Ultrasonically Assisted N-Cyanoacylation and Synthesis of Alkyl(4-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)benzoyl)amino Acid Ester Derivatives

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ABSTRACT: This work represents the use of N-3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropanenitrile as a cyanoacetylating agent for the synthesis of cyanoacetamide benzoic acid and benzophenone derivatives by two different methods, namely, conventional heating and ultrasonication. The cyanoacetamide derivatives were subjected to cyclization to produce N-substituted 2-pyridone derivatives under conventional heating and by an ultrasonic method as well. The ultrasonic method afforded the products in less reaction time with high yields and purities compared to the conventional method, as observed from their spectral data. N-(4-Carboxy phenyl)-4,6-dimethyl-3-cyano-2-pyridone was coupled with different amino acid esters by the OxymaPure/DIC methodology under traditional and ultrasonic conditions. Again, ultrasonication assisted the coupling step and afforded the products with higher yields and purities compared to the traditional method. Fourier transform infrared spectroscopy, NMR (¹H and ¹³C), elemental analysis, and LC–MS were used to determine the structures of all compounds. Finally, a feature of this protocol is exploring the utilization of ultrasonication as an eco-friendly alternative conventional heating method for N-cyanoacylation and synthesis of N-substituted pyridinone derivatives and as a coupling method for the formation of an amide bond, which might be of interest for many researchers.

INTRODUCTION

The conventional method used to carry out organic synthesis faces some disadvantages such as long reaction times, more solvent requirements, high temperatures, unsatisfactory yields, toxic reagent requirements, as well as the formation of inefficient products.¹ The essential challenge for today’s researchers is to make their methodology under environmentally conditions to avoid the use of severe reaction conditions and hazardous reagents.²³

Ultrasonication is now considered an important tool to perform organic reactions; in addition, it is a cost-effective method to support numerous reactions that offer a facile, clean, green, and eco-friendly way for the synthesis of compounds with biological values.⁴ Moreover, this process offers more advantages over the conventional heating method in terms of reaction rate and time.⁵⁻¹¹

Ultrasonad accelerates the reactions through the formation, growth, and implosive collapse of bubbles in liquids, which furnish hot spot regions.¹² Furthermore, these intense collapses of cavitation bubbles also increase the local temperature within the reaction mixture, which finally leads to cross the activation energy barrier.¹³,¹⁴ Such valuable features as a whole have inspired organic researchers to explore the application of ultrasound for the synthesis of various organic scaffolds.

In the last few years, researchers have been involved in the exploration of the potential of activated nitriles in heterocyclic synthesis.¹⁵⁻¹⁷ Especially, cyanoacetic hydrazide has been reported in many literature works as a good intermediate for the synthesis of numerous biologically active heterocyclic compounds and pharmaceutical agents.¹⁸⁻²⁶ N-Cyanoacetylation of aromatic amines can be achieved by various reagents such as cyanoacetyl chloride, cyanoacetyl azide, cyanoacetic ester, N-(cyanoacetyl)imidazole, and 1-cyanoacetyl-3,5-dimethylpyrazole.⁷ Among these reagents, 1-cyanoacetyl-3,5-dimethylpyrazole is commercially available, cheap, and nontoxic reagent that proved to be superior to other cyanoacetylating agents.²⁷ The advantages of using 1-cyanoacetyl-3,5-dimethylpyrazole are that it consumes less reaction time for the formation of N-cyanoacetylation products, the products can be collected in higher yields from the reaction medium, and the leaving group (3,5-dimethylpyr-
azole) is very soluble in most of the organic solvents and stay in the filtrate.28−30 On the other hand, 2-pyridones and their derivatives play an essential role in medicinal chemistry and are proven to possess several biological properties;24,31−35 thus, despite the large number of methods known for their synthesis, new procedures are required to be developed. Many catalysts have been used in the synthesis of 2-pyridinone from 1,3-diketones, such methanesulfonic acid,36 SiO2,37 and triethylamine or piperazine.38 Microwave irradiation in preparing N-substituted 2-pyridones has also been reported recently.39 In addition, compounds containing a 4-aminobezoate moiety were reported to possess various biological and pharmacological activities.40−42 In this regard, we focus in this work on N-cyanoacylation of benzoate derivatives and N-substituted 2-pyridinone amino acid derivatives by taking the advantages of the ultrasonic method over the conventional method.

