morpholinoaziridin-2-carboxylat (4f). Column chromatography (Petroleum Ether / Ethyl Acetate: 4/1; R_f = 0.48) afforded the aziridine **4e** as yellow oil. ; Yield by (C.H) 15%, by (M.W) 89%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm: 1.36 (d, *J*=7.2 3H), 3.45-3.48 (m, 4H), 3.50 (s, 1H), 3.69-3.74 (m, 4H), 3.75 (s, 3H), 6.85 (d, *J*= 8.6 1H), 8.02 (dd, *J*= 6.2 *J*= 2.5 1H), 8.26 (d, *J*= 2.4 1H), ^{13}C NMR (75 MHZ, $CDCl_3$) δ ppm : 16.0, 49.8, 52.2, 66.7, 75.3, 84.3, 116.6, 122.9, 124.1, 125.1, 145.8, 150.8, 169.8; elemental analysis calculated for $C_{15}H_{18}ClN_3O_5$: C 48.99%, H 4.49%, N 15.58%, found: C 49.78%, H 4.73%, N 15.53%.

Conclusion

In conclusion, it is shown that the 1,3-dipolar cycloaddition between the *acyclic enamines* **1** and the *organic azides* **2**, carried out without solvent and under microwave activation, provided in very short times, triazolines with good yields, and which is influenced by several factors: the technique used (microwave or conventional heating); the nature of the azide (arylazids containing electron-withdrawing groups gave excellent results); the nature of the enamine (the enamines substituted by the electron withdrawing groups is more reactive than those substituted by electron donating groups). Moreover, this free-solvent microwave assisted procedure is economically and environmentally attractive, as 1) The use of the microwave technology has not only reduced reaction time, improved efficiency, but also achieved certain reactions inaccessible by conventional heating 2). There is no need to purify the products 3). Without necessitating the use of a copper catalyst, and ultimately making the reaction more useful for biological settings or other applications where the use of copper precludes the utilization of the reaction.

Acknowledgments. The authors are grateful to Professor Jean-Marc Pons (Institute of Molecular Science (ism2)) of Aix-Marseille University (France) for the centesimal analysis and mass spectra.

References

i. A. Speicher, T. Eicher, S. Hauptmann, "The chemistry of heterocycles : structure, reactions, synthesis and applications", Third, Completely Revised and Enlarged Edition, eds Wiley-VCH Verlag & Co. KGaA, Germany (2012).

ii. E. Bokor, T. Docsa, P. Gergely, L. Somsak, *Bioorg. Med. Chem*., **18**, 1171, (2010).

iii. a) C. Gill, G. Jadhav, M. Shaikh, R. Kale, A. Ghawalkar, D. Nagargoje, M. Shiradkar, *Bioorg. Med. Chem*. *Lett.*, **18**, 6244, (2008) ; b) R. P. Tripathi, A. K. Yadav, A. Arya, S. S. Bisht, V. Chaturvedi, S. K. Sinha, *Eur. J. Med. Chem*., **45**, 142, (2010).

iv. S. Syed, M. M. Alam, N. Mulakayala, C. Mulakayala, G. Vanaja, A. M. Kalle, R. Reddanna Pallu, M. S. Alam, *Eur. J. Med. Chem.*, **49**, 324, (2012).

v. a) N. G. Aher, V. S. Pore, N. N. Mishra, A. Kumar, P. K. Shukla, A. Sharma, M. K. Bhat, *Bioorg. Med. Chem. Lett., **19**, 759*, (2009) ; b) J. N. Sangshetti, R. R. Nagawade, D. B. Shinde, *Bioorg. Med. Chem. Lett*., **19**, 3564, (2009) ; c) J. N. Sangshetti, A. R. Chabukswar, D. B. Shinde, *Bioorg. Med. Chem. Lett*., **20**, 742, (2010).

vi. L. Zhou, A. Adel , M. Korn, R. Burda, J. Balzarini, E. Clercq, E. R. Kern, P. F. Torrence, *Antiviral Chem. Chemother*., **16**, 375, (2005) ; b) A. Sh. El-Etrawy, A.A.-H. Abdel-Rahaman, *Chem. Heterocycl. Compd*., **46**, 1105, (2010).

vii. B. S. Holla, M. Mahalinga, M. S. Karthikeyan, B. Poojary, P. M. Akberali, N. S. Suchetha Kumari, *Eur. J. Med. Chem.*, **40**, 1173, (2005) ; b) K. D. Thomas, A. V. Adhikari, N. S. Shetty, *Eur. J. Med. Chem*., **45**, 3803, (2010).

viii. H. C. Kolb, K. B. Sharpless, *Drug Disc. Today*., 8, 1128, (2003).

ix. R. Huisgen, *Angew. Chem. Int. Ed. Engl*. **2**, 565, (1963).

x. a) A. Padwa, *Angew. Chem. Int. Ed.Engl*., **15**, 123, (1976). b) A. Padwa, Comprehensive Organic Synthesis. Chapter 4.9, 1069-1109, (1991) .

xi. a) F. Louërat, K. Bougrin, A. Loupy, A. M. Ochoa de Renata, J. Pagalday, F. Palacios, *Heterocycles*, **48**, 161, (1998). b) A. R. Katritzky, S. K. Singh, *J. Org. Chem*., **67**, 9077, (2002). c) A. R. Katritzky, Y. Zhang, S. K. Singh, P. J. Steel, *Arkivoc*, **15**, 47, (2003). d) F. Pérez-Balderas, M. Ortega-Muñoz, J. Morales-Sanfrutos, F. Hernández-Mateo, F. G. Calvo-Flores, J. A. Calvo-Asin, J. Isac-Garcia, F. Santoyo-González, *Org. Lett*., **5**, 1951, (2003). e) W. J. Sommer, M. Weck, *Langmuir*, **23**, 11991, (2007) f) Y. Gao, Y. Lam, *Org. Lett*., **8**, 3283, (2006). g) L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett*., **9**, 5337, (2007). h) U. Pradere, V. Roy, T. R. McBrayer, R. F. Schinazi, L. A. Agrofoglio, Tetrahedron, **64**, 9044, (2008).

xii. a) B. L. Hayes, Microwave Synthesis: Chemistry at the speed of Light, CEM Publishing, Matthews NC, (2002) ; b) C. O. Kappe, and A. Stadler, Microwaves in Organic and Medicinal Chemistry, Vol. 25 Methods and Principes in Medicinal Chemistry, Wiley-VCH, Weinheim, (2005); c) Microwave-Assisted Organic Synthesis (Eds: P. Lidström, J. P. Tierney), Blackwell, Oxford, (2005) ; d) Microwaves in Organic Synthesis (Ed : A. Loupy), Wiley-VCH, Weinheim, (2006).

xiii. Qi. Han, D. F. Wiemer, J. Am. Chem. Soc, **114**, 20, 7692, (1992).

xiv. D. J. Aberhart, Chou-Hong Tann, *J. Soc. Chem. Perkin I*, **4**, 939, (1979).

Received on May 26, 2018.