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A microwave approach to the synthesis of certain 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones

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Abstract: A study of the synthesis of 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones from ethyl 2-cyano-3-(substituted phenyl) acrylates and acetophenone is presented. The 2-pyridones were obtained using conventional as well as microwave synthesis under solvent and solvent-free conditions in domestic and laboratory microwave ovens. The structure of the obtained pyridones was confirmed by m.p., FT-IR, NMR and UV data.

Keywords: pyridone; acrylate; cyclocondensation reaction; microwave chemistry.

INTRODUCTION

It is well known that many naturally occurring and synthetic compounds containing a 2-pyridone ring system have a broad spectrum of biological activity.[1–3] Some of them, such as milrinone, amrinone and their analogues are cardiotonic agents for the treatment of heart failure.[4–7] Other 2-pyridones possess antitumor,[8,9] antibacterial[10] and other biological activities.[1,2,11–15] In addition, derivatives of 3-cyano-2-pyridones are used in the manufacture of dyes, pigments, additives for fuels and lubricants, stabilizers for polymers and varnishes, acid–base indicators and other practically important materials.[2]

3-Cyano-2-pyridones can be obtained using different procedures starting from various initial substrates.[1,2,16,17] Microwave-assisted chemistry has also been used for the synthesis of 2-pyridones and their derivatives.[18–23]

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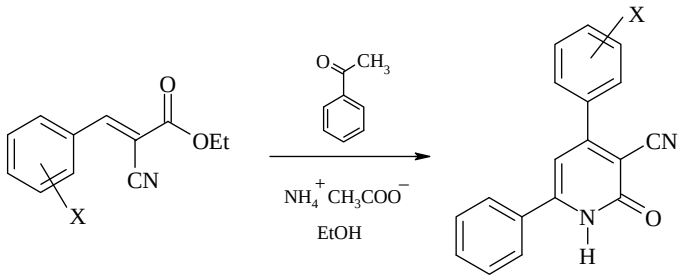
4,6-Diphenyl-3-cyano-2-pyridones (4,6-diaryl-2-oxo-1,2-dihydropyridine-3--carbonitriles) can be obtained by cyclization of ethyl cyanoacetate and ketones by ammonium acetate,[24] reaction between 1,3-diaryl-2-propen-1-one and cyanoacetamide using MeONa,[25] piperidine[26] or DMSO–*tert*-BuOK,[27] by the reaction of *β*-aminoenones with substituted acetonitriles,[28] by the reaction of malononitrile with acetylenic ketones,[29] and by solid-phase[30] and one-pot synthesis *via* three-component cyclocondensation under solvent-free conditions.[31] In addition, 4,6-diphenyl-3-cyano-2-pyridones were prepared by the reaction between 1,3--diaryl-2-propen-1-ones and cyanoacetamide using powdered KOH under microwave irradiation.[32]

One of the less explored synthesis of 4-(substituted phenyl)-6-phenyl-3--cyano-2-pyridones is their synthesis from ethyl 2-cyano-3-(substituted phenyl) acrylates (Scheme 1).[33,34]



Scheme 1. Synthesis of 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones from ethyl 2-cyano-3-(substituted phenyl) acrylates (X = H (**1**), 4-CH_3 (**2**), 4-OCH_3 (**3**), 4-Cl (**4**), 4-NO_2 (**5**), 4-Br (**6**), 3-NO_2 (**7**), 3-Cl (**8**), 2-NO_2 (**9**)).

In this work, a microwave approach to the synthesis of known 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones from ethyl 2-cyano-3-(substituted phenyl) acrylates and acetophenone was applied. Solvent and solvent-free reactions were performed in a modified domestic microwave oven and laboratory microwave ovens. Low to moderate yields were obtained in relatively short reaction time using optimized procedures.

RESULTS AND DISCUSSION

In order to study the synthesis of 4-(substituted phenyl)-6-phenyl-3-cyano-2--pyridones by condensation of ethyl 2-cyano-3-(substituted phenyl) acrylates with acetophenone, it was necessary to prepare ethyl 2-cyano-3-(substituted phenyl) acrylates. These compounds can be easily prepared from substituted benzaldehydes and ethyl cyanoacetate, as described elsewhere.[33,34] The reactions proceed relatively smoothly with good to excellent yields.

In the first part of the pyridone synthesis, 4-(substituted phenyl)-6-phenyl-3--cyano-2-pyridones were prepared by conventional methods.[33,34] Ethyl 2-cyano-

-3-(substituted phenyl) acrylates, acetophenone and ammonium acetate were heated in ethanol under reflux for 1 h and the obtained results are given in Table I. The molar ratio of the reactants was ethyl 2-cyano-3-(substituted phenyl) acrylates, acetophenone and ammonium acetate = 1:1:1.5.

