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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Lazhar Zribi, Fathi Zribi, José Marco-Contelles, Fakher Chabchoub & Lhassane Ismaili (2017): Facile one-pot synthesis of new [1,2,4]triazolo[1,5-a]pyridine derivatives by ultrasonic irradiation, Synthetic Communications, DOI: 10.1080/00397911.2017.1357078

To link to this article: http://dx.doi.org/10.1080/00397911.2017.1357078

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https://doi.org/10.1080/00397911.2017.1357078

Facile one-pot synthesis of new [1,2,4]triazolo[1,5-*a*]pyridine derivatives by ultrasonic irradiation

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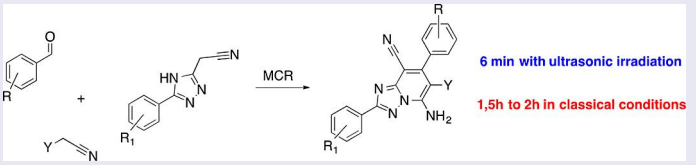
ABSTRACT

Herein, we report an ultrasonic promoted facile and convenient "one-pot" procedure for the synthesis of new [1,2,4]triazolo[1,5-*a*]pyridine derivatives **3, 4** and **5**, using Amberlite IRA-400, in short reaction times and high yields and its comparison with classical reaction conditions. The structures of new compounds were assigned with the help of analytical ^{1}H, ^{13}C NMR, and mass spectral studies.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 4 April 2017

KEYWORDS
Amberlite IRA-400; multicomponent reaction; one-pot synthesis; triazolopyridines; ultrasound irradiation

Introduction

It is well known that triazoles and triazolopyridine derivatives display several biological activities such as anti-inflammatory,[1] antibacterial,[2] antiproliferative,[3] and antidepressant.[4] Furthermore, triazolopyridines have been described as inhibitors of the cardiac channel,[5] p38 MAP kinase,[6] JmjC histone lysine demethylase KDM2A,[7], and identified as p38 inhibitors.[8]

On the other hand, ultrasound-assisted organic synthesis is considered as an important technique for green and sustainable synthetic processes[9] that require small amounts of solvents, and consume less energy,[10] showing important advantages, such as improved chemical yields, shorter reaction times, lower costs, easier manipulation[9,11] as well as minimal secondary side reactions.[12]

Multicomponent reactions (MCRs) are "one-pot" processes in which at least three or more different starting materials react, affording the target products.[13–15] MCRs are a simple and convergent atom-economic synthetic approach that offers advantages over conventional multistep reactions for the synthesis of versatile arrays of molecules without

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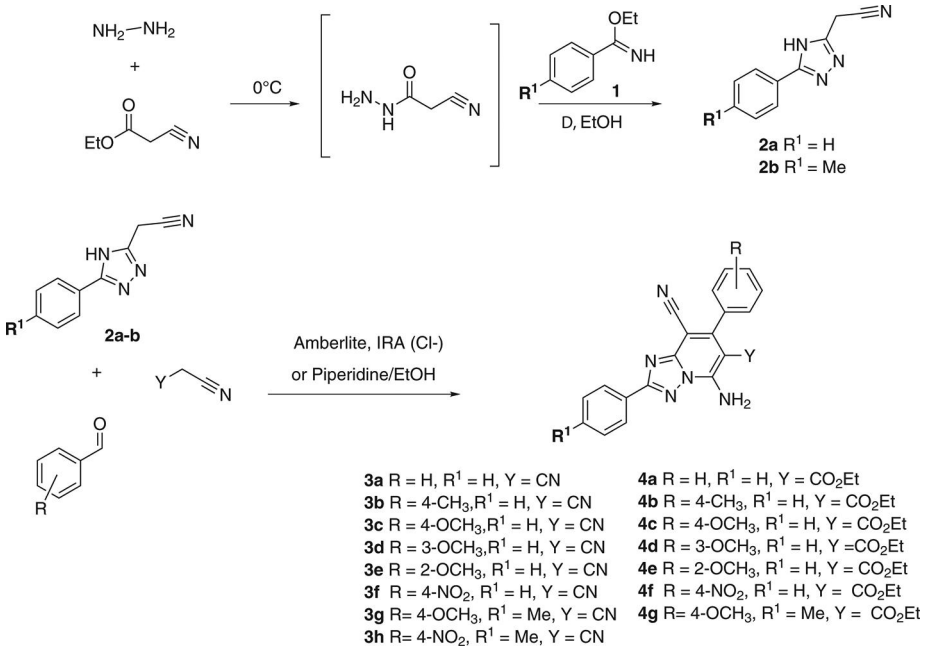
isolation of intermediates, fulfilling thus some of the goals of "green and sustainable chemistry".[16–18]

