Ultrasonics Sonochemistry 19 (2012) 221–226

Contents lists available at ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultsonch

Short Communication

Efficient sonochemical synthesis of alkyl 4-aryl-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate derivatives

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ARTICLE INFO

Article history:
Received 21 April 2011
Received in revised form 7 July 2011
Accepted 7 July 2011
Available online 22 July 2011

Keywords:
Ultrasound irradiation
Sonochemistry
1,4-Dihydropyridine derivatives
Vilsmeier–Haack reaction

ABSTRACT

A facile, efficient and environment-friendly protocol for the synthesis of 6-chloro-5-formyl-1,4-dihydropyridine derivatives has been developed by the convenient ultrasound-mediated reaction of 2(1*H*)pyridone derivatives with the Vilsmeier–Haack reagent. This method provides several advantages over current reaction methodologies including a simpler work-up procedure, shorter reaction times and higher yields.

1. Introduction

The exploration of privileged structures in drug discovery is a rapidly emerging topic in medicinal chemistry [1]. These structures represent a class of molecules capable of binding to multiple receptors with high affinity. The development of these molecules should allow the medicinal chemist to rapidly discover biologically active compounds across a broad range of therapeutic areas on a reasonable time scale [2].

In this sense, 1,4-dihydropyridines are very attractive targets due to their wide range of biological activities [3]. Perhaps the best known pharmacological class of 1,4-dihydropyridines are those acting as calcium channel blockers. These compounds are routinely used in the treatment of a variety of cardiovascular disorders, such as hypertension, cardiac arrhythmias or angina [4].

It is well known that the Vilsmeier–Haack reaction is a mild method for the introduction of a formyl group in various activated aromatic and heteroaromatic compounds [5]. It can be carried out on methylene-active compounds leading mainly to the formation of β-halo-carboxaldehyde derivatives, which are useful precursors in the construction of different heterocyclic compounds by means of further chemical transformations [6].

As part of our program aimed at synthesize 1,4-dihydropyridines endowed with different groups on the carbons of the heterocyclic ring, we have previously reported the synthesis of 6-chloro-5-formyl-2-methyl-3-alkoxycarboxyl-1,4-dihydropyridines which were obtained from the corresponding 4-aryl 3,4-dihydropyridone using the Vilsmeier–Haack reagent [7].

In our case, 6-chloro-5-formyl-1,4-dihydropyridines proved to be an excellent building block for further transformations into other heterocycle-fused 1,4-dihydropyridines such as pyrazolo[3,4-b]pyridines [7], 4,7-dihydrothieno[2,3-b]pyridines [8] and 2-iminodihydropyrido[3,2-e][1,3]thiazines [9]. Furthermore, we have carried out the synthesis of novel fulleropyrrolidines bearing biologically active the preparation of 1,4-DHPs covalently connected to the fullerene core, from the corresponding 6-chloro-5-formyl-1,4-dihydropyridines [10] and the preparation of 1,4-dihydropyridines endowed with a methylenethiocarbazide group on C5 of the heterocyclic ring [11].

The traditional method for 6-chloro-5-formyl-1,4-dihydropyridine synthesis entails the reaction of the corresponding 2(1*H*)pyridone with the Vilsmeier–Haack reagent ($POCl_3$, DMF) in dry chloroform under nitrogen atmosphere at room temperature [7]. However, due to the long reaction time (18 h) this classic thermal reaction presents some disadvantages. Thus, the development of a more efficient method for the synthesis of 6-chloro-5-formyl-1,4-dihydropyridine is highly desirable.

Ultrasounds, an efficient and virtually innocuous means of activation in synthetic chemistry, have been employed for decades with

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doi:10.1016/j.ultsonch.2011.07.003

varied success [12]. This high-energy input enhances not only mechanism effects in heterogeneous processes, but it is also known to induce new reactivity leading to the formation of unexpected chemical species. The remarkable phenomenon of cavitation makes sonochemistry unique. The effects of ultrasound observed during organic reactions are due to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressures inside the bubbles, leading to turbulent flow of the liquid and enhanced mass transfer. When compared with conventional methods, ultrasound-accelerated chemical reactions could be carried out under ultrasound irradiation to give higher yields in shorter reaction times and milder conditions [13].