TABLE I. Conventional and microwave synthesis of 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones

No.	Substituent	Conventional synthesis, %	Microwave synthesis[a]	
			Modified domestic oven, %	Microwave synthesis, %
1	H	35	34	30[b]
2	4-CH_3	40	32	14[c]
3	4-OCH_3	30	34	9[c]
4	4-Cl	32	33	32[c]
5	4-NO_2	No product	23	20[c]
6	4-Br	14	20	29[c]
7	3-NO_2	35	40	24[c]
8	3-Cl	26	29	15[c]
9	2-NO_2	12	16	12[c]

[a]Biotage – yield of compound **1** = 29 %; [b]300 W, 5 min; [c]200 W, 2 min

As can be seen from Table I, the pyridones were obtained in low to moderate yields, except for the 4-nitro derivative, which could not be obtained by this procedure. At this moment of the work, it seemed that an improvement in the isolated yield could be achieved if some other approach were used, such as microwave synthesis.

In the early days of microwave-assisted organic synthesis, the only possible way to do the synthesis was to use domestic or modified domestic microwave ovens. In this work, a microwave oven modified in such a manner to provide stirring and refluxing of the reaction mixture as described in literature was used.[35] First, an optimization of the synthesis of 3-cyano-4,6-diphenyl-2-pyridone was performed. The reactant ratio, power of irradiation and reaction time were varied. In addition, several solvents were used (ethanol, ethylene glycol and DMF). The obtained results showed (optimization results not presented) that the optimal reactant ratio was the same as in the conventional synthesis and that the solvent-free reaction gave the best yield. It was established that the optimal reaction time was 2 min (several times shorter than for the conventional method) and using these parameters, the synthesis of the pyridones was performed (Table I). The solvent-free synthesis of 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones in the modified domestic microwave oven led to similar or slightly better yields in comparison to conventional procedure. Except for the shorter reaction time, another advantage of the microwave synthesis was the synthesis of the 4-nitro derivative, which could not be obtained by the conventional approach. On the other hand, the disadvantages of such a method are the non-uniform heating,

mixing, and the precise determination of the reaction temperature.[36] In order to overcome the disadvantages of using modified domestic microwave ovens, syntheses in dedicated microwave reactors were performed (MicroSYNTH and Biotage). The reactions were controlled by an IR thermometer. Solvent-free microwave synthesis was used to enable comparison of the results with those obtained using the domestic microwave oven. Optimization of the synthesis of 3-cyano--4,6-diphenyl-2-pyridone synthesis in the MicroSYNTH reactor was performed by varying the irradiation power and reaction time using the previously established ratio of reactants (1:1:1.5). It was found that 5 min and 300 W are optimal for the reaction, since shorter or longer reaction times and lower or higher irradiation power decreased the yield of the pyridone. When these reaction parameters were applied to the synthesis of other pyridones, lower yields were obtained in comparison with those obtained in the modified domestic microwave oven (Table I).

To overcome all the disadvantages of solvent-free reactions, the synthesis of 3-cyano-4,6-diphenyl-2-pyridone in the Biotage reactor using ethanol as a solvent was optimized. The influence of reactant ratio, temperature and reaction time on the pyridone yield (HPLC) was studied. A higher concentration of reactants was also used. Even here, low yields were obtained. The highest yield was obtained at 150 °C after 15 min with the ratio of reactants being 1:1:3. The initial amount of acrylate was 1 mmol and solvent volume was 1 cm^3. The yield was 29 %.

Moreover, the influence of the structure of the ammonium salt was studied. Ammonium formate, carbonate and hydrogen carbonate were used. While ammonium formate gave a slightly lower yield than ammonium acetate, ammonium carbonate gave no yield at all. Ammonium hydrogen carbonate gave much lower yield then ammonium acetate.

During optimization, it was observed that the starting acrylate was the compound with the highest reactivity present in the reaction mixture. Acetophenone was much less reactive. Since no influence of the initial concentration of acetophenone was observed on the reaction and since no reaction between acetophenone and ammonium acetate was observed, it seems that the reaction proceeds initially by ammonia attack on the acrylate followed by the reaction of the formed amide with acetophenone.[37] The low yields could be explained by a possible parallel reaction of the acrylate molecules that might lead to dimerization.[38]

EXPERIMENTAL

Materials

All employed materials were obtained commercially, mostly from Sigma–Aldrich, and were used without further purification.