Heterogeneous catalysts have attracted particular attention owing to their remarkable economic and environmental benefits. Indeed, these catalysts can be easily removed from the reaction mixture and reused, unlike to homogeneous catalysts that provide faster reaction rates, certainly, but the separation and recovery of the catalyst from the reaction mixture still remain a major issue.[19]

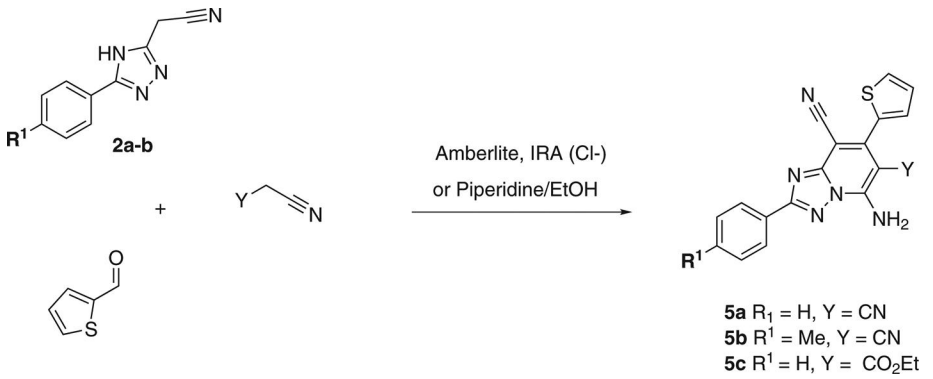
Thus, taking into account and by combining MCRs, ultrasound-assisted organic synthesis, and heterogeneous catalysts, aiming at reducing the environmental and health impacts of chemical synthesis, we report herein the transformation of 2-(5-phenyl-4*H*-1,2,4-triazol-3-yl)acetonitrile into several new [1,2,4]triazolo[1,5-*a*]pyridine derivatives in good yields, through an MCR, under ultrasonic irradiation, and its comparison with classical reaction conditions.

Results and discussion

The synthesis of the target compounds **3, 4**, and **5** has been performed using a short synthetic procedure as follows: first, 2-(5-phenyl-4*H*-1,2,4-triazol-3-yl)acetonitrile (**2**)[20] was prepared by a new and facile method using the "one-pot" MCR, by reacting hydrazine monohydrate with ethyl cyanoacetate, at 0 °C, followed by treatment with imidate **1**, at reflux in absolute ethanol for 4 h (Scheme 1). Next, compound **2** was reacted with malononitrile and aromatic aldehydes under classical reaction conditions using catalytic amounts of piperidine, or using Amberlite IRA-400 as basic catalyst under ultrasound



Scheme 1. Synthesis of 2-(5-phenyl-4*H*-1,2,4-triazol-3-yl)acetonitrile (**2**) and [1,2,4]triazolo [1,5-*a*] pyridine derivatives **3** and **4**.



Scheme 2. Synthesis of [1,2,4]triazolo [1,5-*a*]pyridine derivatives **5**.

irradiation reaction conditions (Schemes 1 and 2). Under the classical heating conditions, the reaction was achieved in 90 min when we used malononitrile and 120 min with ethyl cyanoacetate.

Regarding the Amberlite IRA-400-promoted procedure under ultrasound irradiation reaction conditions, the catalyst type and the ultrasound power intensity were critical. The results are shown in Table 1. When the catalyst was tested for a model reaction without sonication at 80 °C for 2 h, no product was obtained (Table 1, entries 1, 2). Furthermore, it was noted that reaction in the presence of Amberlite IRA400 and ultrasonic irradiation power of 60 W gave the best result with the highest yield (95%) after only 6 min (Table 1, entry 5).