Ali and coworkers have reported on the cyclization and formylation of acetanilides with Vilsmeier–Haack reagent under ultrasound irradiation conditions to afford the corresponding 2-chloro-3-formylquinolines in good yields, using an ultrasonic bath for 60 min at 40 °C. They also observed a similar tendency in the case of the formylation of aromatic hydrocarbons where the desired formylated product was obtained in good to excellent yields under ultrasonic irradiation. In both cases the yields were significantly lower under thermal conditions [14].

Ultrasound irradiation has also been successfully used in the synthesis and chemical modification of a variety of 1,4-dihydropyridines [15].

We have very recently developed an efficient procedure for the synthesis of 3,4-dihydropyridone derivatives under ultrasonic irradiation at room temperature [16], improving the yields and shortening the reaction times compared with the previous conventional methods [17]. These 3,4-dihydro-2-oxopyridines are important key intermediates for the preparation of *o*-chloroformyl 1,4-dihydropyridines.

As a part of our studies aimed at synthesizing 1,4-dihydropyridine derivatives [18] as well as the use of non-conventional techniques in the synthesis of this class of compounds, [19] we describe here in a novel procedure for the preparation of 6-chloro-3-formyl-1,4-dihydropyridine derivatives under mild ultrasound irradiation.

2. Methods

2.1. Apparatus and analysis

Reagents and solvents were purchased from Fluka or Aldrich. Melting points were determined in capillary tubes in an Electrothermal C14500 apparatus and are uncorrected. The progress of the reaction and the purity of compounds were monitored by TLC analytical silica gel plates (Merck 60 F250). The NMR spectra were recorded on a Bruker Avance-300 instrument. ^{1}H and ^{13}C were recorded in DMSO-d_6 at 300 MHz and 75 MHz and are referenced to 2.50 and 39.5 ppm for DMSO, respectively. Chemical shifts are given as δ values and J values are given in Hz. The ultrasonic irradiation experiments were carried out in: (a) a sonochemical apparatus SONIPRED-150. The frequency can be tuned between 17 and 35 kHz and the power can be varied up to a maximum output of 350 W. The reactions were carried out in an open double walled glass tube (diameter: 30 mm; thickness: 1 mm; volume: 50 mL) at 30 °C. The temperature was controlled by a Buchi B-491 water bath at 30 ± 1 °C; (b) a Shanghai Branson-CQX ultrasonic cleaner with a frequency of 25 kHz and a nominal power 250 W. The reaction flask was located in the water bath of the ultrasonic cleaner, and the temperature of the water bath was controlled at 30 °C. The reaction temperature was controlled by addition or removal of water from ultrasonic bath. The reactions were performed in open vessels.

2.2. General procedure

Synthesis of alkyl 4-aryl-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3 carboxylates (**2**) under ultrasound irradiation.

To the Vilsmeier–Haack reagent prepared from a mixture of $POCl_3$ 1.1 mL (12.2 mmol) and 1.4 mL (18.2 mmol) of DMF at 5 °C, 7 mmol of the alkyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate (**1**) in 15 mL of dry chloroform was added. The mixture was sonicated at 30 °C with a sonic horn or in an ultrasonic cleaner. The reaction was monitored by TLC (chloroform:hexane:ethyl acetate, 5:4:3). After the completion of the reaction an aqueous sodium acetate solution was added (12 g in 21 mL of water) and sonicated for 10 min. The product was extracted twice from water with dichloromethane. The organic phases were collected and dried under $MgSO_4$. The organic solvent was removed in vacuo and the solid residue was washed twice with small portions of cold ether to afford **2**. All experiments performed in this work were repeated three times. The yield reported represents the average of the values obtained for each reaction. The identity of the products was confirmed by comparing their melting points and NMR data with those reported in the literature [7,18b,23] (see Supporting Information).

