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Ultrasound-Assisted Synthesis of 2-amino-4H-Pyran Derivatives under Aqueous Media

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Abstract: The study aims to design and synthesize a new series of ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate that were pleasantly synthesized in various yields. The one-pot multi-component reaction is crucial due to the use of simple and easily available chemicals, less reaction time, economically friendly, and good accessory yield. The structures of the new prepared products were identified by elemental analysis, IR, ^{1}H, and ^{13}C NMR and Mass spectra data.

Keywords: 4H-Pyran; ultrasound irradiation; multi-component reaction.

1. Introduction

In the modern era, the focus is on green chemistry using eco-friendly reagents, and mild reaction conditions are one of the most appealing growth in the synthesis of widely used organic compounds. The use of water as a promising solvent for organic reactions has received substantial attention in the area of organic synthesis due to its green credentials [1,2] and organic synthesis in aqueous media, offering key advantages such as rate improvement and insolubility of the final products, which facilitates their isolation by simple filtration.

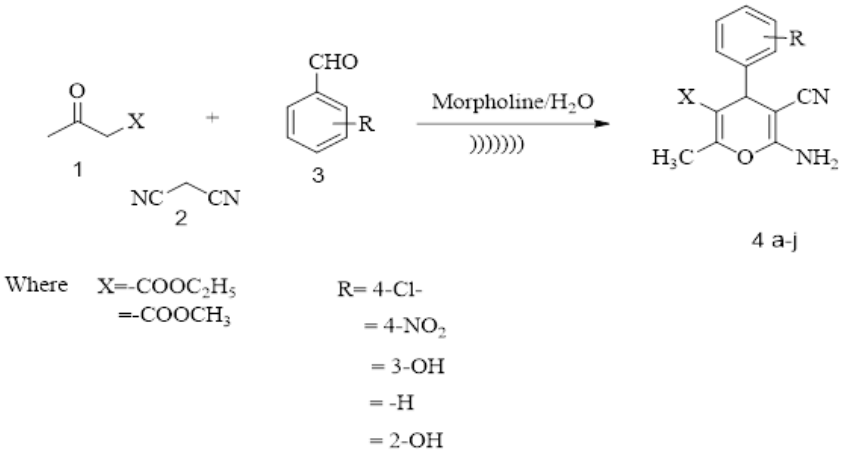
MCRs (multi-component reactions) are becoming increasingly popular in organic and medicinal chemistry since their techniques provide considerable benefits over traditional linear synthesis [3]. MCRs are one of the most powerful emerging synthetic tools for creating molecular diversity and complexity as they allow the creation of multiple bonds in a single operation [4].

Oxygen-containing heterocyclic compounds are widespread in natural products and medicinal agents, and their applications in biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important [5-9].

Among these, 4H-pyran derivatives have attracted much interest due to their biological activity and potential as a template for medicinal chemistry. The conventional method for synthesizing 4H-pyran is to react with methyl acetoacetate at a high temperature or in a sealed tube. Recently, several improved methods have been reported in the literature to synthesize this heterocyclic system. Multi-step methods, extensive reaction durations, inadequate yields, and the use of organic solvents or hazardous reagents are shortcomings of most of these approaches. These facts prompted us to further investigate in search of more efficient methods for preparing these kinds of compounds.

In recent years, ultrasonic irradiation has become more common in chemical synthesis. A large number of organic reactions can be carried out in a better yield, shorter reaction time,

milder reaction conditions under ultrasonication. Compared with traditional methods, this method is more appropriate and easily controlled [10]. Moreover, the use of ultrasound in heterocyclic systems has not been fully explored [11,12]. As a result of our interest in the synthesis of heterocyclic compounds under ultrasound irradiation [13-18], we report herein for the first time a facile one-pot synthesis of ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3- carboxylate derivatives via three-component reactions of a substituted aldehyde, ethyl acetoacetate, and malononitrile in water with catalyzed by morpholine under ultrasound irradiation. (Scheme-1).



Scheme 1. Ultrasonicated synthetic pathway.

