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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2513–2517

Rapid preparation of pyranoquinolines using microwave dielectric heating in combination with fractional product distillation

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Received 29 December 2006; revised 5 February 2007; accepted 7 February 2007
Available online 15 February 2007

Abstract—4-Hydroxy-6-methyl-2*H*-pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione was prepared by microwave-assisted cyclocondensation of *N*-methylaniline with 2 equiv of diethyl malonate. Key to the success of the synthesis was the use of open vessel controlled microwave heating technology, allowing the simultaneous removal of the formed ethanol from the reaction mixture by fractional distillation.

In the past few years, heating and driving chemical reactions by microwave energy has been an increasingly popular theme in the scientific community. This non-classical heating technique is slowly moving from a laboratory curiosity to an established technique heavily used in both academia and industry. The efficiency of 'microwave flash heating' in dramatically reducing reaction times and increasing product yields/purities is one of the key advantages of this enabling technology.[1,2]

Most of the published applications of controlled microwave-assisted organic synthesis (MAOS) today involve the use of sealed vessel technology. Here the advantages of rapid and direct volumetric microwave heating are combined with the capability to superheat solvents far above their boiling points in a sealed vessel (autoclave). This method allows higher reaction temperatures to be reached than under conventional reflux conditions, and therefore often results in significant rate enhancements when compared to the experiment carried out at the boiling point of the solvent.[1,2] There are some cases, however, where the use of open vessel microwave technology is essential for a particular transformation to proceed efficiently.[3,4] Typically, this is the case when one of the (volatile) products or by-products needs to be eliminated from the reaction mixture, for example, in the case of an equilibrium process.[3,4]

Despite the large body of published work on microwave chemistry using solvents under open vessel conditions,[5,6] we are not aware of any report that describes the combination of microwave heating with the simultaneous preparative distillation of one of the reaction products.[7] In the present Letter we disclose the one-pot preparation of a synthetically valuable pyranoquinolone heterocycle employing a microwave-assisted cyclocondensation reaction. This process requires the use of open vessel microwave technology with continuous removal of the ethanol product from the reaction mixture by fractional distillation from the reagents.

The specific example discussed herein involves the condensation of *N*-methylaniline with 2 equiv of diethyl malonate, producing pyrano[3,2-*c*]quinolone **2** in a one-pot double cyclocondensation process (Scheme 1).[8,9] Pyranoquinolone heterocycles of type **2** are valuable intermediates for the preparation of a variety of functionalized 2-quinolone derivatives via chemical degradation of the pyrone ring.[10] Traditionally, the preparation of **2** (and its analogs) is performed in a round bottom flask equipped with a reflux condenser and distillation head.[8–10] The setup is immersed into an oil bath (or heating mantle) and during 3–5 h of conductive heating, the formed ethanol product (4 equiv) is continuously removed by distillation from the reaction mixture.[8,9] Employing diphenyl ether (bp 259 °C) as a

Keywords: Heterocycles; Cyclocondensation; Microwave irradiation; Distillation.
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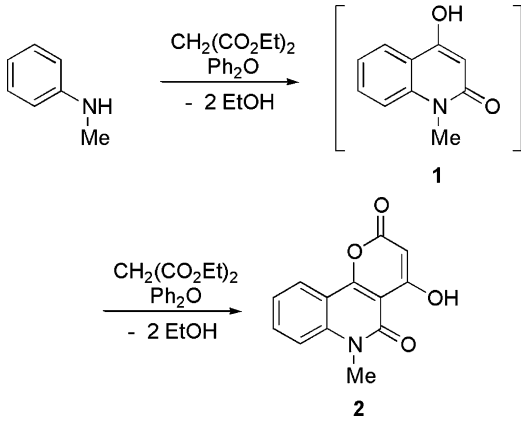
doi:10.1016/j.tetlet.2007.02.052



Scheme 1.

solvent, the temperature of the reaction mixture gradually rises to the boiling point of diphenyl ether as the two substrates, *N*-methylaniline (bp 196 °C), and diethyl malonate (bp 199 °C) are being consumed. At this stage the formation/distillation of ethanol stops and the double cyclocondensation is completed.