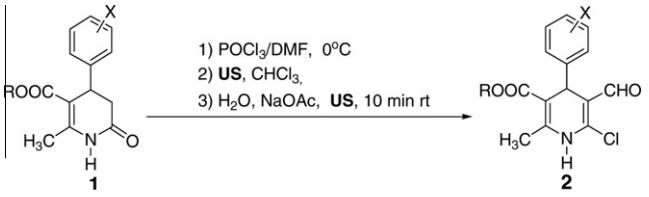
3. Results and discussion

Compounds **2** were obtained as we previously reported [7] from the corresponding methyl 2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate (**1**) via Vilsmeier–Haack chloroformylation by conventional methods. Even though this procedure allows the preparation of the desired 6-chloro-5-formyl-1,4-dihydropyridines **2** in a straightforward fashion, it demands long reaction times, and the usual product purification procedures such as recrystallization or column chromatography require large volumes of organic solvent. In order to achieve milder reaction conditions, lower temperatures as well as speeding up the reaction, in this work we have developed the synthesis of compounds **2**, under heterogeneous conditions and ultrasound irradiation.

To achieve suitable conditions for the synthesis of compounds **2**, different reaction conditions have been investigated in the reaction of the corresponding 3,4-dihydro-2-pyridones **1** with the Vilsmeier–Haack reagent. (See Scheme 1).

To determine the effect of ultrasound on this reaction, the experiments were carried out under the same conditions used in the conventional experiments [7]. Therefore, they were carried out using anhydrous chloroform as solvent.

To determine the influence of the source of ultrasonic irradiation on the development of the process, we carried out and monitored the reactions using an ultrasonic cleaner and a sonic horn. First, we developed the synthesis using an ultrasonic cleaner; the reaction flask was located in the cleaner bath, where the surface of reactants is slightly lower than the level of the water.



2a, X = H R = CH_3 **2g**, X = H R = CH_2CH_3
2b, X = 2-NO_2 R = CH_3 **2h**, X = 2-NO_2 R = CH_2CH_3
2c, X = 3-NO_2 R = CH_3 **2i**, X = 3-NO_2 R = CH_2CH_3
2d, X = 4-NO_2 R = CH_3 **2j**, X = 4-NO_2 R = CH_2CH_3
2e, X = 2-Cl R = CH_3 **2k**, X = 2-Cl R = CH_2CH_3
2f, X = 3-pyridyl R = CH_3 **2l**, X = 3-pyridyl R = CH_2CH_3

Scheme 1. Synthesis of 6-chloro-5-formyl-1,4-dihydropyridines (2a–l) under ultrasound irradiation.

Table 1
Synthesis under heterogeneous conditions of 6-chloro-5-formyl-1,4-dihydropyridines (**2a–e**) and ultrasound irradiation (25 kHz) at 30 °C.

Product	X	R	Bath cleaner		Sonic horn	
			Time (min)	Yield (%)	Time (min)	Yield (%)
2a	H	$-CH_3$	40	75	18	78
2b	2-NO_2	$-CH_3$	30	76	15	80
2c	3-NO_2	$-CH_3$	30	78	15	80
2d	4-NO_2	$-CH_3$	30	80	15	87
2e	2-Cl	$-CH_3$	40	80	18	82

Observation of the surface of the reaction solution during vertical adjustment of vessel depth will show the optimum position by the point at which maximum surface disturbance occurs. The reaction temperature was controlled by addition or removal of water from ultrasonic bath. The chloroformylation methodology involved the interaction of the halomethylenium salt, formed in situ from $POCl_3$ and DMF at 5 °C, with alkyl 4-aryl-6-methyl-2-oxo-1,3,3,4-tetrahydropyridine-5-carboxylate **1** in dry chloroform. Further irradiation at 25 kHz of the reaction mixture in an ultrasonic bath at 30 °C for 30–40 min and subsequent hydrolysis with aqueous solution of sodium acetate, afforded the desired 6-chloro-5-formyl 1,4-DHP derivative **2** in good yields. (See Table 1).

