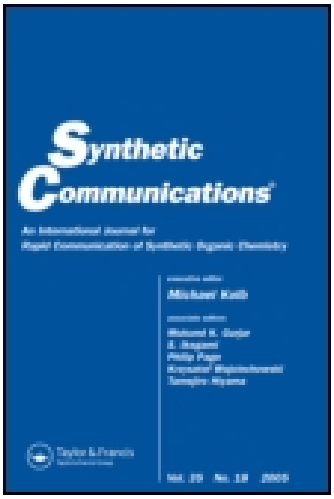

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LIMITATIONS OF THE JACOBS–GOULD REACTION USING MICROWAVE IRRADIATION

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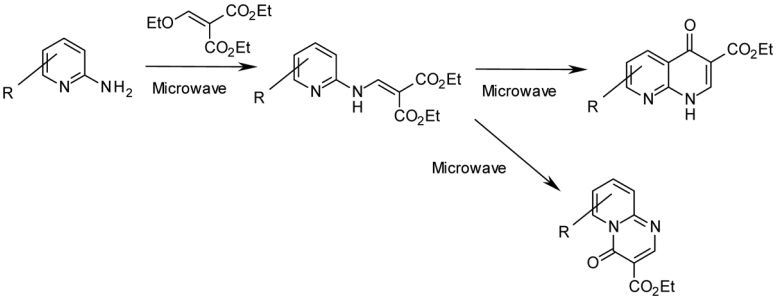
GRAPHICAL ABSTRACT



Abstract *Upon investigating the green synthesis of some antimicrobial quinolone compounds, some atypical ring-closing patterns were observed during the synthesis of various intermediates using the Jacobs–Gould reaction.*

Keywords Cyclization; Jacobs–Gould reaction; microwave synthesis; quinolones

INTRODUCTION

The quinolones, in particular the clinically used fluoroquinolones, are broad-spectrum antibiotics that inhibit bacterial deoxyribonucleic acid (DNA) gyrase or the topoisomerase IV enzyme; these are required for DNA replication and transcription.[1–3] Scheme 1 shows the synthesis of the second-generation antibacterial norfloxacin **(4)**,[4] the antibacterial fluoroquinolone used in the treatment of urinary tract infections.[5] The key intermediate **(2)** in this synthesis is formed through a heat-mediated Jacobs–Gould intramolecular cyclization reaction.[6] Although the cyclization step seems simplistic, problems do exist that often lead to poor yields

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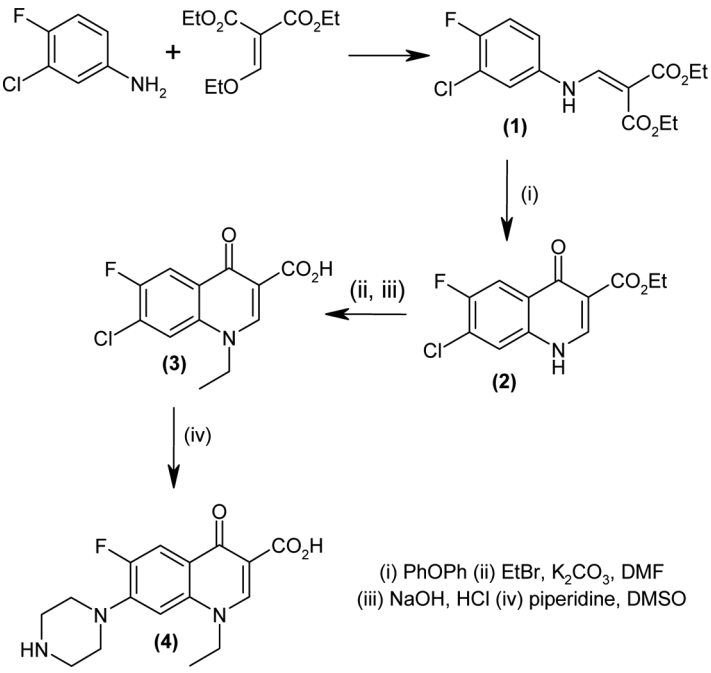
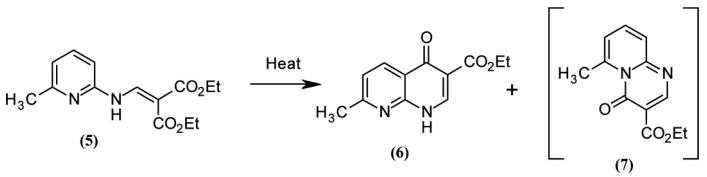


Scheme 1. Synthesis of the second-generation antibacterial norfloxacin.