■ RESULTS AND DISCUSSION

N-Cyanoacylation. N-Cyanoacylation of 4-aminobenzoic acid and its ester derivative or 4-aminoacetophenone with 1-cyanoacetyl-3,5-dimethylpyrazole 1 is a useful preparative method for the synthesis of difficultly available N-substituted cyanoacetamides. This method appeared to be more convenient and economical and occurs at a much faster rate to afford a good yield of the product when compared with other cyanoacytating agents.27

In the present study, cyanoacytating agent 1 was prepared as described in Method S1 (Supporting information) following the reported procedure in literature works,35,44 where cyanocetyl hydrazide was prepared from the ethylacetoacetate first and then reacted with acetylaceton via condensation−cyclization in water containing a catalytic amount of HCl. The spectral data agreed with the reported data (Figure S1, Supporting information). Cyanoacytating agent 1 was reacted ethyl-4-aminobenzoate 2, 4-aminoacetophenone 5, or 4-aminobenzoic acid 8 in dry toluene employing conventional heating and ultrasonication to give cyanoacytating products 3, 6, and 9, respectively (Scheme 1). The ultrasonic method afforded the products in less reaction time with high yields and purities, as shown in Table 1. The spectral data of the products (Figures S2−S4, Supporting information) agreed with the reported data [ref 26 for compound 6: mp 225 °C, yield 91%; ref 45 for compound 9: 267−269 °C, yield 90%]. Figure 1 indicates that the ultrasonic method affords compound 3 in higher purity, as shown in Figure 1B,
compared to that obtained by conventional heating (Figure 1A).

The $^1$H NMR spectrum of compound 3 (Figures 2 and S2, Supporting information) showed a triplet at $\delta$ 1.29 and a quartet at $\delta$ 4.25 for the ethyl ester residue (CH$_2$CH$_3$). The singlet peak at $\delta$ 3.92 represented the protons of the methylene group, the two doublets at $\delta$ 7.65 and $\delta$ 7.93 were related to the four aromatic protons ($H_a$ and $H_b$, respectively), and the singlet at $\delta$ 10.62 represented NHCO. The $^{13}$C NMR spectrum (Figure S2, Supporting information) showed peaks at $\delta$ 14.1 (methyl of the ethyl ester residue), 26.8 (CH$_2$), 60.7 (methylene group of the ethyl ester residue), 103.9 (related to the carbon of the active methylene group; $-\text{CO}-\text{CH}_2-\text{CN}$), 114.4 (representing the carbon of the cyano group; $\text{CN}$), 118.9 ($C_a$), 125.9 ($C-\text{COOC}_2\text{H}_5$), 130.8 ($C_b$), 141.8 ($C-\text{NH}$), 160.2 (representing the carbonyl ester residue), and 165.9 ppm (representing the carbonyl; CO).

**Synthesis of N-Substituted 2-Pyridone Derivatives.** The synthesis of 2-pyridone derivatives (4, 7, and 10) was accomplished by the reaction of acetylacetone with $N$-cyanoacetamide derivatives 3, 6, or 9 in ethanol as a solvent.
and in the presence of the catalytic amount of triethylamine (0.7 equiv.) using conventional heating as well as the ultrasonic method (Scheme 1). Again, the ultrasonic method afforded 4, 7, and 10 in less reaction time with high yield and purity compared with the conventional method, as shown in Table 1.

The IR spectra of compound 10 (Figure S7, Supporting information) showed an absorption band in the region 3067 cm⁻¹ related to OH carboxylic; 2222 cm⁻¹ related to CN; and broad 1728, 1643, and 1608 cm⁻¹ for the two carbonyls and a phenyl residue. The ¹H NMR spectrum of compound 10 (Figures 3 and S8, Supporting information) showed two singlet peaks at δ 1.96 and 2.38 for the two methyl groups (a’ and b’, Figure 3), a singlet peak at δ 6.46 related to (CH₂), two doublet peaks at δ 7.45 and 8.08 for the four aromatic protons (Hₐ and Hₐ’, respectively), and a broad singlet peak at δ 13.21 for the carboxylic group (COOH). The ¹³C NMR spectrum of 10 (Figure S8, Supporting information) showed peaks at δ 20.6 and 21.4 for the two carbons (a’ and b’), 100.0 (C₅), 109.1 (C=CN), 115.8 (CN), 128.5 (C₆), (C=COOH), 130.7 (C₃'), 131.5, 141.2 (C₆), 151.8 (C(phenyl)=N), 160.0 (C₄), 160.4 (CO), and 166.6 (CO, carboxylic).