Following the same work up the reaction was developed using a sonic horn as source of ultrasound. In this case the reaction mixture was irradiated at 25 kHz during a variable time (15–18 min) at 30 °C. The results are shown in Table 1.

When the reaction was carried out in a cleaner bath, it comparatively gave slightly lower yields of products and the reaction time was approximately duplicated to that when it was performed using a sonic horn. Comparing these results, it is possible to assert the advantages of using a sonic horn in comparison with the bath cleaner as they get higher yields in lesser reaction times. This is probably due to the fact that the ultrasound works under more focused conditions.

Nevertheless, both methodologies work better than the conventional method (reaction time 18 h and slightly lower yields (75–80%) [7]), they are more efficient, less time consuming and more environmentally friendly, particularly when considering the basic green chemistry concepts.

We have also determined the effect of the frequency of the ultrasound irradiation on the reaction progress. In this case, we carried out the reaction under the same experimental conditions, using a sonic horn at 35 and 18 kHz. (See Table 2).

When the frequency used was 25 kHz, the reactions yields were quite similar to those obtained when the cleaner bath was used (Table 1). Under 35 kHz the yields decreased significantly and, at 18 kHz, they remarkably increased. These data reveal that using a lower frequency of ultrasound irradiation results in an improved of the yield. The reason for this experimental finding could stem from the better cavitations produced at lower frequency irradiation [12,13,20,21].

To study the effect of the temperature on this synthesis, we also performed four experiments at 5, 20, 30 and 50 °C under optimized ultrasonic irradiation at 18 kHz. (Table 3) We found that at 5 °C the reaction does not occur, and at 50 °C the yield decreases significantly, possibly due to the decomposition of the Vilsmeier-Haack reagent. Yields at 20 °C are however, slightly lower that at 30 °C. At this temperature the cavitation increases and enhances the reactivity of the respective substrates.

Thus, we have carried out a series of experiments under optimized conditions, namely at 30 °C and using a sonic horn at 18 kHz, and the results are summarized in Table 4. In order to show the advantages of the present experimental conditions, in Table 4 we have also collected the results obtained under conventional conditions.

Table 2
Synthesis under heterogeneous conditions of 6-chloro-5-formyl-1,4-dihydropyridines (**2a–e**) and ultrasound irradiation at 30 °C for 15 min. using a sonic horn.

Product	X	R	35 kHz Yield (%)	25 kHz Yield (%)	18 kHz Yield (%)
2a	H	$-CH_3$	68	75	83
2b	2-NO_2	$-CH_3$	70	80	85
2c	3-NO_2	$-CH_3$	74	80	86
2d	4-NO_2	$-CH_3$	74	87	95
2e	2-Cl	$-CH_3$	78	85	92

Table 3
Synthesis under heterogeneous conditions of 6-chloro-5-formyl-1,4-dihydropyridines (**2a–d**) and ultrasound irradiation using a sonic horn (18 kHz) for 15 min at different temperatures.

Product	X	R	20 °C Yield (%)	30 °C Yield (%)	50 °C Yield (%)
2a	H	$-CH_3$	76	83	15
2b	2-NO_2	$-CH_3$	78	85	32
2c	3-NO_2	$-CH_3$	78	90	30
2d	4-NO_2	$-CH_3$	84	95	30