(with the reactants still present) and/or a mixture of cyclized products. This is highlighted in Scheme 2, using the cyclization of diethyl *N*-(6-methyl-2-pyridyl)-aminomethylenemalonate **(5)** as an example. In both cases, purification is required to isolate the intermediate, which can prove tedious because of the polar nature of these compounds.

It was our aim to form novel derivatives of nalidixic acid using microwave-enhanced synthesis, isolate the key intermediates in good yield, and limit purification procedures. Although the compounds presented in this article are not novel, we believe the green methodology used to make these compounds is. It allows an easy and clean isolation of the key intermediates, which is something that has not previously been achieved. We thus present this work as a clean and novel way to prepare these types of heterocyclic compounds. However, it was noticed that some atypical ring closures were occurring, and we also report this herein.



Scheme 2. Formation of naphthyridone **(6)** and pyrimidinone **(7)**.

RESULTS AND DISCUSSION

The first stage proceeds initially via a conjugate (Michael) addition/elimination reaction as outlined in Scheme 2. This enamine bond formation was achieved in excellent yields by condensation of diethyl ethoxymethylenemalonate (DEEM) using microwave synthesis. This reaction historically has been accomplished using traditional wet synthetic methods such as refluxing in ethanol[7] for 16 h or reacting in the presence of a base such as potassium hydroxide. Performing this reaction using microwave synthesis opens up a possible new avenue in protection group chemistry, as DEEM has been reported as a protecting group for amines.[8] Using the aforementioned microwave method we were able to prepare substituted aminomethylenemalonates using four different isomers of 2-aminopicolene in good yields. Recrystallization in ethanol for each of these intermediates gave pure products, and these reactions are highlighted in Table 1.

The second stage in the synthesis displays an example of electrophilic aromatic substitution, specifically the Jacobs–Gould reaction, to yield the cyclized product as shown in Table 2.

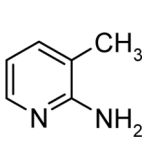
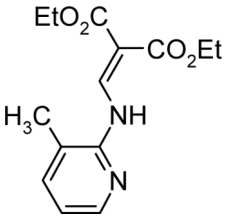
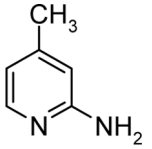
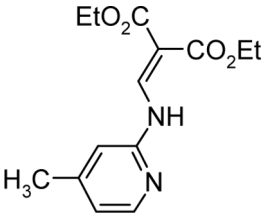
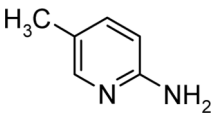
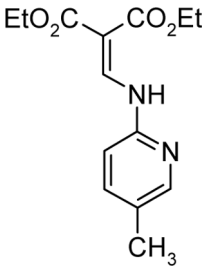
The Jacobs–Gould reaction can be achieved using conventional synthetic methods; however, this can only be successfully accomplished if high-temperature reflux conditions are employed.[7]

Strauss et al.[9] demonstrated that with established methods using heat-transfer oils, this reaction proceeded in high conversion, rapidly and controllably, at temperatures near 400 °C. He also noted that this reaction can be accomplished without solvent in a stainless steel coil; the temperature for this reaction has to be maintained at 380 °C using a fused sand bath. Over a 2-h period, three compounds were produced in the following yields: naphthyridone **(6)** (79%), pyrimidone **(7)** (8%), and other unknown compounds (5%). The pure product was isolated as a precipitate using diethyl ether once the reaction mixture had cooled. Although this reaction is green, it would not be considered economically favorable within an industrial environment.