2. Materials and Methods

Reagents and solvents used were obtained from commercial sources. Analytical thin-layer chromatography was carried out on TLC plates. Its coated with silica gel G for reaction monitoring and the determination of retardation factor. Spots of TLC were visualized in an iodine chamber. Melting points of newly synthesized derivatives were determined on An electrothermal melting point apparatus and were found uncorrected. Elemental analysis (% C, H, N) was confirmed by a Perlin-Elmer 2400 CHN analyzer. Mass spectra were obtained on SHIMADZU LC-MS 2010 spectrometer. ^{1}H NMR spectra were recorded on a Bruker Advance II 400 MHz while ^{13}C NMR spectra (Figure 1) on Varian Mercury-400, 100 MHz in DMSO-d_6 as a solvent and TMS an internal standard using 5 mm tube.

2.1. Typical procedure.

2.1.1. Conventional method for the synthesis of titled derivatives.

A mixture of methyl acetoacetate/ethylacetoacetate (0.015 mol), substituted aldehyde (0.015 mol), and malononitrile (0.015) in water (10 mL) with a catalytic amount of morpholine (0.00075 mol) was stirred at room temperature. The completion of the reaction was monitored periodically by TLC using n-hexane: ethyl acetate (60:40 v/v) was used as the mobile phase. Thus obtained product was filtered and washed with water (5mL), dried, and recrystallized from ethanol:water mixture (90:10 v/v).

2.1.2. Ultrasound irradiation for the synthesis of titled derivatives.

A mixture of methyl acetoactate/ethylacetoacetate (0.015 mol), substituted aldehyde (0.015 mol), and malononitrile (0.015 mol) in water (10 mL) with a catalytic amount of

morpholine (0.00075 mol) was irradiated by ultrasonic bath irradiation at room temperature (33 kHz). The mixture of n-hexane:ethyl acetate (60:40 v/v) was used as a mobile phase to monitor the completion of the reaction. Thus obtained product was filtered and washed with water (5 mL), dried, and recrystallized from ethanol:water (90:10 v/v).

3. Results and Discussion

To reach appropriate conditions for the synthesis of ethyl 6-amino-5-cyano-2-methyl 4-phenyl- 4H- pyran-3 carboxylate derivatives, various reaction conditions have been investigated in the reaction of ethyl/methyl acetoacetate 1, malononitrile 2, and various substituted benzaldehyde 3 as a model reaction.

3.1. Effect of the solvents under ultrasound irradiation

Initially, we conducted various tests to investigate the effects of the solvent. As a consequence, we experimented with polar solvents such as methanol, ethanol, and water; the results indicated that the reaction with water as the solvent produced the greatest results, yielding products not only in good yield but also at faster reaction rates (80% yield in 2 minutes) (Table 1, entry 4). Methanol and ethanol produced intermediate quantities of desirable compounds, although they needed a longer time to react (Table 1, entries 2 and 3).

Table 1. The model reaction in different conditions under ultrasound irradiation.

Entry	Solvent	Time (min)	Yield %
1	Solvent free	60 min.	Trace
2	Methanol	40 min	55
3	Ethanol	30 min	60
4	Water	02	80

3.1.1. Comparison of ultrasonic irradiation and heating methods.

All previously mentioned syntheses were carried out under the conventional method (Table 2). It was observed poor yields of products and took greater reaction time. In contrast, the same reaction carried under ultrasound irradiation (Table 3) was found to have an advantageous effect on the synthesis of ethyl 6-amino- 5-cyano-2-methyl 4-phenyl- 4H–pyran-3 carboxylate derivatives, which were superior to the traditional method concerning yield, reaction time, particularly when considering the basic green chemistry concept [19-20].

Table 2. Synthesis of ethyl 6-amino-5-cyano-2-methyl 4-phenyl-4H pyran-3 carboxylate derivatives under sonication and conventional conditions.

Entry	Compound	-X	- R	Ultrasonic irradiation		Conventional method	
				Time (min)	Yield	Time (min)	Yield
1	4a	$-COOC_2H_5$	4-Cl	02	65	120	50
2	4b	$-COOC_2H_5$	3-OH	02	60	90	47
3	4c	$-COOC_2H_5$	$4-NO_2$	01	74	120	54
4	4d	$-COOC_2H_5$	2-OH	03	55	60	41
5	4e	$-COOC_2H_5$	-H	02	65	110	51
6	4f	$-COOCH_3$	4-Cl	02	70	100	52
7	4g	$-COOCH_3$	3-OH	02	55	90	34
8	4h	$-COOCH_3$	$4-NO_2$	02	80	120	65
9	4i	$-COOCH_3$	2-OH	02	67	80	52
10	4j	$-COOCH_3$	-H	02	58	90	46

Table 3. Effect of amount of catalyst in the synthesis of the product 4.