The results show that the method to obtain 6-chloro-5-formyl-1,4-dihydropyridine derivatives (**2a–l**) under ultrasonic irradiation from 3,4-dihydropyridone derivatives (**1a–l**) offers several significant advantages including faster reaction rates, higher purity, and higher yields. In comparison with conventional methods, the main advantage of ultrasound application is the significant decrease in the reaction times and milder experimental conditions. Thus, while conventional method requires 18 h, ultrasonic irradiation affords the respective products in only 15–20 min (see Table 4). These results support that the energy provided by ultrasound significantly accelerates these reactions. The difference in yields and reaction times may be a consequence of the specific effects of ultrasound. In particular, to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid, thus enhancing the mass transfer [13] and allowing chemical reactions to occur. The creation of the so-called hot spots in the reaction mixture produces intense local temperatures and high pressures generated inside the cavitation bubble and its interfaces when it collapses. Under these conditions, the 6-chloro-5-formyl-1,4-dihydropyridines derivatives (**2a–l**) are efficiently formed in shorter times and in better yields.

The structures of all the synthesized compounds were corroborated by their ^1H and ^{13}C NMR spectra. The structure of **2h** was further confirmed by X-ray analysis [22]. The molecular structure of the product **2h** is shown in Fig 1a. The host molecule ($C_{16}H_{15}ClN_2O_5$) crystallizes forming a *tri*-hemihydrate (three molecules of water *per* two host molecules). Contrary to most 1,4-dihydropyridine (1,4-DHP) rings previously studied by us [18a,c,d,23] where this ring adopts a boat conformation with the N1 and C4 atoms defining the stern and bow positions, in this crystal structure the 1,4-DHP ring is rather flat. The average ring bond distance is 1.413(2) Å. The conformation of **2h** in the solid state shows an *ap,ap* orientation of the carboxylic groups with respect to the endocyclic double bonds of the 1,4-DHP ring. The nitrophenyl ring is positioned above the concave site of the 1,4-DHP bisecting this ring (torsion angle C3–C4–C1′–C6′ = 46.1(4)°). The nitro group is *syn-periplanar* to the H4 atom on C4.

The crystal structure is stabilized by means of strong intermolecular hydrogen bonds involving the water molecules (see Fig 1b and Table A.2 in Supporting Information). The O7 atom of one of the water molecules is located in a special position coincidently with a crystallographic two-fold axis. Also some weak interactions of the type C–H. . .O and C–H..Cl are present.

Table 4
Synthesis under heterogeneous conditions of 6-chloro-5-formyl-1,4-dihydropyridines (**2a–l**) and ultrasound irradiation at 30 °C using a sonic horn at 18 kHz.

Product	X	R	US		Conventional method[a]	m.p °C (Ref)
			t (min)	Yield (%)	Yield (%)[b]	
2a	H	$-CH_3$	15	83	80	181–182 (181–182 [7])
2b	2-NO_2	$-CH_3$	15	85	80	178–180 (179–181 [18b])
2c	3-NO_2	$-CH_3$	15	90	75	212–214 (213–214 [7])
2d	4-NO_2	$-CH_3$	15	95	85	190–192 (190–192 [18b])
2e	2-Cl	$-CH_3$	15	92	82	196–198 (197–198 [23])
2f	3-pyridyl	$-CH_3$	20	80	74	199–201 (200–201 [18b])
2g	H	$-CH_2CH_3$	15	84	78	201–202 (200–202 [18b])
2h	2-NO_2	$-CH_2CH_3$	15	85	80	198–200 (199–201 [18b])
2i	3-NO_2	$-CH_2CH_3$	15	88	82	225–227 (224–226 [18b])
2j	4-NO_2	$-CH_2CH_3$	15	94	85	251–253 (251–253 [18b])
2k	2-Cl	$-CH_2CH_3$	15	90	82	210–212 (210–211 [18b])
2 l	3-pyridyl	$-CH_2CH_3$	20	78	72	217–219 (217–219 [18b])

[a] For comparison, reaction time 1080 min.
[b] Yield of isolated and recrystallized product.