In our quest to form novel quinonolones, *N*-(6-methyl-2-pyridyl)aminomethylenemalonate (see Table 2, reaction 2d) was irradiated by microwaves (MW) for 15 min in the presence of diphenyl ether as a solvent, and the formation of the naphthyridone in 79% yield was observed. No other side products or starting materials were present. This was confirmed by both 1D and 2D NMR spectroscopy. It is important to note that a high dilution factor is essential for these reactions to be successful in a CEM microwave.

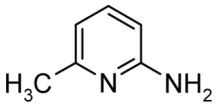
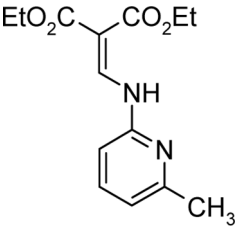
This reaction was also attempted using MW irradiation on *N*-(3-methyl-2-pyridyl)aminomethylenemalonate to confirm the lack of cyclization due to the 3-methyl substituent acting as a blocking group. However, it was noted that another type of intramolecular cyclization occurred though the pyridine nitrogen, resulting in the formation of a pyrimidone in a yield of 77% (see Table 2, reaction 2a). The literature shows that pyrimidones form in preference to the naphthyridones at low temperatures. Because of the superheating effect from the MW, the two other derivatives (4-methyl and 5-methyl substituents) were investigated. In the case of these reactions, conventional heating would take the lower energy path to produce the kinetic product (i.e., the pyrimidones). Using MW-enhanced synthesis, it was

Table 1. Spectroscopic information for the aminomethylenemalonates

Reaction	Starting 2-amino-picoline	Product	Yield (%)	^{1}H, ^{13}C (ppm) and MS
1a			**81**	^{1}H NMR (d-$CDCl_3$) δ ppm: 1.29–1.39 (t x2, 6H, $C\underline{H}_3$), 2.31 (s, 3H, Ar-$C\underline{H}_3$), 4.19–4.35 (q x2, 4H, $C\underline{H}_2$), 6.93 (t, 1H, J = 6.1 Hz, Ar-$\underline{H}$), 7.46 (d, 1H, J = 6.5 Hz, Ar-$\underline{H}$), 8.18 (d, 1H, J = 6.2 Hz, Ar-$\underline{H}$), 9.26 (d, 1H, J = 12.5 Hz, C=C-$\underline{H}$), 11.32 (br d, 1H, J = 12.3 Hz, N-$\underline{H}$). ^{13}C NMR (d-$CDCl_3$) δ ppm: 14.35, 14.48, 16.41, 60.12, 60.60, 95.66, 119.49, 120.21, 139.27, 146.07, 149.12, 149.98, 165.38, 169.32; MS (LCMS) $m/z = 278$
1b			**76**	^{1}H NMR (d-$CDCl_3$) δ ppm: 1.21–1.34 (t x2, 6H, $C\underline{H}_3$), 2.25 (s, 3H, Ar-$C\underline{H}_3$), 4.14–4.29 (q x2, 4H, $C\underline{H}_2$), 6.61 (s, 1H, Ar-$\underline{H}$), 6.78 (d, 1H, J = 5.0 Hz, Ar-$\underline{H}$), 8.12 (d, 1H, J = 5.2 Hz, Ar-$\underline{H}$), 9.08 (d, 1H, J = 13.0 Hz, C=C-$\underline{H}$), 10.98 (br d, 1H, J = 13.0 Hz, N-$\underline{H}$). ^{13}C NMR (d-$CDCl_3$) δ ppm: 14.28, 14.43, 21.01, 60.09, 60.49, 95.14, 112.45, 120.95, 148.27, 149.94, 150.08, 150.74, 165.38, 168.86; MS (LCMS) $m/z = 278$
1c			**87**	^{1}H NMR (d-$CDCl_3$) δ ppm: 1.29–1.40 (t x2, 6H, $C\underline{H}_3$), 2.28 (s, 3H, Ar-$C\underline{H}_3$), 4.20–4.34 (q x2, 4H, $C\underline{H}_2$), 6.76 (d, 1H, J = 8.0 Hz, Ar-$\underline{H}$), 7.45 (d, 1H, J = 6.2 Hz, Ar-$\underline{H}$), 8.15 (s, 1H, Ar-$\underline{H}$), 9.12 (d, 1H, J = 13.0 Hz, C=C-$\underline{H}$), 11.06 (br d, 1H, J = 13.0 Hz, N-$\underline{H}$). ^{13}C NMR (d-$CDCl_3$) δ ppm: 14.34, 14.49, 17.80, 60.12, 60.53, 94.80, 111.46, 130.05 139.25, 148.60 150.07, 165.49, 169.08, 169.12; MS (LCMS) $m/z = 278$