Entry	Amount of morpholine (Equiv %)	Time (min)	Yield %
1	Trace	30	Trace
2	5	02	80
3	10	05	79
4	20	07	79

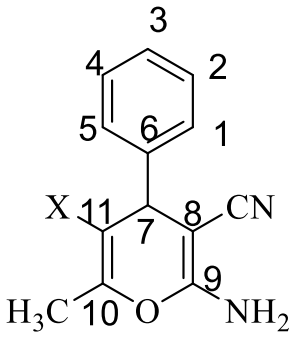


Figure 1. Numbering of C atoms in ^{13}C NMR.

3.1.2. Experimental data.

3.1.2.1. Synthesis of ethyl 6–amino-5-cyano-2-methyl-4-(4-chlorophenyl)-4H-pyran-3-carboxylate (4a).

M.p.: 341-345°C; Yield: 65%; IR (ATR, cm^{-1}): 834 (-C-Cl), 1675 (-C=O), 2191 (-CN), 3365, 3404 (-NH primary amine); Anal. calcd. for $C_{16}H_{15}ClN_2O_3$: C-60.20, H-4.71, N-8.75; Found: C-60.29, H-4.74, Cl-l1.12, N-8.79; ^1H NMR: 6.4-6.7 (m,4H,Ar-H), 6.80 (s,2H,NH_2), 2.2 (s,3H,CH_3), 1.29 (t,3H,-CH_3 ester), 4.03 (m,2H,-CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 13.67 (C-14), 18.18 (CH_3), 39.09 (C-7), 56.90 (C-11), 60.09 (C-13), 106.74 (C-8), 119.47 (CN), 128.25 (C-2,C-4), 128.97 (C-1,C-5), 131.41 (C-3), 143.83 (C-6), 156.92 (C-9), 158.39 (C-10), 165.16 (C-12). m/z:319.7

3.1.2.2. Synthesis of ethyl 6-amino-5-cyano-2-methyl-4-(3-hydroxyphenyl)-4H-pyran-3-carboxylate (4b).

M.p.: 410-415°C; Yield: 60%; IR (ATR, cm^{-1}): 1675 (-C=O), 2191 (-CN), 3365, 3404 (-NH primary amine), 3580 (-OH); Anal. calcd. for $C_{16}H_{16}N_2O_4$: C-63.78, H-5.27, N-9.24; Found: C-63.99, H-5.37, N-9.33%.^1H NMR: 6.4-6.7 (m,4H,Ar-H), 6.80 (s,2H,NH_2), 2.2 (s,3H,CH_3), 1.29 (t,3H,CH_3 ester), 4.03 (m,2H,CH_2), 4.41 (s,1H,OH); ^{13}C NMR (100 MHz, DMSO-d_6, , ppm): 13.69 (C-14), 18.20 (CH3), 39.08 (C-7), 56.96 (C-11), 60.12 (C-13), 106.81 (C-8), 119.41 (CN), 126.22 (C-3), 126.35 (C-5), 128.10 (C-1), 134.10 (C-2), 130.41 (C-4), 144.11 (C-6), 156.94 (C-9), 158.47 (C-10), 165.31 (C-12). m/z:301.1

3.1.2.3. Synthesis of ethyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4H-pyran-3-carboxylate(4c).

M.p.: 400-410°C; Yield: 74%; IR (ATR, cm^{-1}): 1516 (-N=O), 1680 (-C=O), 2198 (-CN), 3370, 3440 (-NH primary amine); Anal. calcd. for $C_{16}H_{15}N_3O_5$: C-58.00, H-4.43, N-l2.07; Found: C-58.36, H-4.59, N-l2.76%.; ^1H NMR: 7.4-8.1(m,4H,Ar-H), 6.80(s,2H,NH_2), 2.2(s,3H,CH_3), 1.29(t,3H,CH_3 ester), 4.03(m,2H,CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 13.61 (C-14), 18.29 (CH3), 39.07 (C-7), 56.21 (C-11), 60.18 (C-13), 105.97 (C-8), 119.19