Synthesis of Alkyl (4-(3-Cyano-4,6-dimethyl-2-oxo-pyridin-1(2H)-yl)benzoyl) Amino Acid Ester Derivatives.

To explore the utility of employing ultrasonication in organic synthesis, especially for amide bond formation, compound 10 was coupled with an equimolecular amount of a different amino acid ester hydrochloride by OxymaPure/DIC as a coupling reagent, N,N-dimethylformamide (DMF) as a solvent, and diisopropylethylamine (DIEA) as a base at room temperature and the ultrasonic method at 30 °C as well to afford the target products 11a−h (Scheme 2). The ultrasonic method was very efficient and afforded the target products in less reaction time with high yields and purities compared to the traditional method (Table 2).

The IR spectra of compound 11a (Figure S9, Supporting information) showed an absorption band in the region 3367 cm⁻¹ related to NH, 2218 cm⁻¹ related to the CN, 1751 cm⁻¹ related to the ester group, and 1650 and 1608 cm⁻¹ for the carbonyl and phenyl residues. The ¹H NMR spectrum of compound 11a (Figure 4, Figure S10, Supporting information) as a prototype showed two singlet peaks at δ 1.97 and 2.39 for the two methyl group (pyridone residue), a singlet at δ 3.66 representing the three protons of methyl ester (OCH₃), a peak at δ 4.04 related to the methylene group (glycine residue), a singlet peak at δ 6.47 representing Hc, two doublet peaks at δ 7.45 and 7.99 related to the four aromatic protons (Ha and Hb), and a triplet at δ 9.11 representing NH. The ¹³C NMR spectrum of 11a (Figure S10, Supporting information) showed

| compd | conventional overnight at RT, yield (%) | ultrasonic method (1−2 h) at 30 °C, yield (%) |
|-------|----------------------------------------|----------------------------------------|
| 11a   | 83                                     | 93                                     |
| 11b   | 81                                     | 95                                     |
| 11c   | 80                                     | 94                                     |
| 11d   | 80                                     | 92                                     |
| 11e   | 80                                     | 94                                     |
| 11f   | 82                                     | 95                                     |
| 11g   | 80                                     | 93                                     |
| 11h   | 78                                     | 92                                     |

Table 2. Yield (%) and Reaction Time during Conventional Heating and the Ultrasonic Method for Coupling N-Substituted 2-Pyridone Derivatives with Amino Acid Esters
peaks at δ 20.7 and 21.3 for the two methyl groups, 41.5 for the methylene group of the glycine residue, 51.8 for the methyl ester, 99.9 for the carbon (C\(_\text{5}\), pyridone residue), 109.0 for C–CN (C\(_\text{7}\)), 115.7 for the cyano group (CN), 128.2 and 128.6 for the two carbons (C\(_\text{8}\) and C\(_\text{9}\)), 134.2 (C\(_\text{6}\)), 140.0 (C\(_\text{6}\)), 151.8 (C\(_\text{7}\)), 159.9 (CO, pyridine residue), 165.7 (CO, amide), and 170.3 (CO, ester).

**CONCLUSIONS**

This work described the synthesis of cyanacetamide benzoic acid derivatives and the synthesis of the cyanoacetamide benzophenone and their corresponding 2-pyridone derivatives by employing two different methods, namely, conventional heating and ultrasonication. The ultrasonic method afforded the product in less reaction time with high yield and purity compared to the conventional method. In addition, it gave a better yield compared to the previously reported method using microwave irradiation.39 The ultrasonic method also assisted the coupling of the weak carboxylic group of compound 10 with different amino acid esters using the Oxympure/DIC methodology and afforded the reaction product in less reaction time with higher yield and purity compared to the traditional method.

Finally, the feature of this protocol is exploring the utilization of ultrasonication as an eco-friendly alternative method for the conventional heating or traditional technique to assist N-cyanoacetylation and synthesis of N-substituted 2-pyridone derivatives and as a coupling method for the formation of an amide bond.

**MATERIALS AND METHODS**

All reagents, chemicals, and solvents were purchased from commercial suppliers. Reactions were monitored using TLC (silica gel 60-F254-protected aluminum sheets). All melting points were determined in open capillary tubes using a Gallenkamp melting point apparatus (Sigma-Aldrich Chemie GmbH, Tauferkichen, Germany) and were uncorrected. Fourier transform infrared (FTIR) spectra were recorded on a Nicolet 6700 spectrometer using KBr disks. 1H and 13C NMR spectra were recorded on a Jeol instrument. Elemental analyses were recorded on a PerkinElmer 2400 elemental analyzer (PerkinElmer Inc., Waltham, MA). An ultrasonic bath was purchased from Selecta (Barcelona, Spain).