(*Continued*)

Table 1. Continued

Reaction	Starting 2-amino-picoline	Product	Yield (%)	^{1}H, ^{13}C (ppm) and MS
1d			**85**	^{1}H NMR (d_6-DMSO) δ ppm: 1.32–1.37 (t x2, 6H, C<u>H</u>$_3$), 2.47 (s, 3H, Ar-C<u>H</u>$_3$), 4.24 (q, 2H, J = 6.3 Hz, C<u>H</u>$_2$), 4.29 (q, 2H, J = 6.3 Hz, C<u>H</u>$_2$), 6.63 (d, 1H, J = 8.0 Hz, Ar-<u>H</u>), 6.85 (d, 1H, J = 7.6 Hz, Ar-<u>H</u>), 7.50 (t, 1H, J = 7.8 Hz, Ar-<u>H</u>), 9.17 (d, 1H, J = 12.0 Hz, C<u>H</u>=C), 11.03 (d, 1H, J = 12.8 Hz, N<u>H</u>). ^{13}C NMR (d_6-DMSO) δ ppm: 14.23, 14.34, 24.02, 59.76, 59.96, 94.84, 109.73, 119.28, 139.40, 148.14, 149.89, 157.17, 165.13, 167.05; MS (LCMS) $m/z = 278$

considered that the thermodynamic product (which was expected to be the naphthyridone) would be produced because of superheating.

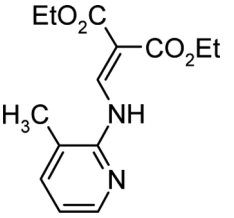
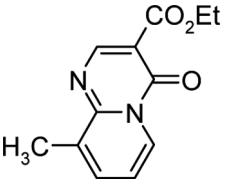
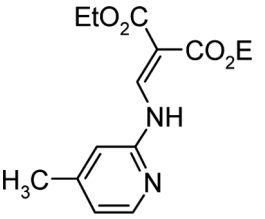
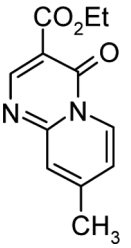
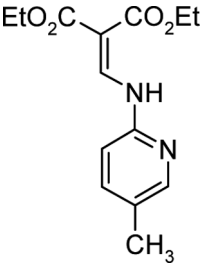
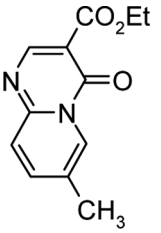
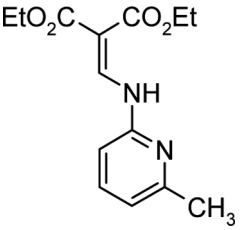
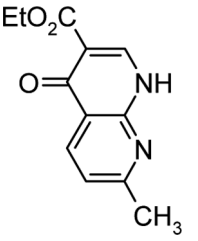
Table 2 shows the results of the MW irradiation for a range of *N*-(*n*-methyl-2-pyridyl)aminomethylenemalonates (*n* denotes position of the methyl group on the pyridine ring), over a period of 15 min. It is interesting to note that for reactions 2a–2c (Table 2), the pyrimidone was formed with no naphthyridone present. Attempts at a solventless synthesis for this six-member cyclization were investigated, which led to the decomposition of the starting material with no naphthyridone or pyrimidone detected by thin-layer chromatography (TLC) and NMR spectroscopy.

