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# Green synthesis of lactone derivatives using *N*-formylmorpholine as green solvent: Study of antimicrobial activity

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**Abstract:** The reaction between propiolates and OH-acids in N-formylmorpholine at room temperature leads to lactone derivatives in good yields. The present protocol offers the advantages of clean reaction, short reaction time, high yield, easy purification and affordability of the catalyst. The antimicrobial activity of some synthesized compounds was studied employing the disk diffusion test on Gram-positive bacteria and Gram-negative bacteria. The results of disk diffusion test showed that these compounds prevented the bacterial growth.

**Keywords:** Lactone, 8-Hydroxyquinoline, Cathechol, propiolate.

## Introduction

The lactones are an important structure unit in natural products and intermediates in organic synthesis [1, 2]. There has been considerable work on the synthesis of these compounds due to the discovery of many naturally occurring cytotoxic or antitumor agents. Although this ring system has been the objective of synthestic projects in a number of laboratories, the number of basically different approaches is not large [3-6]. Green chemistry techniques continue to grow in importance, and alternative processes are developed with the aim to conserve resources and reduce costs [7-9]. A major challenge in modern chemistry is the design of highly efficient chemical reactions with the minimum number of synthetic steps and short reaction times. At present, bacteria that are resistant to drugs have generated considerable problems in the performance of many communicable diseases.

Therefore, discovering new ways to extirpate these pathogens are important. For this reason, recent studies have focused on the study of the antibacterial effects of new synthesized compounds**.**

## Results and discussion

We now report a synthesis of lactone derivatives **2** through the reaction of propiolate with phenols in *N*-formylmorpholine.

Our results are summarized in Table **1**. The reaction of phenol (**1a**) with DMAD in *N*-formylmorpholine at room temperature leads to the butyrolactone derivative **2a** in 93% yield (Table **1**). No other compound was obtained from the residue by column chromatography. The structure of the product was deduced from its elemental analyses and its IR, $^{1}$H NMR, $^{13}$C NMR, and mass spectral data. The $^{1}$H NMR spectrum of **2a** exhibited two singlets identified as methoxy ($\delta$ = 3.72 ppm) and olefinic ($\delta$ = 7.01 ppm) protons along with multiplets ($\delta$ = 6.65, 7.23, 7.31, and 7.48 ppm) for the aromatic protons. The $^{13}$C NMR spectrum of **2a**

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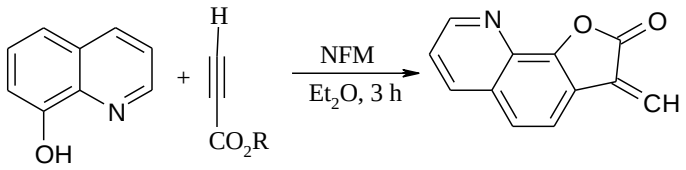
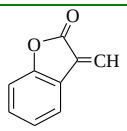
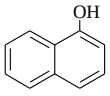
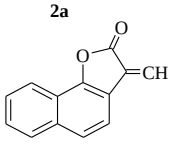
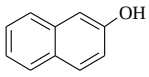
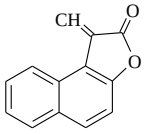
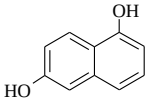
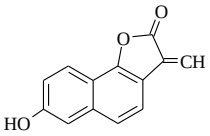
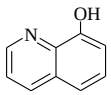
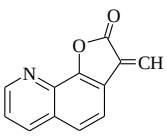
showed eleven distinct resonances in agreement with the proposed structure. Also, The $^{1}$H NMR spectrum of **2d** exhibited two singlets identified as methoxy ($\delta$ = 3.88 ppm) and olefinic ($\delta$ = 6.67 ppm) protons along with multiplets ($\delta$ = 7.27-8.46 ppm) for the aromatic protons. The OH proton resonance appears at $\delta$ = 9.34 ppm. The $^{13}$C NMR spectrum of **2d** showed 15 distinct resonances in agreement with the proposed structure.