**Synthesis of 3-(3,5-Dimethyl-1H-pyrazol-1-yl)-3-oxopropanenitrile (1).** First, cyanoacetic hydrazide was prepared following the reported method63 as follows.

Hydrazine hydrate (0.1 mol) in ethanol—ether (1:2, 300 mL) was added dropwise to ethyl cyanoacetate (0.1 mol) in ethanol (50 mL) at 5–10 °C under vigorous stirring. The resulting reaction mixture was stirred at 5–10 °C for 30 min and then at rt for 2 h. Filtered and washed ether to obtain the product as a white solid in yield 73%.

Then, an equimolar amount of 2-cyanoacetoxydrazide was mixed with acetylacetone in water (15 mL) and in the presence of a catalytic amount of HCl at 0 °C.44 The mixture was stirred at room temperature for 2 h. The white precipitate was filtered, washed with ice-cold water, and then dried under vacuum.

White solid in yield 91%, mp 113–114 °C; 1H NMR (400 MHz, CDCl\(_3\)) ppm: δ 2.20 (s, 3H, CH\(_3\)), 2.52 (s, 3H, CH\(_3\)), 4.26 (s, 2H, CH\(_2\)-CN), 6.03 (s, 1H, pyrazole-H).13C NMR (100 MHz, CDCl\(_3\)) (ppm): δ 13.7 (CH\(_3\)), 14.0 (CH\(_3\)), 26.8 (CH\(_2\)), 112.4 (C=C), 113.4 (CN), 144.7 (CH\(_3\)-C=C-N), 153.8 (C=C—N—N), 162.4 (C=O).

**General Method N-Cyanoacetylation. Conventional Method.** A solution of p-aminobenzoic acid derivatives (10 mmol) or p-aminocetophenone (10 mmol) in dry toluene (30 mL) was added to a solution of 1-cyanoacetyl-3,5-dimethylpyrazole (1.63 g, 10 mmol) in the same solvent (30 mL), and the mixture was heated under reflux for 6 h. After cooling, the solid product was isolated and washed with ethanol and then dried.

**Ultrasonic Method.** A solution of p-aminobenzoic acid derivatives (10 mmol) or p-aminocetophenone (10 mmol) in dry toluene (20 mL) was added to a solution of 1-cyanoacetyl-3,5-dimethylpyrazole (10 mmol) in the same solvent (20 mL) at rt, and then, the reaction mixture was subjected to ultrasound irradiation (20–30 min) at 60 °C. TLC was used to monitor the completion of reaction followed by a workup similar to the conventional methodology to obtain products with high yields (90–95%) and purities.

**Ethyl 4-(2-Cyanoacetamido)benzoate (3).** White solid in yields 82% (conventional heating, 6 h) and 91% (US 30 min at 60 °C) mp 163–164 °C (ref 42: mp 162 °C, yield 92%). 1H NMR (400 MHz, CDCl\(_3\)) δ: 1.29 (t, 3H, J = 7.2 Hz, CH\(_3\)), 3.54 (s, 2H, CH\(_2\)), 4.26 (q, 2H, CH\(_2\)), 7.55 (d, 2H, J = 8.8 Hz, Ar), 7.42–7.89 (d, 2H, J = 8.8 Hz, Ar), 10.09 (s, 1H, NH) ppm; 13C NMR (100 MHz, CDCl\(_3\)) δ: 14.1, 26.5, 60.7, 103.9, 114.4, 118.9, 125.9, 130.4, 141.8, 142.4, 160.2, 165.9 ppm.

**N-(4-Acetylphenyl)-2-cyanoacetamide (6).** White solid in yields 88% (conventional heating, 4 h) and 95% (US, 20 min), mp 226–227 °C (ref 26: 225 °C, yield 91%). 1H NMR (400 MHz, DMSO-d\(_6\)) δ: 2.94 (s, 3H, CH\(_3\)), 3.92 (s, 2H, CH\(_2\)), 7.64 (d, 2H, J = 8.8 Hz, Ar), 7.42–7.91 (d, 2H, J = 8.8 Hz, Ar), 10.59 (s, 1H, NH) ppm; 13C NMR (100 MHz, DMSO-d\(_6\)) δ: 26.5, 27.0, 115.6, 118.5, 128.3, 132.7, 142.3, 143.2, 151.7, 197.6 ppm.