We have generalized, this reaction using several aldehydes to obtain 5-amino-2, 7-diphenyl-[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitriles **3a–h** and ethyl 5-amino-8-cyano-2,7-diphenyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylates **4a–g** using malononitrile or ethyl cyanoacetate, respectively (Table 2). In the aim to extend the scope of this method, heterocyclic aldehyde (thiophene-2-carbaldehyde) was used in the same condition and conducted to 5-amino-2-phenyl-7-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*] pyridine-6,8-dicarbonitrile and ethyl 5-amino-8-cyano-2-phenyl-7-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate **5a–c**. All compounds were characterized by the usual spectroscopic methods and elemental analyses. As shown in Table 2, compounds **3, 4**, and **5** were isolated in good yields ranging from 67 to 71% under the classical reaction conditions, and from 79 to 95% yields under the ultrasonic irradiation reaction conditions, thereby demonstrating that ultrasound method improves not only the reaction time but also the yields. It can also be noted that the reaction

Table 1. Optimization of the effect of ultrasonic irradiation on the synthesis of **3a**[a].

Entry	Power (W)	Time (min)	Temperature (°C)	Yield (%)[b]
1	—	120	r.t	—
2	—	120	80	—
3	40	20	60	91
4	50	12	60	92
5	60	6	60	95

[a]2-(5-Phenyl-4*H*-1,2,4-triazol-3-yl)acetonitrile (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol), Amberlite IRA-400, 6 min, 60 °C, EtOH (5 cm^3) under ultrasound irradiation (60% of amplitude).
[b]Isolated yields.

Table 2. MCR synthesis of **3a–e** and **4a–e** under classical and under ultrasound irradiation conditions.

				Classical condition[a]		Ultrasonic irradiation[b]		
Entry	Y	R	R_1	Yields (%)[c]	Time (min)	Yields (%)[c]	Time (min)	Melting point (°C)
1	CN	H	H	71	90	95	6	>260
2	CN	4-CH_3	H	70	90	95	6	>260
3	CN	4-OCH_3	H	68	90	93	6	>260
4	CN	3-OCH_3	H	67	90	93	6	>260
5	CN	2-OCH_3	H	67	90	92	6	>260
6	CN	4-NO_2	H	61	110	85	6	>260
7	CN	4-OCH_3	CH_3	65	110	92	6	>260
8	CN	4-NO_2	CH_3	59	110	83	6	>260
9	CO_2Et	H	H	71	120	83	6	256
10	CO_2Et	4-CH_3	H	71	120	81	6	>260
11	CO_2Et	4-OCH_3	H	69	120	80	6	240
12	CO_2Et	3-OCH_3	H	69	120	79	6	250
13	CO_2Et	2-OCH_3	H	67	120	80	6	230
14	CO_2Et	4-NO_2	H	57	140	84	6	>260
15	CO_2Et	4-OCH_3	CH_3	66	120	91	6	254
16[d]	CN	—[d]	H	67	90	94	6	>260
17[d]	CN	—[d]	CH_3	66	90	93	6	>260
18[d]	CO_2Et	—[d]	H	64	120	93	6	>260

[a]Compound **2** (1 mmol), aromatic aldehydes (1 mmol), malononitrile (1 mmol), piperidine, 90 min, 80 °C, EtOH (15 cm^3).
[b]Compound **2** (1 mmol), aromatic aldehydes (1 mmol), malononitrile (1 mmol), Amberlite IRA-400, 6 min, 60 °C, EtOH (5 cm^3) under ultrasound irradiation (60% of amplitude).
[c]Isolated yields.
[d]Reactions with heteroaromatic aldehyde (thiophene-2-carbaldehyde).

performed using the ultrasonic irradiation procedure gave better results with malononitrile than with ethyl cyanoacetate

The proposed mechanism of this reaction starts by the formation of arylidene intermediate **I**; next, the carbanion **II** attacks intermediate **I** to obtain **III**. The intramolecular cyclization and oxidation give the required compounds **3** or **4** (Scheme 3). Compounds **5** were probably obtained by the same mechanism.

