4-(Dimethylamino)pyridine as an Efficient Catalyst for One-Pot Synthesis of 1,4-Pyranonaphthoquinone Derivatives via Microwave-Assisted Sequential Three Component Reaction in Green Solvent

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Abstract

Novel 1,4-pyranonaphthoquinone derivatives were successfully synthesized via the microwave-assisted three-component reaction of 1,4-naphthoquinone, malononitrile, and various arylaldehydes in ethanol in the presence of 4-(dimethylamino)pyridine (DMAP) as a catalyst, and subsequently evaluated in terms of their antimicrobial and antifungal activities. This synthetic procedure has the notable advantages of environmental friendliness, short reaction time, good yield, and convenient operation.

Keywords

1,4-pyranonaphthoquinone, 2-amino-3-cyano-chromene, 4-(dimethylamino)pyridine, sequential three component reaction, DMAP

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Introduction

Naphthoquinone derivatives, including naphtho[2,3-β]furan, naphtho[2,3-β]furan, pyranonaphthoquinone, and benzoquinoline, are known redox-active compounds that are found in several families of plants, and have been isolated from fungi, algae, and bacteria. Especially, some 1,4-pyranonaphthoquinone derivatives represent a “privileged” structural motif well distributed in naturally occurring compounds such as β-lapachone (1), α-xiloidone (2), pentalongin (3), and dehydroherbarin (4) (Figure 1). These derivatives possess a wide range of pharmacological activities, for example, anticancer, antitumor, leishmanicidal, antibacterial, antifungal, and cytotoxic.

On the other hand, chromenes, which are components of numerous naturally occurring products, like calanolides and calophyllolides, have been “key” scaffolds associated with a wide range of pharmacological activities including anticancer, anti-HIV, antitumor, antiproliferation, antibacterial, and antimalarial. Moreover, a huge number of synthetic 2-amino-3-cyano-chromene derivatives possess potential biological activities, for example, compound 5 has exhibited antibacterial activity against Staphylococcus aureus, compounds 6, 7, and 8 have strong inhibitory activity against Epidermophyton floccosum, and compound 8 has exhibited activity against Aspergillus clavatus, Candida glabrata, C. dubliniensis, C. albicans, and C. tropicalis (Figure 1).

Due to the potential biological activities of 1,4-pyranonaphthoquinone derivatives, as well as 2-amino-3-cyano-chromene skeletons, the synthesis of 1,4-pyranonaphthoquinone derivatives bearing amino and cyano groups has attracted the attention of many researchers.

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So far, several synthetic methods have been reported for the synthesis of derivatives of this structural type via three-component reactions of 2-hydroxy-1,4-naphthoquinone, malononitrile, and arylaldehydes. The conventional synthesis utilizes a catalyst such as bases (DABCO, DBU, or triethylamine), and phase transfer catalysts (benzyl triethyl ammonium chloride or urea), using ethanol, acetic acid, H2O, or DMF as solvents. Although each of the reported methods has its own merit, they have some drawbacks, including high temperatures, long reaction time, drastic reaction conditions, difficult work-up, low yields, and environmental problems associated with the chemicals.

4-(Dimethylamino)pyridine (DMAP), a base catalyst, has been used widely in the synthesis of pyran annulated heterocycles via multicomponent reactions (MCRs). To the best of our knowledge, there has been no study of the synthesis of 1,4-pyranonaphthoquinone derivatives using DMAP as a catalyst so far. Thus, in continuation of our interests in the synthesis of naphthoquinone derivatives and chromene structures, herein, we report the synthesis of 1,4-pyranonaphthoquinone derivatives bearing amino and cyano groups via a microwave-assisted three-component reaction between 1,4-naphthoquinone, malononitrile and arylaldehydes using DMAP as an efficient catalyst in ethanol, an environmentally preferable solvent. Besides that, with the aim to discover potent antimicrobial and antifungal agents, the antimicrobial and antifungal activities of the synthetic compounds were evaluated against Gram-positive and Gram-negative bacteria, and fungal strains.