**4-(2-Cyanoacetamido)benzoic Acid (9).** Off-white powder in yield 86% (conventional heating, 6 h) and 93% (US, 30 min), mp 261–263 °C (ref 45: mp 267–269 °C, yield 90%). IR (KBr, cm\(^{-1}\)): 3322 (NH), 3100 (OH), 2260 (CN), broad 1695, 1650 (2CO); 1H NMR (400 MHz, DMSO-d\(_6\)) δ: 3.92 (s, 2H, CH\(_2\)), 7.64 (d, 2H, J = 8.8 Hz, Ar-H), 7.95 (d, 2H, J = 8.8 Hz, Ar-H), 10.59 (s, 1H, NHCOO) ppm; 13C NMR (100 MHz, DMSO-d\(_6\)) δ: 27.0, 115.8, 118.5, 125.8, 130.6, 142.4, 161.7, 166.8 (CO) ppm. Anal. Calcd. for C\(_{10}\)H\(_8\)NO\(_3\) (204.19). Found. C, 58.97; H, 4.06; N, 13.93.

**General Method for the Synthesis of 2-Pyridine Derivatives (4, 7, and 10). Conventional Heating.** To a mixture of compounds 3, 6, or 9 (5 mmol) and acetylacetone (0.51 mL, 5.5 mmol) in absolute ethanol (30 mL) was added triethylamine (0.5 mL, 1.5 equiv. in case of an acid 2 equiv of DIEA was used). The reaction mixture was refluxed for 10–12 h, then cooled down to room temperature, and poured onto (100 mL) ice/water, and the medium was neutralized by dilute HCl. The obtained solid was filtered off, washed with water, and recrystallized from ethanol to afford the target compound.

**Ultrasonic Method.** Compound 3, 6, or 9 (5 mmol) was mixed with acetylacetone (5.5 mmol) in ethanol (20 mL), and then, triethylamine was added (1.5 equiv.) at rt with stirring. The reaction mixture was subjected to ultrasonic irradiation (1–2 h) at 60 °C. TLC was used to monitor the completion of reaction followed by workup similar to conventional methodology to obtain products with high yields (90–95%) and purities.
Ethyl 4-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)benzoate (4). Off-white solid in yields 84% (conventional heating, 10 h), 93% (US, 1.5 h at 60 °C), mp 223–224 °C. 1H NMR (100 MHz, DMSO-d6): δ 1.33 (t, 3H, J = 7.2 Hz, CH3) 1.93 (s, 3H, CH3); 2.39 (s, 3H, CH3), 4.34 (q, 2H, J = 6.4, 7.7 Hz, CH2); 6.47 (d, 1H, CH), 7.48 (d, 2H, J = 8.4 Hz, Ar), 8.10 (d, 2H, J = 8.4 Hz, Ar) ppm; 13C NMR (100 MHz, DMSO-d6): δ 14.1, 20.7, 21.4, 61.1, 100.0, 119.1, 115.7, 128.7, 130.6, 141.4, 151.1, 160.0, 160.3, 165.0 ppm. Anal. Calc'd for C15H12N2O3 (268.27) C, 67.16; H, 4.51; N, 10.44. Found C, 131.5, 141.2, 151.8, 160.0, 163.5, 170.3 ppm. LC/MS (ESI): 340.25 [M + H]+. Anal. Calc'd for C16H14N2O2 (266.11) C, 72.17; H, 5.41; N, 10.77.

N-(4-Carboxyphenyl)-4,6-dimethyl-3-cyano-2-pyridine-3-carbonitrile (7). White solid in yields 82% (conventional heating, 12 h, 2 reflux) and 91% (US, 2 h), mp 321 °C (dec) [ref.35 mp 259–261 (MW) and 80% (conventional heating) and 91% (MW)]. 1H NMR (400 MHz, DMSO-d6): δ 1.96 (s, 3H, CH3); 2.39 (s, 3H, CH3); 2.64 (s, 3H, CH3); 6.48 (s, 1H, CH), 7.49 (d, 2H, J = 8.8 Hz, Ar); 8.11 (d, 2H, J = 8.4 Hz, Ar) ppm; 13C NMR (100 MHz, DMSO-d6): δ 20.7, 21.4, 26.5, 100.0, 115.8, 137.2, 141.3, 151.7, 159.9, 160.3, 197.4 ppm. Anal. Calc'd for C14H13N3O2 (266.11) C, 72.17; H, 5.30; N, 10.52. Found C, 72.32; H, 5.41; N, 10.77.