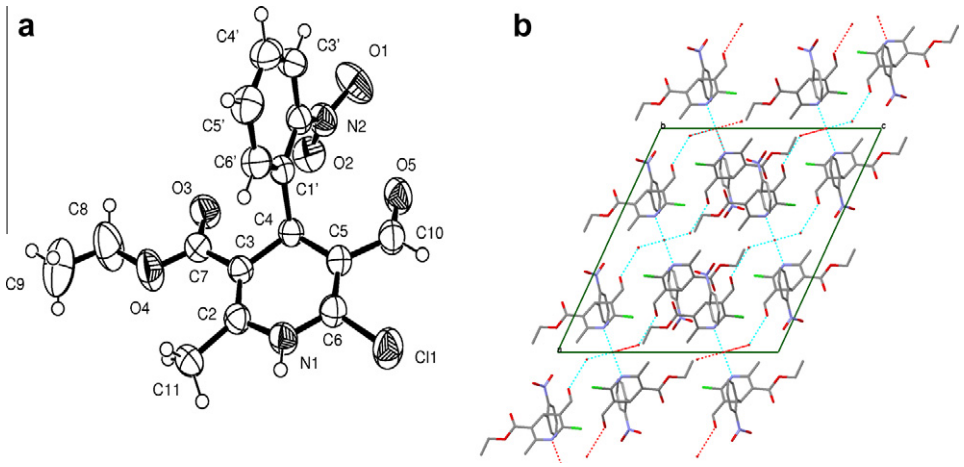


Fig. 1. X-ray crystallography of compound 2 h. (a) Plot showing the atomic numbering scheme. Displacement ellipsoids are drawn at 50% probability level for non-H atoms. (b) Packing of the molecules in the unit cell showing their hydrogen bond network.

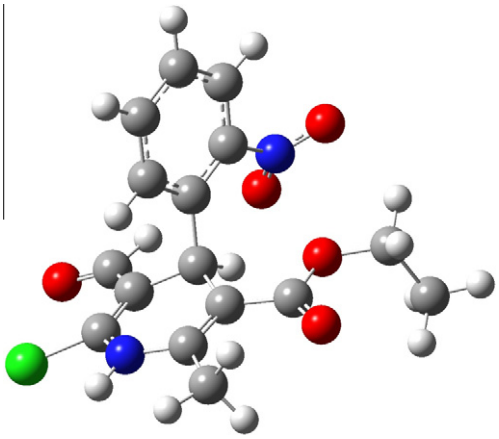


Fig. 2. Most stable conformation for compound 2 h calculated at B3LYP/6–31G(d,p).

In order to gain better understanding of the minimum energy conformation of **2h**, we performed a conformational study using the Molecular Mechanic Force Field (MMFF) [24] methods and the semiempirical Hamiltonian AM1 [24]. Calculations were carried out using the programs package PC Spartan Pro [24] and Gaussian 03 [25]. The conformers distribution was accomplished by the Monte Carlo methods [24]; and twenty possible minimum structures were studied which were ordered according to their own energy values. All these molecules were re-optimized using DFT methods [24] with functional B3LYP [26] and 6–31G(d,p) base [26]. In all cases, each conformation converges to the same structure (see Fig 2), which is very near to those determined by X-ray analyses. Only five of the calculated bond angles move over from the X-ray parameters reported. The gas phase model predicts quite well the geometrical parameters of the molecule which nicely match with those obtained experimentally by X-ray analysis. The structural data are collected in the Supplementary Material.

4. Conclusions

In summary, we have described an ultrasound assisted synthesis of a wide variety of 6-chloro-5-formyl-1,4-dihydropyridines that offers several practical advantages including faster reaction rates, higher purity, and higher yields, as well as cleaner conditions when compared with the conventional thermal method. Furthermore, we have determined unambiguously the X-ray structure of compound **2h** and calculated its minimum energy conformation which compares quite well with that obtained by means of the diffraction technique.

Acknowledgements

This work was supported by the MICINN of Spain (Project CT2008-00795/BQU and Consolider-Ingenio 2010C-07-25200) and the CAM (Project P-PPQ-000225-0505). M. Suárez is grateful to SAB2010-0132 from Ministerio de Educación de España.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ultsonch.2011.07.003.

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