Results and Discussion

In order to assess the efficiency of DMAP as a catalyst, several different catalysts, including NH4OAc, pyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and triethylamine (Et3N) were tested in the synthesis of 2-amino-5,10-dioxo-4-(p-tolyl)-5,10-dihydro-4H-benzol[g] chromene-3-carbonitrile (12a) (Table 1). All the reactions were carried out on a 1 mmol scale in 3 mL of EtOH in 20 min under microwave at 150 W at an equimolar ratio of reactants 9, 10a, and 11.

It was worth noting that 20 mol% of DMAP in ethanol furnished the best result in terms of yield (Table 1, entry 3). Based on the optimized condition, various arylaldehydes, 1,4-naphthoquinone, and malononitrile were subjected to the microwave-assisted three-component reaction at 150 W using DMAP in ethanol for 20 min to afford compounds 12 (Figure 2). Compounds 12a-i were furnished in good yield (67-73%) and their structures were fully characterized by IR, 1H, and 13C nuclear magnetic resonance (NMR) spectroscopy, and high-resolution electrospray ionization mass spectrometry (HRESIMS).

The two different reaction pathways from starting materials to final products (12a-i) are described in Figure 3. In path A, DMAP (13) effectively catalyzed the Knoevenagel condensation between arylaldehydes and 2-hydroxy-1,4-naphthoquinone to give 15, which then dehydrated to form intermediate 16. DMAP (13) also catalyzed the generation of a dicyanomethanide ion, which reacted with 16 to furnish intermediate 16. After that, intermediate 16 underwent intramolecular cyclization and [1,3]-hydrogen shift to afford the final product 12. However, the formation of arylidenemalononitriles (21) by Knoevenagel condensation proceeded at first in path B, followed by Michael addition with 2-hydroxy-1,4-naphthoquinone, intramolecular cyclization and [1,3]-hydrogen shift sequence of steps to form 12a-i. Based on the proposed reaction pathways, it is worth pointing out that DMAP (13) as a catalyst has played a significant role in the formation of the title products 12a-i.

The synthetic derivatives 12a-i were then subjected to evaluation for their antimicrobial and antifungal activities using a broth microdilution assay. The compounds were screened against Staphylococcus aureus, Bacillus subtilis, Lactobacillus fermentum (Gram-positive bacteria), Escherichia coli, Pseudomonas aeroginosa, Salmonella enterica (Gram-negative bacteria), and Candida albicans. Unfortunately, these compounds exhibited no activity, with IC50 values ≥100 µM.

Materials and Methods

General Experimental Procedures

IR spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer in KBr pellets, and 1H and 13C NMR
spectra on a Bruker Avance III spectrometer (500 and 125 MHz, respectively) in DMSO-d6. TMS was used as an internal standard. HRMS were recorded on a SCIEX X500 QTOF mass spectrometer in ESI (+) and ESI (−) mode. Melting points were determined using a Büchi B-545 melting point apparatus and are uncorrected. All reagents and solvents were purchased from either Aldrich or Merck, unless noted otherwise. Reactions were performed in an Anton Paar Microwave Synthetic Reactor Monowave 400. TLC was performed using Merck silica gel 60 F254 plates and visualized under UV light at 254 nm. Purification of compounds was carried out using open silica gel column flash chromatography with Merck silica gel 60 (240-400 mesh) as stationary phase.

Synthesis of Compounds 12a–i (see Supplemental Figures S1-S44)

A vial containing a mixture of 2-hydroxy-1,4-naphthoquinone (9) (174 mg, 1.0 mmol), malononitrile (11) (66 mg, 1.0 mmol), arylaldehyde 10a–i (1.0 mmol), and DMAP (0.2 mmol) in EtOH (10 mL) was sealed and placed in a microwave reactor. The vial was subjected to microwave irradiation, programmed at 80 °C and 150 W. After 30 s, the temperature reached a plateau at 80 °C and remained constant. After 20 min, the vial was cooled to room temperature. The crude products were purified by column chromatography using DCM–EtOAc, 20:1, as eluent.