(CN), 123.5 (C-1,C-5), 128.3 (C-2,C-4), 146.3 (C-3), 152.41 (C-6), 157.87 (C-9), 158.50 (C-10), 164.90 (C-12); m/z:330.1

3.1.2.4. Synthesis of ethyl 6-amino-5-cyano-2-methyl-4-(2-hydroxyphenyl)-4H-pyran-3-carboxylate(4d).

M.p.: 410-415°C; Yield: 55%; IR (ATR, cm^{-1}): 1675 (-C=O), 2191 (-CN), 3365, 3404 (-NH primary amine), 3580 (-OH);Anal. calcd. for $C_{16}H_{16}N_2O_4$: C-63.42, H-5.30, N-9.07; Found: C-63.99, H-5.37, N-9.33%. ^{1}H NMR: 6.86-7.27(m,4H,Ar-H), 6.80(s,2H,NH_2), 2.2(s,3H,CH_3), 1.29(t,3H,CH_3 ester), 4.03(m,2H,CH_2), 9.68(s,1H,OH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 13.65 (C-14), 18.24 (CH3), 39.09 (C-7), 56.93 (C-11), 60.20 (C-13), 106.79 (C-8), 119.39 (CN), 126.57 (C-5), 126.90 (C-4), 127.15 (C-3), 128.78 (C-2), 131.4 (C-1), 143.90 (C-6), 156.89 (C-9), 158.28 (C-10), 165.25 (C-12). m/z:301.1

3.1.2.5. Synthesis of ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate(4e).

M.p.: 295-300°C; Yield: 65%; IR (ATR, cm^{-1}): 1692 (-C=O), 2186 (-CN), 3340, 3397 (-NH primary amine), Anal. calcd. for $C_{16}H_{16}N_2O_3$: C-67.42, H-5.43, N-9.80; Found: C-67.59, H-5.67, N-9.85%. ^{1}H NMR: 6.86-7.27(m,5H,Ar-H), 6.80(s,2H,NH_2), 2.2(s,3H,CH_3), 1.29(t,3H,CH_3 ester), 4.03(m,2H,CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): (C-3), 126.8 (C-1,C-5), 128.9 (C-2,C-4), 145.1 (C-6), 157.12 (C-9), 158.33 (C-10), 164.98 (C-12).m/z:285.11

3.1.2.6. Synthesis of methyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate(4f).

M.p.: 325-330°C; Yield: 70%; IR (ATR, cm^{-1}): 834 (-C-Cl), 1675 (-C=O), 2191 (-CN), 3365, 3404 (-NH primary amine); Anal. calcd. for $C_{15}H_{13}ClN_2O_3$: C-59.00, H-4.15, N-9.07; Found: C-59.12, H-4.30, N-9.19%.^{1}H NMR: 7.15-7.21 (m,4H,Ar-H), 6.80(s,2H,NH_2), 2.31(s,3H,CH_3), 3.61 (s,3H,CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm):13.67 (C-14), 18.18 (CH3), 39.09 (C-7), 56.90 (C-11), 60.09 (C-13), 106.74 (C-8), 119.47 (CN), 128.25 (C-2,C-4), 128.97 (C-1,C-5), 131.41 (C-3), 143.83 (C-6), 156.92 (C-9), 158.39 (C-10), 165.16 (C-12). m/z: 305.0

3.1.2.7. Synthesis of methyl 6-amino-5-cyano-4-(3-hydroxyphenyl)-2-methyl-4H-pyran-3-carboxylate(4g).

M.p.: 395-400°C; Yield: 55%; IR (ATR, cm^{-1}): 1675 (-C=O), 2191 (-CN), 3365, 3404 (-NH primary amine), 3580 (-OH); Anal. calcd. for $C_{15}H_{14}N_2O_4$: C-62.42, H-4.73, N-9.65; Found: C-62.93, H-4.93, N-9.79%.^{1}H NMR: 6.7-7.0 (m,4H,Ar-H), 6.80(s,2H,NH_2), 2.31(s,3H,CH_3), 3.61 (s,3H,CH_3), 9.29(s,1H,OH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 13.69 (C-14), 18.20 (CH3), 39.08 (C-7), 56.96 (C-11), 60.12 (C-13), 106.81 (C-8), 119.41 (CN), 126.22 (C-3), 126.35 (C-5), 128.10 (C-1), 134.10 (C-2), 130.41 (C-4), 144.11 (C-6), 156.94 (C-9), 158.47 (C-10), 165.31 (C-12).m/z: 287.09