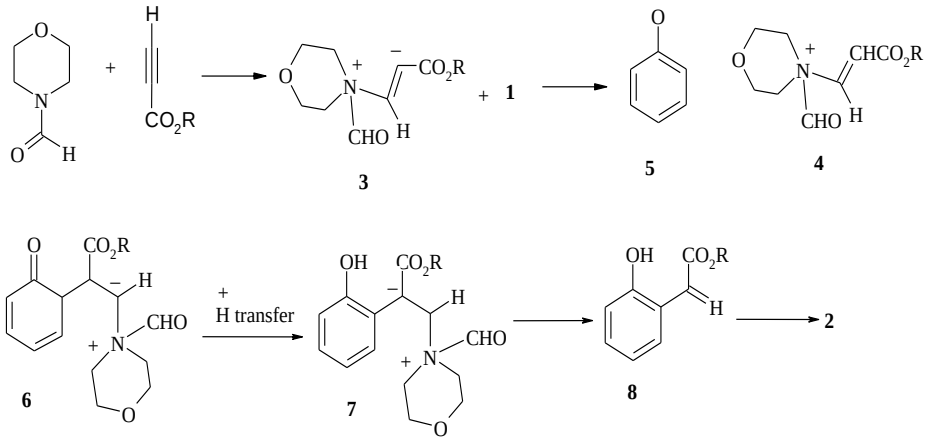
A possible mechanism for the formation of **2a** is proposed in Scheme 1. It is reasonable to assume that **2a** results from initial addition of NFM as green solvent to the acetylenic ester and subsequent protonation of the 1,3-dipolar intermediate **3** by **1a**. Then, the positively charged ion **4** might be attacked by the conjugated base of the OH-acid to produce the nitrogen ylide **6**, which undergoes proton-transfer reaction to produce **7**. The 1,3-dipolar ion **7** is converted to **8** by elimination of NFM. The product **2a** is formed by intramolecular lactonization of **8**. Similar mechanism can be proposed for the formation of **2b-2e**.




**1** **2**

**Table 1**: Reaction of DMAD with phenols *N*-formylmorpholine.

| Entry | Starting materials | Product | Yield (%) |
|---|---|---|---|
| 1 |  **1a** |  **2a** | **93** |
| 2 |  **1b** |  **2b** | **94** |
| 3 |  **1c** |  **2c** | **90** |
| 4 |  **1d** |  **2d** | **85** |
| 5 |  **1e** |  **2e** | **86** |



**Scheme1:** Proposed mechanism for formation of **2**

Also, a comparison between the activity of our synthesized compounds with Streptomycin and Gentamicin as standard drug was discussed. The results of the antimicrobial activity of some synthezized compounds on bacterial species are shown in Table **2**. The present study indicated that the type of bacteria and concentration of compounds are effective on the diameter of the inhibition zone. It is apparent from the data listed in Table **2**, the antimicrobial activity of the most synthesized compounds **2b**, **2c**, **2e** and **2g** were good active against Gram positive bacteria and Gram negative bacteria So that the diameter of the inhibition zone of compounds has the maximum effect on *Escherichia coli*.

**Table 2.** The antibacterial activity of the tested compounds **2a-4e**

| Compounds | Staphylococcus aureus (+) | Bacillus cereus (+) | Escherichia coli(-) | Klebsiella pneumoniae (-) |
|---|---|---|---|---|
| 2a | 8 | 10 | 9 | --- |
| 2b | 17 | 20 | 21 | 18 |
| 2c | 18 | 22 | 23 | 17 |
| 2d | --- | 5 | 10 | 6 |
| 2e | 15 | 21 | 23 | 20 |
| 2f | 7 | 7 | 8 | ---- |
| 2g | 15 | 21 | 24 | 20 |
| Streptomycin | 16 | 24 | 25 | 23 |
| Gentamicin | 19 | 23 | 24 | 21 |

## Conclusion

In summary, the reaction between DMAD and phenols *N*-formylmorpholine leads to butyrolactone derivatives in excellent yields. The presented one-pot reaction carries the advantage that not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification. The obtained results of disk diffusion test showed that compound **2b, 2c, 2e and 2g** prevented the bacterial growth. Some advantages of this procedure are performing reactions under solvent-free conditions and simplicity of separation of catalyst and product. In addition, green synthesis, high yields, easy procedure, easy separation of catalyst from the mixture of reactions are the advantages of these reactions.