Equipment

The IR spectra were recorded on a Bomem MB series FTIR spectrophotometer, in the form of KBr pellets. The ^{1}H-NMR spectra were recorded as solutions in DMSO-d_6 using a

Varian Gemini-200 instrument, with tetramethylsilane as the internal standard. The UV absorption spectra were taken using a Shimadzu 1700 UV–Vis spectrophotometer in 1.00 cm cells at 25±0.1 °C in ethanol at a concentration of 5×10^{-5} mol dm^{-3}. The spectral data of the synthesized compounds together with their melting points are given in the Supplementary material to this paper.

A Samsung domestic microwave oven was modified as given in the literature[35] in order to provide mixing and refluxing of the reaction mixture. A MicroSYNTH Milestone and a Biotage Initiator 2.5 EXP were used for the microwave experiments. Analytical HPLC analysis (Shimadzu LC20) was performed on a C 18 reversed-phase analytical column (150 mm×4.6 mm, particle size 3 mm) using the mobile phases A (water:acetonitrile 90:10 (*V*/*V*) + 0.1 % TFA) and B (acetonitrile + 0.1 % TFA) at a flow rate of 0.5 cm^3 min^{-1}. The following gradient was applied: linear increase from 30 to 100 % B in 9 min, hold at 100 % solution B for 5 min.

Conventional synthesis of 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones[33,34,37]

A mixture of ethyl 2-cyano-3-(substituted phenyl) acrylate (0.1 mol), acetophenone (0.1 mol) and ammonium acetate (0.15 mol) in ethanol was heated under reflux for 1 h. After cooling, the obtained crystals were removed by filtration, washed with diethyl ether and purified by recrystallization (DMF/ethanol, 1:1).

Microwave synthesis of 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones in a modified domestic oven

A mixture of ethyl 2-cyano-3-(substituted phenyl) acrylate (0.1 mol), acetophenone (0.1 mol) and ammonium acetate (0.15 mol) was heated in a domestic microwave oven (100 or 200 W) for 2 minutes. Alternatively, a mixture in the chosen solvent was heated in the modified domestic microwave oven. After cooling, the obtained crystals were removed by filtration, washed with diethyl ether and purified by recrystallization (DMF/ethanol, 1:1).

Microwave synthesis of 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones in the MicroSYNTH reactor

A mixture of ethyl 2-cyano-3-(substituted phenyl) acrylate (2 mmol), acetophenone (2 mmol) and ammonium acetate (3 mmol) was heated in a microwave reactor in a glass tube (∅ 29 mm) equipped with a condenser for 2 to 5 min. After cooling, the obtained crystals were removed by filtration, washed with diethyl ether and purified by recrystallization (pyridine/ethanol, 1:1).

Microwave synthesis of 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones in the Biotage reactor

A mixture of ethyl 2-cyano-3-(substituted phenyl) acrylate (1 mmol), acetophenone (1 mmol) and ammonium acetate (3 mmol) in ethanol (1 cm^3) was heated in a Biotage microwave reactor for a period of 15 min at 150 °C. The product yield was established by HPLC analysis at 215 nm.

CONCLUSIONS

The synthesis of 4-(substituted phenyl)-6-phenyl-3-cyano-2-pyridones from ethyl 2-cyano-3-(substituted phenyl) acrylates and acetophenone using microwave irradiation showed that the reaction time could be shortened from 60 to 2 min while the isolated yields remained constant. The 4-nitro derivative could be

only prepared under microwave irradiation. Solvent-free reactions in comparison to those run in solvents gave better results.

SUPPLEMENTARY MATERIAL

Melting points and spectral data of the synthesized pyridones are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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И З В О Д

МИКРОТАЛСНИ ПРИСТУП СИНТЕЗИ ОДРЕЂЕНИХ 4-(СУПСТИТУИСАНИХ ФЕНИЛ)-6-ФЕНИЛ-3-ЦИЈАНО-2-ПИРИДОНА

АЛЕКСАНДАР МАРИНКОВИЋ[1], ДУШАН МИЈИН[1], ЈЕЛЕНА МИРКОВИЋ[1], ВЕСЕЛИН МАСЛАК[2] и C. OLIVER KAPPE[3]

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У оквиру рада приказана је синтеза 4-(супституисаних фенил)-6-фенил-3-цијано-2--пиридона полазећи од етил-2-цијано-3-(супституисаних фенил) акрилата и ацетофенона. 2-Пиридони су добијени како у присуству тако и у одсуству растварача користећи класичну и микроталасну синтезу, у модификованој микроталасној пећници за домаћинство као и у лабораторијском микроталасном реактору. Структура добијених пиридона потврђена је температурама топљења, IC, NMR и UV подацима.

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