2-Amino-5,10-Dioxo-4-(p-Tolyl)-5,10-Dihydro-4H-Benzo[g]Chromene-3-Carbonitrile (12a). Yield 243 mg (71%), orange solid, mp. 243 °C, lit29 240 to 242 °C. 1H NMR (DMSO-d6, 500 MHz): δ 8.05 (1H, dd, J = 2.0, 7.5 Hz), 7.89 to 7.86 (1H, m), 7.85 to 7.82 (2H, m), 7.26 (2H, s), 7.18 (2H, d, J = 8.0 Hz), 7.10 (2H, d, J = 8.0 Hz), 4.57 (1H, s), 2.24 (3H, s). 13C NMR (DMSO-d6, 125 MHz) δ 182.5, 176.8, 158.3, 148.7, 140.6, 136.3, 134.5, 134.1, 131.0, 129.1, 127.5 (2C), 126.0, 125.8, 122.1, 119.3, 57.5, 36.0, 20.6. HRESIMS: Found m/z 341.0919 [M-H]−, calcd. for [C21H13N2O3]: 341.0931.

2-Amino-4-(4-Methoxyphenyl)-5,10-Dioxo-5,10-Dihydro-4H-Benzo[g]Chromene-3-Carbonitrile (12b). Yield 240 mg (67%), orange solid, mp. 247 °C, lit29 247 to 248 °C. 1H NMR (DMSO-d6, 500 MHz): δ 8.04 (1H, dd, J = 2.0, 7.5 Hz), 7.90 to 7.86 (1H, m), 7.86 to 7.82 (2H, m), 7.26 (2H, d, J = 9.0 Hz), 6.86 (2H, d, J = 8.5 Hz), 4.56 (1H, s), 3.71 (3H, s). 13C NMR (DMSO-d6, 125 MHz) δ 182.5, 176.9, 158.3, 148.7, 148.5, 135.6, 134.5, 134.1, 131.0, 130.5, 128.8, 125.9, 125.7, 122.2, 119.3, 113.9 (2C), 57.6, 55.0, 35.6. HRESIMS: Found m/z 357.0874 [M-H]−, calcd. for [C21H13N2O4]: 357.0881.

2-Amino-4-(4-Chlorophenyl)-5,10-Dioxo-5,10-Dihydro-4H-Benzo[g]Chromene-3-Carbonitrile (12c). Yield 247 mg (68%), orange solid, mp. 256 °C, lit29 254 to 256 °C. 1H NMR (DMSO-d6, 500 MHz): δ 8.03 to 8.00 (1H, m), 7.86 to 7.82 (2H, m), 7.26 (2H, s), 7.22 (2H, d, J = 9.0 Hz), 6.86 (2H, d, J = 8.5 Hz), 4.56 (1H, s), 3.71 (3H, s). 13C NMR (DMSO-d6, 125 MHz) δ 182.2, 176.8, 158.2, 147.0, 143.8, 134.0, 134.0, 131.0, 130.5, 128.7, 125.9, 125.7, 122.2, 119.3, 113.9 (2C), 57.6, 55.0, 35.6. HRESIMS: Found m/z 357.0874 [M-H]−, calcd. for [C21H13N2O4]: 357.0881.
2-Amino-4-(4-Bromophenyl)-5,10-Dioxo-5,10-Dihydro-4H-Benzo[g]Chromene-3-Carbonitrile (12d). Yield 285 mg (70%), orange solid, mp. 253 °C, lit29 253 to 255 °C. 1H NMR (DMSO-d6, 500 MHz): δ 8.87 (1H, dd, J = 1.5, 7.0 Hz), 8.72 to 8.65 (3H, m), 8.32 (2H, d, J = 8.5 Hz), 8.17 (2H, s), 8.12 (2H, d, J = 8.5 Hz), 5.46 (1H, s). HRESIMS: Found m/z 404.9858, 406.9865 [M-H]− calcd. for [C20H10BrN2O3]−: 404.9880, 406.9859.