We were interested to explore how direct microwave dielectric heating[1,2] of the reaction mixture would influence the outcome of this cyclocondensation reaction. Based on our experience with a related cyclocondensation process,[3] we were not surprised to find that experiments using sealed vessel microwave heating in a single-mode reactor failed. Microwave irradiation of a mixture of 0.005 mol of *N*-methylaniline, 0.01 mol of diethyl malonate and 4 mL of diphenyl ether in a 10 mL sealed reaction vessel at 250 °C for 90 min led to only a small amount (<5%) of the desired pyranoquinolone **2** being formed. As confirmed by HPLC and ^{1}H NMR analysis, the majority of the crude reaction mixture under these conditions still consisted of unreacted starting materials and a minor amount (ca. 10%) of the monocondensation product *N*-methyl-4-hydroxy-2(1*H*)-quinolinone (**1**). The progress of the reaction could be monitored online by following the pressure build up in the microwave vessel. While the reaction temperature quickly reached the desired set temperature of 250 °C within 2–3 min, the initially observed autogenic pressure at 250 °C of 4 bar gradually increased to 6.5 bar after 90 min as a consequence of the produced volatile ethanol (see Supplementary data for more details).

We therefore moved to open vessel microwave technology and since we were also interested in the scale-up possibilities of this process,[6] we decided to use a larger multimode microwave reactor and to perform the reaction on a 0.2 mol scale. Our experimental setup was designed to closely mimic the traditional oil bath experiment (Fig. 1). Thus, a 500 mL 2-necked round bottom flask was placed inside the multimode reactor and was fitted with a 60 cm Vigreux column through the protective mount in the ceiling of the microwave cavity. A standard atmospheric pressure distillation kit was attached to the top of the column and was connected to a graduated receiver for measuring the amount of the collected ethanol.

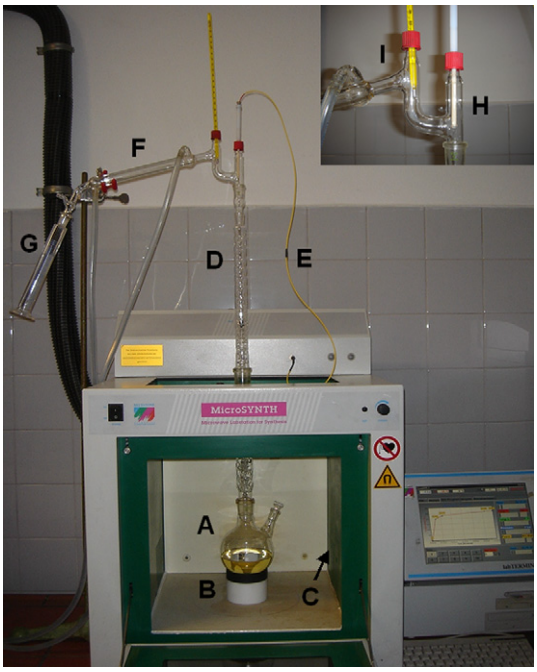


Figure 1. Multimode microwave reactor setup (MicroSYNTH, Milestone s.r.l.) for combined synthesis and simultaneous fractionated product distillation. A: round bottom reaction flask with magnetic stir bar (Pyrex, 500 mL); B: 8 × 6.5 cm cylinder made of Weflon (black, top) and PTFE (white, bottom); C: remote infrared temperature sensor; D: Vigreux column (60 cm length); E: fiber-optic temperature sensor; F: distillation head with condenser (water cooled); G: graduated receiver. Inset H: fiber-optic temperature probe in protective thermowell mounted on distillation head. Inset I: mercury thermometer on distillation head.