In conclusion, the Jacobs–Gould reaction can be achieved using MW irradiation over a 15-min period. Complex purification procedures are not required as the product precipitates from the reaction mixture upon the addition of hexane; this also aids the removal of the solvent diphenyl ether. As the pyrimidone forms at low temperatures (kinetic product), it postulated that the naphthyridone should form the major product for each of the reactions in Table 2 (except for reaction 2a, because of the methyl blocking group) as a result of superheating. However, as the results show, this is not the case, and it can be assumed that the pyrimidone products from reactions 2b and 2c are both kinetically and thermodynamically more stable, judging by the high yields produced. It is assumed that the product from reaction 2d, which is the naphtyridone, is indeed more thermodynamically stable.

EXPERIMENTAL

MW synthesis was preformed using a CEM Discover microwave reactor. NMR spectra were measured on a Jeol ECX 400-MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX mass

Table 2. Spectroscopic information for the Jacobs–Gould cyclization reactions

Reaction	Starting material	Product	Yield (%)	^{1}H, ^{13}C (ppm) and MS
2a			**77**	^{1}H NMR (d_6-DMSO): 1.29 (t, 3H, J = 7.1 Hz, C<u>H</u>$_3$), 2.53 (s, 3H, Ar-C<u>H</u>$_3$), 4.24 (q, 2H, J = 7.2 Hz, C<u>H</u>$_2$), 7.44 (t, 1H, J = 7.1 Hz, Ar-<u>H</u>), 8.05 (d, 1H, J = 6.9 Hz, Ar-<u>H</u>), 8.83 (s, 1H, Ar-<u>H</u>), 9.01 (d, 1H, J = 7.3 Hz, Ar-<u>H</u>). ^{13}C (d_6-DMSO) δ ppm: 14.21, 17.43, 60.08, 103.68, 117.53, 126.53, 134.68, 139.30, 152.16, 154.06, 157.19, 164.16. (LCMS) $m/z = 232$
2b			**81**	^{1}H NMR (d_6-DMSO) δ ppm: 1.28 (t, 3H, J = 7.1 Hz, C<u>H</u>$_3$), 2.52 (s, 3H, Ar-C<u>H</u>$_3$), 4.25 (q, 2H, J = 7.1 Hz, C<u>H</u>$_2$), 7.42 (d, 1H, J = 8.8 Hz, Ar-<u>H</u>), 7.66 (s, 1H, Ar-<u>H</u>) 8.81 (s, 1H, Ar-<u>H</u>), 8.03 (d, 1H, J = 7.2 Hz, Ar-<u>H</u>). ^{13}C (d_6-DMSO) δ ppm: 14.27, 20.94, 60.00, 102.97, 120.46, 124.63, 127.96, 152.61, 153.05, 153.92, 158.51, 164.12. (LCMS) $m/z = 232$
2c			**56**	^{1}H NMR (d_6-DMSO): 1.37 (t, 3H, J = 7.2 Hz, C<u>H</u>$_3$), 2.51 (s, 3H, Ar-C<u>H</u>$_3$), 4.35 (q, 2H, J = 7.1 Hz, C<u>H</u>$_2$), 7.72 (d, 1H, J = 8.9 Hz, Ar-<u>H</u>), 8.03 (d, 1H, J = 8.9 Hz, Ar-<u>H</u>), 8.91 (s, 1H, Ar-<u>H</u>), 9.06 (s, 1H, Ar-<u>H</u>). ^{13}C (MeOD) δ ppm: 14.65, 18.32, 61.93, 105.08, 126.62, 127.62, 130.66, 144.41, 153.39, 156.30, 159.07, 165.92. (LCMS) $m/z = 232$
2d			**79**	^{1}H NMR (d_6-DMSO): 1.26 (t, 3H, J = 7.1 Hz, C<u>H</u>$_3$), 2.57 (s, 3H, Ar-C<u>H</u>$_3$), 4.19 (q, 2H, J = 7.1 Hz, C<u>H</u>$_2$), 7.34 (d, 1H, J = 8.1 Hz, Ar-<u>H</u>), 8.37 (d, 1H, J = 8.2 Hz, Ar-<u>H</u>), 8.45 (s, 1H, Ar-<u>H</u>). ^{13}C (d_6-DMSO) δ ppm: 14.23, 24.28, 59.71, 110.91, 119.66, 121.19, 135.48, 145.48, 149.44, 163.02, 164.23, 173.68. (LCMS) $m/z = 232$