2-Amino-4-(4-Fluorophenyl)-5,10-Dioxo-5,10-Dihydro-4H-Benzo[g]Chromene-3-Carbonitrile (12e). Yield 253 mg (73%), orange solid, mp. 285 °C, lit29 286 to 288 °C. 1H NMR (DMSO-d6, 500 MHz): δ 8.05 (1H, dd, J = 2.0, 8.5 Hz), 7.89 to 7.85 (1H, m), 7.85 to 7.82 (2H, m), 7.37 (1H, dd, J = 2.0, 8.5 Hz), 7.35 (1H, dd, J = 2.0, 8.5 Hz), 7.31 (2H, s), 7.13 (1H, dd, J = 2.0, 8.5 Hz), 7.11 (1H, dd, J = 2.0, 8.5 Hz), 4.64 (1H, s). 13C NMR (DMSO-d6, 125 MHz) δ 182.59, 176.78, 158.47, 149.37, 147.96, 145.81, 134.50, 134.17, 130.98, 130.72, 130.08, 126.05, 125.81, 11.48, 122.18, 120.61, 119.02, 56.65. HRESIMS: Found m/z 345.0670 [M-H]− calcd. for [C20H10FN2O3]−: 345.0681.

2-Amino-4-(3-Nitrophenyl)-5,10-Dioxo-5,10-Dihydro-4H-Benzo[g]Chromene-3-Carbonitrile (12f). Yield 250 mg (67%), orange solid, mp. 298 °C, lit29 295 to 297 °C. 1H NMR (DMSO-d6, 500 MHz): δ 8.19 (1H, t, J = 2.0 Hz), 8.09 (1H, dd, J = 2.0, 8.0 Hz), 8.05 (1H, dd, J = 1.5, 7.5 Hz), 7.88 to 7.81 (4H, m), 7.62 (1H, t, J = 8.0 Hz), 7.44 (2H, s), 4.56 (1H, s). 13C NMR (DMSO-d6, 125 MHz) δ 182.59, 176.78, 158.47, 149.37, 147.96, 145.81, 134.50, 134.17, 130.98, 130.72, 130.08, 126.05, 125.81, 11.48, 122.18, 120.61, 119.02, 56.65. HRESIMS: Found m/z 372.0605 [M-H]− calcd. for [C20H10N3O5]−: 372.0626.

2-Amino-4-(Naphthalen-1-yl)-5,10-Dioxo-5,10-Dihydro-4H-Benzo[g]Chromene-3-Carbonitrile (12g). Yield 265 mg (70%), orange solid, mp. 250 °C. 1H NMR (DMSO-d6, 500 MHz): δ 8.51 (1H, d, J = 8.5 Hz), 8.08 (1H, d, J = 7.5 Hz), 7.94 (1H, d, J = 8.0 Hz), 7.84 (1H, td, J = 2.0, 7.5 Hz), 7.81 to 7.76 (2H, m), 7.65 (1H, t, J = 7.5 Hz), 7.57 (1H, t, J = 7.5 Hz), 7.45 to 7.39 (2H, m), 7.24 (2H, s), 5.61 (1H, s). 13C NMR (DMSO-d6, 125 MHz) δ 182.68, 177.00, 158.34, 149.43, 141.24, 134.63, 134.28, 133.35, 131.03, 130.73, 130.64, 128.52, 127.51, 126.35 (2C), 126.19, 125.98, 125.94, 125.83, 123.69, 122.97, 119.38, 58.20, 50.75. HRESIMS: Found m/z 377.0930 [M-H]− calcd. for [C24H13N2O3]−: 377.09317.