General Method for the Reaction of 10 with Amino Acid Esters Using OxymaPure/DIC. Traditional Method (TM). A mixture of an acid 10 (1 mmol) and OxymaPure (1 mmol) was dissolved in 5 mL of DMF at 0 °C, followed by the dropwise addition of DIC (1.1 mmol) at 0 °C. The reaction mixture was preactivated for 5 min, and then, a mixture of 1 mmol amine acid ester hydrochloride and 1 mmol DIEA in DMF (3 mL) was added dropwise at the same temperature. After that, the mixture was stirred at 0 °C for 1 h and then left overnight under stirring at rt. The progress of the reaction was followed by TLC (etheracetate–n-hexane, 4:6; or MeOH–CHCl3, 1:9). Excess water was added, and the solid product was filtered or extracted with ethylacetate, washed with water, and then dried and recrystallized from ethylacetate.

Ultrasonic Method (US). A mixture of an acid 10 (1 mmol) and OxymaPure (1 mmol) was dissolved in 5 mL of DMF at 0 °C, followed by the dropwise addition of DIC (1.1 mmol) at 0 °C. The reaction mixture was preactivated for 5 min, and then, a mixture of 1 mmol amine acid ester hydrochloride and 1 mmol DIEA in DMF (3 mL) was added dropwise at the same temperature. After that, the mixture was stirred at 0 °C for 1 h and then the reaction mixture was subjected to ultrasound irradiation (1–2 h) at 30 °C. TLC was used to monitor the completion of reaction followed by a workup similar to the traditional methodology to obtain products with higher yields (92–95%) and purities.

Methyl (4-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)benzoyl)glycinate (11a). Off-white solid in yields 83% (TM) and 93% (US), mp 256–258 °C; FTIR (KBr): 3258 (NH), 2260 (CN, cyano), 1730 (CO, ester), 1620 (C=N amide), 1650 (CO, pyridine), 1371 (O–CH3) cm−1; 1H NMR (400 MHz, DMSO-d6): δ 1.97 (s, 3H, CH3); 2.39 (s, 3H, CH3); 3.66 (s, 3H, OCH3); 4.04 (d, 2H, J = 6.0 Hz, CH2); 6.47 (s, 1H, CH), 7.45 (d, 2H, J = 8.0 Hz, Ar), 8.0 (d, 2H, J = 8.0 Hz, Ar), 9.11 (t, 1H, J = 5.6 Hz, NH) ppm; 13C NMR (100 MHz, DMSO-d6): δ 20.7, 21.5, 41.2, 51.8, 99.9, 109.0, 115.8, 128.3, 128.7, 134.3, 140.0, 151.9, 159.9, 160.4, 165.9, 170.3 ppm. LC/MS (ESI): 340.25 [M + H]+. Anal. Calc'd for C19H19N3O4 (353.38) C, 64.58; H, 5.42; N, 11.89. Found C, 64.69; H, 5.49; N, 11.74.
ppm: \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 177.1, 21.1, 23.3, 31.1, 42.2, 58.2, 102.2, 109.7, 114.9, 127.9, 128.8, 135.3, 139.8, 150.5, 157.0, 159.6, 160.9, 166.2, 162.5 ppm. LC/MS (ESI): 382.36 [M + H]\. Anal. Calcd for C\(_{24}\)H\(_{22}\)N\(_3\)O\(_6\) (411.43) C, 66.13; H, 6.08; N, 11.02. Found C, 66.30; H, 6.19; N, 11.33.

**Methyl (4-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)benzoyl)phenylalaninate (11f).** Off-white solid in yields 82% (TM) and 95% (US), mp 115–116 °C; FTIR (KBr): 3264 (NH), 2265 (CN, cyano), 1735 (CO, ester), 1620 (C–N, amide), 1645 (CO, pyridine), 1375 (O–CH\(_3\)) cm\(^{-1}\). \(^{1}\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 1.95 (s, 3H, CH\(_3\)), 2.38 (s, 3H, CH\(_3\)), 3.06–3.33 (m, 2H, CH\(_2\)), 6.38 (s, 3H, OCH\(_3\)), 5.01–5.08 (m, 1H, CH), 7.05 (s, 1H, Ar), 7.17 and 7.22 (s, 1H, Ar). FTIR spectra of the prepared compounds 10 and 11a–h; Figures S7 and S9, FTIR spectra of compounds 10 and 11a (PDF).