spectrometer. All chemicals and solvents were bought from either Sigma Aldrich or Alfa Aesar and used without further purification.

N-(3-Methyl-2-pyridyl)aminomethylenemalonates (Table 1, Reaction A)

A mixture of 2-amino-3-picoline (1.08 g, 10 mmol) and diethyl (ethoxymethylene)malonate (2 ml, 10 mmol) was irradiated for 30 s in a CEM microwave at half power. Ethanol (10 ml), was added to the reaction mixture and heated until a clear solution was obtained, which was treated with activated charcoal, filtered, and allowed to cool naturally. The solid was filtered under suction and dried under vacuum to yield *N*-(3-methyl-2-pyridyl)aminomethylenemalonate (81%) as white crystals.

^{1}H NMR (d-$CDCl_3$) δ ppm: 1.29–1.39 (t x2, 6H, C$\underline{H_3}$), 2.31 (s, 3H, Ar-C$\underline{H_3}$), 4.19–4.35 (q x2, 4H, C$\underline{H_2}$), 6.93 (t, 1H, $J = 6.1$ Hz, Ar-H), 7.46 (d, 1H, $J = 6.5$ Hz, Ar-H), 8.18 (d, 1H, $J = 6.2$ Hz, Ar-$\underline{H}$), 9.26 (d, 1H, $J = 12.5$ Hz, C=C-$\underline{H}$), 11.32 (br d, 1H, $J = 12.3$ Hz, N-$\underline{H}$). ^{13}C NMR (d-$CDCl_3$) δ ppm: 14.35, 14.48, 16.41, 60.12, 60.60, 95.66, 119.49, 120.21, 139.27, 146.07, 149.12, 149.98, 165.38, 169.32; MS (LCMS) $m/z = 278$.

Each of the reactions are based on the same quantities and procedures as the cyclization of *N*-(3-methyl-2-pyridyl)aminomethylene malonate.

Ethyl-9-methyl-4-oxo-4H-Pyrido[1,2a]pyrimidine-3-carboxylate (Table 2, Reaction A)

A mixture of *N*-(3-methyl-2-pyridyl)aminomethylene malonate (0.70 g, 2.5 mmol) and diphenyl ether (10 ml) was irradiated for 15 min in a CEM microwave at full power. The mixture was allowed to cool to room temperature, and hexane (50 ml) was added with stirring. The yellow solid produced was filtered under suction and washed with additional hexane (50 ml). The solid was dried under vacuum to yield ethyl-9-methyl-4-oxo-4H-pyrido[1,2a]pyrimidine-3-carboxylate (0.45 g, 77%) as a white solid.

^{1}H NMR (d_6-DMSO) δ ppm: 1.29 (t, 3H, $J = 7.1$ Hz, C$\underline{H_3}$), 2.53 (s, 3H, Ar-C$\underline{H_3}$), 4.24 (q, 2H, J = 7.2 Hz, C$\underline{H_2}$), 7.44 (t, 1H, J = 7.1 Hz, Ar-H), 8.05 (d, 1H, $J = 6.9$ Hz, Ar-H), 8.83 (s, 1H, Ar-$\underline{H}$), 9.01 (d, 1H, $J = 7.3$ Hz, Ar-H). ^{13}C (d_6-DMSO) δ ppm: 14.21, 17.43, 60.08, 103.68, 117.53, 126.53, 134.68, 139.30, 152.16, 154.06, 157.19, 164.16.

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