Figure 3. Plausible reaction pathways for the synthesis of 1,4-pyranonaphthoquinone derivatives 12a-i.
2-Amino-4-(Naphthalen-2-yl)-5,10-Dioxyo-5,10-Dihydro-4H-Benz[g]Chromene-3-Carbonitrile (12f). Yield 268 mg (71%), orange solid, mp. 258 °C. 1H NMR (DMSO-d6, 500 MHz): δ 8.08 to 8.05 (1H, m), 7.91 to 7.88 (1H, m), 7.87 to 7.80 (6H, m), 7.50 to 7.46 (3H, m), 7.35 (2H, s), 4.80 (1H, s). 13C NMR (DMSO-d6, 125 MHz) δ 182.60, 176.89, 158.28, 148.96, 141.05, 134.48, 134.10, 132.92, 132.13, 131.01, 130.64, 128.23, 127.72, 127.43, 126.21, 126.15, 126.02 (2C), 125.85, 125.71, 119.30, 57.42, 36.74. HRESIMS: Found m/z 377.0930 [M-H]− calcld. for [C22H11N2O3S]: 377.0932.

2-Amino-4-(Benzo[b]Thiophen-3-yl)-5,10-Dioxyo-5,10-Dihydro-4H-Benzo[g]Chromene-3-Carbonitrile (12i). Yield 276 mg (72%), red brown solid, mp. 253 °C. IR (KBr) νmax/cm−1 3443, 3407, 3318, 3253, 3217, 3191, 3070, 2919, 1658, 1629, 1593, 1587, 1459, 1423, 1399, 1355, 1339, 1301, 1279, 1242, 1201, 1180, 1093, 1067, 1045, 946, 776, 726, 713. 1H NMR (DMSO-d6, 600 MHz): δ 8.08 (1H, dd, J = 2.4, 7.8 Hz), 8.05 (1H, d, J = 8.4 Hz), 7.98 (1H, d, J = 8.4 Hz), 7.90 to 7.82 (3H, m), 7.70 (1H, s), 7.46 (1H, t, J = 7.2 Hz), 7.40 (1H, t, J = 7.8 Hz), 7.33 (2H, s), 5.18 (1H, s). 13C NMR (DMSO-d6, 125 MHz) δ 182.47, 176.87, 158.62, 149.14, 139.82, 139.01, 137.32, 134.51, 134.15, 130.99, 130.67, 126.07, 125.80, 125.45, 124.45, 124.21, 122.93, 121.98, 121.59, 119.43, 56.92, 29.53. HRESIMS: Found m/z 383.0471 [M-H]− calcld. for [C22H13N2O3S]: 383.0496.

Antimicrobial and Antifungal Evaluation

The investigated bacterial and fungal strains were obtained from the American Type Culture Collection (ATCC, USA). Compounds 12a-i were evaluated against Staphylococcus aureus (ATCC 13709), Bacillus subtilis (ATCC 6633), Lactobacillus fermentum (N4) (Gram-positive bacteria), Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 15442), Salmonella enterica (Gram-negative bacteria), and Candida albicans (ATCC 10231).

Bacterial strains were cultured in Mueller-Hinton broth (Merck), and Candida albicans was cultured overnight in Sabouraud dextrose broth. Each well containing 10 μL of compound dissolved in DMSO was diluted together with 190 μL of microorganism suspension (5×105 CFU/mL). The negative control wells (without inoculants) and the positive growth control wells (without antimicrobial agents) were reserved in this experiment. The experiments were repeated three times and the results were determined as an average value. Optical density 600 nm (OD600) measurements with a BIOTEK microplate reader spectrophotometer were used to determine the growth/ viability in a liquid sample after 20 h incubation at 37 °C. The results were expressed as % reduction of microorganism viability compared with the positive growth control well.

Conclusions

A synthetic procedure is described for the synthesis of compounds 12a-i via a microwave-assisted three-component reaction in ethanol using DMAP as a base catalyst for the synthesis of a series of 1,4-pyrononaphthoquinones. This report provides an efficient and convenient synthetic method, which features mild reaction conditions, commercially available materials, a very simple and inexpensive workup, and a good yield of products. Moreover, the use of ethanol for these reactions is environmentally friendly and cost-effective.

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The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Trial Registration

Not applicable, because this article does not contain any clinical trials.

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Supplemental Material

Supplemental material for this article is available online.

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