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**Author Contributions**

H.H.A. and Z.A carried out the synthesis. The series designed and supervised by A.E.-F. All authors contributed to the results and discussion. H.H.A. and Z.A. prepared the first draft of the manuscript; all authors contributed to the final version.

**Notes**

The authors declare no competing financial interest.

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**REFERENCES**

(1) Gharat, N. N.; Rathod, V. K. Ultrasound-Assisted Organic Synthesis. Green Sustainable Process for Chemical and Environmental Engineering and Science. I. M., Abdullah; A.: Asiri; S., Kanchi, eBook; Elsevier, 2020; Chapter 1.

(2) Brahmachari, G.; Banerjee, B. Catalyst-free organic synthesis at room temperature in aqueous and non-aqueous media: an emerging field of green chemistry practice and sustainability. Current Green Chem. 2015, 2, 274–305.

(3) Sankar, M.; Dimitrach, N.; Miedziak, P. J.; Wells, P. P.; Kiely, C. J.; Hutchings, G. J. Designing bimetallic catalysts for a green and sustainable future. Chem. Soc. Rev. 2012, 41, 8099–8139.

(4) Al-Shamary, D. S.; Al-Othman, Z. A.; Al-Ashaikh, M. A. Synthesis of thiooxoquinazolin-4(3H)-one derivatives under microwave and ultrasonic irradiation with classical heating. Asian J Chem. 2013, 25, 6569–6574.

(5) Popiolski, A. S.; Dallago, R. M.; Steffens, J.; Mignoni, M. L.; Veniquarturo, L. D.; Santos, D.; Duarte, F. A. Ultrasound-Assisted Extraction of Cr from Residual Tannery Leather: Feasibility of Ethylenediamine tetracetic Acid as the Extraction Solution. ACS Omega 2018, 3, 16074–16080.

(6) Hosseini, R.; Mamaghani, M.; Tabatabaeian, K.; Shirini, F.; Rassa, M. An expedient regioselective synthesis of novel bioactive indole-substituted chromene derivatives via one-pot three-component reaction. Bioorg. Med. Chem. Lett. 2012, 22, 5956–5960.

(7) Safari, J.; Javadian, L. Ultrasound assisted the green synthesis of 2-amino-4-Hchromene derivatives catalyzed by Fe\(_2\)O\(_3\)-functionalized nanoparticles with chitosan as a novel and reusable magnetic catalyst. Ultrason. Sonochem. 2015, 22, 341–348.