## Experimental

Typical procedure for the synthesis of **2a**: To a stirred solution of **1a** (0.19 g, 2 mmol) and DMAD (0.28 g, 2 mmol) in 10 mL dry ether was added NFM (5 mL) as green solvent at room temperature. The reaction mixture was then stirred for 3 h. The solvent was removed under reduced pressure and the residue was separated by silica gel column chromatography

(Merck 230-400 mesh) using *n*-hexane-EtOAc (4:1) as eluent to give **2a**.

Yellow oil; yield 0.38 g, 93%. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1735 and 1650 (C=O). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$= 3.72 (3 H, s, OMe), 6.65 (1 H, d, $^3J_{HH}$ =7.9 Hz, CH), 7.01 (1 H, s, CH), 7.23 (1 H, dd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 7.5 Hz, CH), 7.31(1 H, dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 7.5 Hz, CH), 7.48 (1 H, d, $^3J_{HH}$ =7.8 Hz, CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 52.6 ($OCH_3$), 111.2 (CH), 122.1 (CH), 123.1 (CH), 123.5 (C), 124.3 (CH), 130.6 (CH), 138.2 (C), 153.5 (C), 165.3 (C=O), 166.5 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 204 ($M^+$, 12), 189 (17), 160 (47), 145 (73), 144 (36), 132 (100), 91 (14), 76 (68), 59 (42). Anal. Calcd for $C_{11}H_8O_4$ (204.2): C, 64.71; H, 3.95%. Found: C, 65.18; H, 3.99%.

Compound **2b**: Brown crystals, mp 176-178 °C, yield 0.48 g, 94%. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1715 and 1616 (C=O). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 4.02 (3 H, s, OMe), 6.94 (1 H, s, CH), 7.59 (1 H, dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 6.9 Hz, CH), 7.62 (1 H, dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 5.1 Hz CH), 7.63 (1 H, d, $^3J_{HH}$ = 5.1 Hz, CH), 7.81 (1 H, d, $^3J_{HH}$ = 6.3 Hz, CH), 8.10 (1 H, d, $^3J_{HH}$ = 6.9 Hz, CH), 8.46 (1 H, d, $^3J_{HH}$ = 6.3 Hz, CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 53.2 ($OCH_3$), 111.4 (CH), 118.2 (C), 121.7 (CH), 122.5 (CH), 122.9 (C), 124.5 (CH), 127.2 (CH), 127.6 (CH), 129.2 (CH), 134.8 (C), 143.2 (C), 151.7 (C-O), 159.9 (C=O), 164.5 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 254 ($M^+$, 5), 251 (22), 223 (100), 195 (38), 135 (56), 113 (84), 109 (54), 55 (78). Anal. Calcd for $C_{15}H_{10}O_4$ (254.2): C, 70.86; H, 3.96%. Found: C, 70.40; H, 3.81%.

Compound **2c**: Green powder, mp 113-115 °C, yield 0.46 g, 90%. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1724 and 1620 (C=O). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 4.06 (3 H, s, OMe), 6.59 (1 H, s, CH), 7.46 (1 H, d, $^3J_{HH}$ = 8.1 Hz, CH), 7.55 (1H, dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 6.1 Hz, CH), 7.64 (1 H, dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 8.1 Hz, CH), 7.77 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.92 (1 H, d, $^3J_{HH}$ = 6.1 Hz, CH), 8.02 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 53.5 ($OCH_3$), 110.1 (CH), 115.5 (CH), 117.3 (CH), 123.3 (C), 126.1 (CH), 127.9 (CH), 128.1 (CH), 129.4 (C), 130.9 (C), 134.6 (CH), 145.9 (C), 154.9 (C), 159.5 (C=O), 167.8 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 254 ($M^+$, 10), 251 (45), 223 (100), 135 (50), 113 (84), 109 (65), 55 (75). Anal. Calcd for $C_{15}H_{10}O_4$ (254.2): C, 70.86; H, 3.96%. Found: C, 70.39; H, 3.82%.