Conclusion

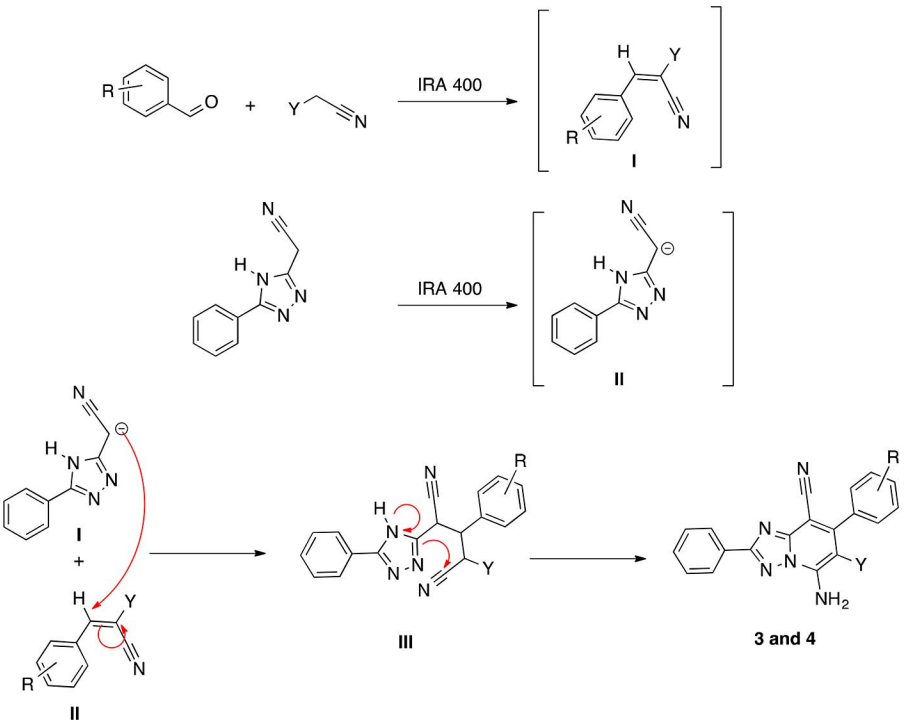
In this work, we have reported the MCR of [1,2,4]triazolo[1,5-*a*]pyridine derivatives under classical condition and under ultrasound irradiation reaction conditions. From these results, we conclude that the ultrasound method is an efficient, green, fast, and convenient procedure for the synthesis of these triazolopyridines, with significant advantages such as reduced reaction time, mild reaction condition, productivity and higher yield, easier of execution, and economic viability respect to the classical procedure.

Experimental

This includes general procedure for the synthesis of compounds **3a–h, 4a–g**, and **5a–c**. Experimental procedures for the intermediate and spectral data of all derivatives are presented in Supporting Information.

Materials and methods

Melting points were determined on a Kofler apparatus (Wagner Munz) and are uncorrected. An ultrasonic model Bioblock Scientific 750 W probe was used to generate



Scheme 3. Proposed mechanism of [1,2,4]triazolo[1,5-*a*]pyridine derivatives.

ultrasonic irradiation and homogenize the reaction mixture. The reactions were monitored with TLC using aluminum sheets with silica gel 60 F254 from Merck. IR spectra were performed on a Perkin–Elmer PARAGON FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer using DMSO-d_6 as a solvent. The chemical shifts are reported in parts per million, using tetramethylsilane as an internal reference. The multiplicities of the signals are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quadruplet; and m, multiplet, the coupling constants are expressed in Hz. Elemental analysis was performed on Thermofinnigan Flash EA 1112. High-resolution mass spectra were obtained at Centre Commun de Spectrométrie de Masse (Lyon, France) on a Bruker micrOTOF-Q II spectrometer (Bruker Daltonics) in positive electrospray ionization-time of flight.

General procedure for the synthesis of [1,2,4]triazolo[1,5-a]pyridine (3), (4) and (5)

Method 1

A solution of 2-(5-phenyl-4*H*-1,2,4-triazol-3-yl)acetonitrile (**2**) (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol) and aromatic aldehydes (1 mmol) in absolute ethanol (5 cm^3), in the presence of IRA-400 (0.3 g), was placed in flask equipped with an ultrasonic probe. The reaction was heated in an oil bath at 60 °C and sonicated in the ultrasonic generator (Bioblock Scientific 70 W) at low 20 kHz (amplitude of 60%) for 6 min. After the reaction was completed, the mixture was filtered, washed with ethanol, and dried to give compounds **3a–h, 4a–g**, and **5a–c**.

Method 2

A solution of compound **2** (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol) and aromatic aldehydes (1 mmol) in absolute ethanol (15 cm^3), in the presence of piperidine (1 mmol), was heated at 80 °C for 90 min. After the completion of reaction, the mixture was filtered, washed with ethanol, and dried to give compounds **3a–h, 4a–g**, and **5a–c**.

Funding

This work was supported by Regional Council of Franche-Comte [Grant Numbers 2016YC-04540, 04560].

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