(8) Wang, J.; Bai, X.; Xu, C.; Wang, Y.; Lin, W.; Zou, Y.; Shi, D. Ultrasound-promoted one-pot, three-component synthesis of spiro-
some new mono-heterocyclic and 2-carboxamides. Arch Pharm. Chem. Life Sci. cytotoxicity evaluation of new imidazo[2,1-b]thiazole derivatives. Heterocycl. Chem. J. Med. Chem. 2012 [indoline-3,10-pyrazolo[1,2-b]phthalazine] derivatives. Molecules ACS Omega http://pubs.acs.org/journal/acsodf N2-quinolyl- and N2-acrydinylhydrazones as potent antimalarial hydrazone pharmacophore. Eur. J. Med. Chem. Szebeni, G. J.; Wodimsky, M. J.; Hornyak, M. Effective cyanoacetylating agent and a new building pyrazole and pyridone derivatives bearing sulfisoxazole moiety. N-acylhydrazone derivatives, designed as LASSBio-294 analogues. Barreiro, E. J.; Sudo, R. T. Synthesis and vasodilatory activity of new 2-pyridone rings new synthetic methods to 2-pyridone rings. Curr. Org. Chem. 2005, 9, 1757–1779. (28) Chigorina, E. A. 1-cyanoacetyl-3,5-dimethylpyrazole. Synlett 2014, 24, 453–454. (29) Abumelha, H. M. A. Synthesis and antioxidant assay of new nicotinonitrile analogues clubbed thiazole, pyrazole and/or pyridine ring systems. J. Heterocycl. Chem. 2020, 57, 1011–1022. (30) Kaping, S.; Boiss, I.; Indira Singh, L.; Helissey, P.; Vishwakarma, J. N. Synthesis, cytotoxic characterization, and SAR study of imidazo[1,2-b]pyrazole-7-carboxamides. Mol. Divers. 2016, 20, 379–390. (31) Zhuo, L.-S.; Xu, H.-C.; Wang, M.-S.; Zhao, X.-E.; Ming, Z.-H.; Zhu, X.-L.; Huang, W.; Yang, G.-F. 2,7-naphthyridinone-based MET kinase inhibitors: A promising novel scaffold for antitumor drug development. Eur. J. Med. Chem. 2019, 178, 705–714. (32) Hana, M. A. Abumelha. Synthesis and antioxidant assay of new nicotinonitrile analogues clubbed thiazole, pyrazole and/or pyridine ring systems. J. Heterocycl. Chem. 2020, 57, 1011–1022. (33) Al-Saied, M. S.; El-Gazzaz, M. G.; Gorah, M. M. In-vitro cytotoxic and radiosensitizing evaluation of novel 2-pyridone, isoquinoline, chromene and chromenopyridone derivatives. Eur. J. Chem. 2012, 3, 228–234. (34) Andreati, A.; Leani, A.; Ville, G. 4-Aminopyridine derivatives with antiinammses activity. Eur. J. Med. Chem. 2000, 35, 77–82. (35) Bhupathy, M.; Conlon, D. A.; Wells, K. M.; Wells, M.; Nelson, J. R.; Reider, P. J.; Rossen, K.; Sager, J. W.; Volante, R. P. A practical synthesis of 5-(chloromethyl)furo[2,3-b]pyridine, a key intermediate for the HIV protease inhibitor, L-754,394. J. Heterocycl. Chem. 1995, 32, 1283–1287. (36) Choi, W.; Houpis, I. N.; Charchil, H. R. O.; Molina, A.; Lynch, J. E.; Volante, R. P.; Reider, P. J.; King, A. O. A Practical synthesis of the 5-chloromethyl-furo[2,3-h]pyridine pharmacophore. Tetrahedron 1995, 56, 4571–4575. (37) Torres, M.; Gil, S.; Parra, M. New Synthetic methods to 2-pyridone rings new synthetic methods to 2-pyridine rings. Curr. Org. Chem. 2005, 9, 1757–1779. (38) Mijin, D.; Marinkovic, A. Synthesis of N-substituted 4,6-dimethyl-3-cyano-2-pyridones under microwave irradiation. Synth. Commun. 2006, 36, 193–198. (40) Prasad, R. S.; Sarasarathi, T.; Niraimathi, V.; et al. Synthesis, characterization and antimicrobial activity of some heterobenzocaine derivatives. Int. J. Pharm. Sci. 2012, 4, 285–287. (41) Balabi, M. F.; Shakir, R. M.; Bardy, D. A.; Al-Wajeeh, N. S.; Ablat, A.; Hassanardvish, P.; Hajrezia, M.; Norazit, A.; Abdulla, M. A. Gastroprotective activity of ethyl-4-(3,5-di-tert-butyl-2-hydroxybenzylidene) amino[2-methyl-5-chloromethyl-furo[2,3-h]pyridine] and the 5-chloromethyl-furo[2,3-b]pyridine pharmacophore. Eur. J. Med. Chem. 2005, 40, 272–278. (42) Madhavi, K.; Pavani, Ch. Synthesis and evaluation of alkyl 4-(2-substituted 4,6-dimethyl-3-cyanoacetamido) benzoates for antioxidant and analgesic activities. J. Chem. Pharm. Res. 2017, 9, 341–345. (43) Pokhodylo, N.; Shyyka, O.; Matyichuk, V. Synthesis and antitumor activity evaluation of new 1,2,3-triazole-4-carboxamide derivatives. Med. Chem. Res. 2014, 23, 2426–2438. (44) Desantis, J.; Nannetti, G.; Massari, S.; Barreca, M. L.; Manfroni, G.; Cecchetti, V.; Palù, G.; Goracci, L.; Rogezian, A.; Tabarrini, O. Exploring the cycloheptathiophene-3-carboxamide scaffold to disrupt the interactions of the influenza polymerase subunits and obtain potent anti-influenza activity. Eur. J. Med. Chem. 2017, 141, 690–702. (45) Fadda, A.; Mukhtar, M. M.; Refat, H. M. Utility of Activated Nitriles in the Synthesis of Some New Heterocyclic Compounds. Am. J. Org. Chem. 2012, 2, 32–40. (46) Abd Alhameed, R.; Almarhoom, Z.; Bukhari, S. I.; El-Faham, A.; de la Torre, B. G.; Albericio, F. Synthesis and antimicrobial activity of a new Series of thiazolidine-2,4-diones carboxamide and amino acid derivatives. Molecules 2020, 25, 105.