3.1.2.8. Synthesis of methyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4H-pyran-3-carboxylate(4h).

M.p.: 400-410°C; Yield: 80%; IR (ATR, cm^{-1}): 1516 (-N=O), 1680 (-C=O), 2198 (-CN), 3370, 3440 (-NH primary amine); Anal. calcd. for $C_{15}H_{13}N_3O_5$: C-57.09, H-4.10, N-l3.13; Found: C-57.14, H-4.16, N-l3.33%.^{1}H NMR:7.0-8.0 (m,4H,Ar-H), 6.80(s,2H,NH_2), 2.31(s,3H,CH_3), 3.61 (s,3H,CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 13.61 (C-14), 18.29 (CH3), 39.07 (C-7), 56.21 (C-11), 60.18 (C-13), 105.97 (C-8), 119.19 (CN), 123.5 (C-1,C-5), 128.3 (C-2,C-4), 146.3 (C-3), 152.41 (C-6), 157.87 (C-9), 158.50 (C-10), 164.90 (C-12);m/z: 316.09

3.1.2.9. Synthesis of methyl 6-amino-5-cyano-4-(2-hydroxyphenyl)-2-methyl-4H-pyran-3-carboxylate(4i).

M.p.: 395-400°C; Yield: 67%; IR (ATR, cm^{-1}): 1675 (-C=O), 2191 (-CN), 3365, 3404 (-NH primary amine), 3580 (-OH);Anal. calcd. for $C_{15}H_{14}N_2O_4$: C-92.82, H-4.83, N-9.70; Found: C-92.93, H-4.93, N-9.79%.^{1}H NMR: 6.7-7.2 (m,4H,Ar-H), 6.80(s,2H,NH_2), 2.31(s,3H,CH_3), 3.61 (s,3H,CH_3), 9.68(s,1H,OH); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 13.65 (C-14), 18.24 (CH3), 39.09 (C-7), 56.93 (C-11), 60.20 (C-13), 106.79 (C-8), 119.39 (CN), 126.57 (C-5), 126.90 (C-4), 127.15 (C-3), 128.78 (C-2), 131.4 (C-1), 143.90 (C-6), 156.89 (C-9), 158.28 (C-10), 165.25 (C-12). m/z: 287.09

3.1.2.10. Synthesis of methyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate(4j).

M.p.: 285-300°C; Yield: 58%; IR (ATR, cm^{-1}): 1692 (-C=O), 2186 (-CN), 3340, 3397 (-NH primary amine),; Anal. calcd. for $C_{15}H_{14}N_2O_3$: C-66.42, H-5.13, N-l0.27; Found: C-66.66, H-5.22, N-l0.36%.^{1}H NMR: 6.5-7.5 (m,5H,Ar-H), 6.80 (s,2H,NH_2), 2.31(s,3H,CH_3), 3.61 (s,3H,CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): (C-3), 126.8 (C-1,C-5), 128.9 (C-2,C-4), 145.1 (C-6), 157.12 (C-9), 158.33 (C-10), 164.98 (C-12). m/z: 271.1

4. Conclusions

In conclusion, we report here a de novo approach to explore the use of ultrasound irradiation to synthesize ethyl 6-amino-5-cyano-2-methyl 4-phenyl- 4H-pyran-3 carboxylate derivatives using the aqueous medium and ambient condition within 2 min. It can be observed that principles of green chemistry are applied to generate interesting products using aqueous media that are less expensive and less toxic than those with organic solvents. Compared to traditional methods, the reported procedure offers numerous benefits, including outstanding yields, reduced reaction time, mild reaction conditions, and negligible ecological effects.

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Conflicts of Interest

The authors declare no conflicts of interest.

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