Compound **2d**: Orange powder, mp 187-189 °C, yield 0.46 g, 85%. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3435 (OH), 1712 and 1617 (C=O). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 3.89 (3 H, s, OMe), 6.67 (1 H, s, CH), 7.27 (1 H, d, $^4J_{HH}$ = 3.2 Hz, CH), 7.29 (1 H, dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 3.2 Hz, CH), 7.50 (1 H, d, $^3J_{HH}$ = 8.5 Hz, CH), 7.96 (1 H, d, $^3J_{HH}$ = 8.7 Hz, CH), 8.45 (1 H, d, $^3J_{HH}$ = 8.5 Hz, CH), 9.34 (1 H, s, OH). $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 52.6 ($OCH_3$), 111.3 (CH), 114.2 (C), 114.4 (CH), 120.5 (CH), 121.9 (C), 123.0 (CH), 124.7 (CH), 124.9 (CH), 124.9 (C), 134.9 (C), 139.7 (C), 151.7 (C), 159.9 (C=O), 164.4 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 270 ($M^+$, 20), 242 (100), 239 (26), 211 (78), 155 (100), 126 (42), 77 (26). Anal. Calcd for $C_{15}H_{10}O_5$ (270.2): C, 66.67; H, 3.73%. Found: C, 66.91; H, 3.65%.

Compound **2e**: Pale yellow crystals, mp 155-157 °C, yield 0.44 g, 86%. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1714 and 1619 (C=O). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 3.91 (3 H, s, OMe), 7.2 (1 H, s, CH), 7.35 (1 H, d, $^3J_{HH}$ = 8.5 Hz, CH), 7.45 (1 H, dd, $^3J_{HH}$ =8.5 Hz, $^3J_{HH}$ = 6.7 Hz, CH), 7.50 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 8.15 (1 H, d, $^3J_{HH}$ = 6.7 Hz, CH), 8.78 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH). $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 52.8 ($OCH_3$), 112.7 (CH), 116.9 (C), 117.6 (CH), 122.1 (CH), 127.9 (C), 129.4 (C), 136.1 (CH), 137.95 (C), 148.2 (CH), 148.2 (CH), 150.4 (C), 159.5 (C=O), 164.4 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 255 ($M^+$, 5), 224 (100), 195 (45), 128 (65), 109 (54), 77 (24), 59 (78), 31 (52). Anal. Calcd for $C_{14}H_9NO_4$ (255.2): C, 65.88; H, 3.55%. Found: C, 65.50; H, 3.46%.

**Evaluation of antibacterial activity**

The antibacterial effect of synthesized compounds against Gram-positive and Gram-negative bacteria was investigated using the disk diffusion method. All microorganisms were obtained from the Persian type culture collection (PTCC), Tehran, Iran. Microorganisms were cultured for 16 to 24 h at 37°C and prepared to turbidity equivalent to McFarland Standard No. 0.5. Streptomycin and Gentamicin at a concentration 40 $\mu$g/mL, were used as standard against bacteria. The bacterial suspension was prepared to match the turbidity of the 0.5 McFarland (Approximately 1.5 × 108 CFU/mL) standards and cultured with a sterile swab on Mueller Hinton agar. All synthesized compounds were screened for their antibacterial (Gram-positive and Gram-negative) at a concentration of 25 µg/ml that was poured on sterile blank disks. The plates were incubated overnight at 37 °C for 24 h in an incubator. The result was studied by measuring the diameter of the inhibition zone and compared to with the control.

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