For accurately monitoring the reaction temperature in the microwave heated runs, we investigated both the possibility of internal temperature measurement via a fiber-optic probe and the determination of the outside surface temperature of the reaction vessel with the built-in IR sensor mounted in the sidewall of the cavity.[11] Since simultaneous monitoring of both temperature values revealed only minor discrepancies between the two methods, we decided to employ the IR sensor for establishing the reaction temperature and to use the fiber-optic probe for online monitoring of the temperature at the distillation head (Fig. 1). Our initial trial runs were conducted with 0.2 moles of *N*-methylaniline (ca. 23 mL), 0.4 moles of diethyl malonate (ca. 62 mL) and 100 mL of diphenyl ether as solvent in a set-up similar to the one shown in Figure 1, but using a shorter Vigreux column (30–45 cm). Attempts to heat the reaction mixture as quickly as possible to the boiling point of diphenyl ether (259 °C) in the 1000 W microwave reactor showed that ethanol started to be produced at around 150 °C and that it was possible to raise the temperature within 5 min to ca. 200 °C. In the case of too rapid heating (i.e., by applying high levels of microwave power), the observed refluxing of the reaction mixture was very intense and the temperature at the distillation head (at both positions, see Fig. 1) increased above 80 °C, indicating an undesired co-distillation of the *N*-methylaniline (bp 196 °C) and/or diethyl malonate (bp

199 °C) starting materials. A careful balance between the length of the Vigreux column, the amount of microwave power used and the programmed temperature profile ultimately allowed us to complete the synthesis of pyranoquinolone **2** in 82 min following the temperature-power-time profile shown in Figure 2. After several programmed heating ramps from room temperature to 233 °C (21 min), the temperature of the reaction mixture was continuously raised to 259 °C within a 55 min time period and then kept at this temperature for an additional 6 min. At this point the double cyclocondensation shown in Scheme 1 was completed, all starting material consumed and the formation/distillation of ethanol (44.5 mL, theoretical amount: 46.5 mL) had ceased, clearly indicated by a drop of the distillation head temperature (Fig. 2). Addition of dioxane to the ca. 120 °C warm reaction mixture led to crystallization of the crude reaction product, which was subsequently collected by filtration to furnish pyranoquinolone **2** in 81% yield and excellent purity (>98% by HPLC and ^{1}H NMR). The published oil bath protocol requires 3–5 h and provided a 66% product yield.[8]

Having optimized the synthesis of pyranoquinolone **2** via open vessel microwave technology on a 0.2 mol scale, we were interested to compare these results with the previously published traditional oil bath protocol,[8] not only in terms of reaction time and product yield, but also in terms of the required energy consumption. For this purpose we have conducted two additional control experiments on the same scale employing a similar experimental set-up: one in a conventional oil bath (3.3 L of oil, max temperature 240 °C) and one employing a high-powered heating mantle (300 W, max temperature >350 °C). Confirming previous literature reports,[8–10] the formation of pyranoquinolone **2** in the comparatively inert oil bath with a temperature limit of 240 °C required 26 h to reach completion, but otherwise provided the desired product in similar yield and purity as in the microwave experiment. In contrast, the heating mantle experiment allowed us to more closely mimic the time–temperature profile followed in the microwave run (Fig. 2), and therefore also required a similar time period (120 min).

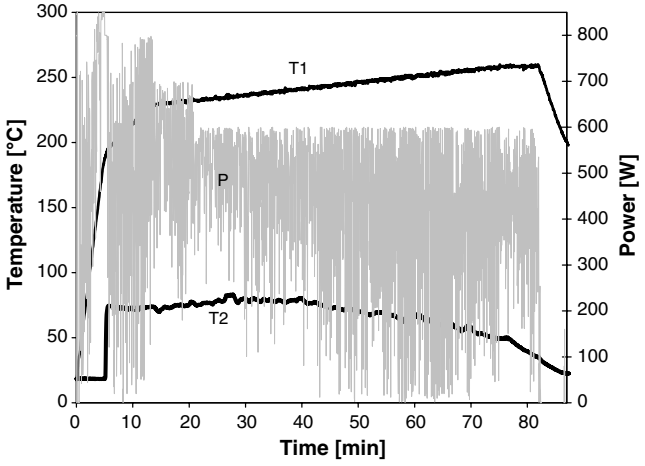


Figure 2. Temperature and power profile for the open vessel cyclocondensation of *N*-methylaniline and diethyl malonate in diphenyl ether (Scheme 1). Multimode microwave irradiation with simultaneous distillation of ethanol product (Fig. 1). The following heating profiles were programmed: step 1: 18–193 °C (5 min, max power 850 W), step 2: 193–230 °C (8.5 min, max power 800 W), step 3: 230–233 °C (7.5 min, max power 700 W), step 4: 233–259 °C (55 min, max power 600 W), step 5: hold at 259 °C (6 min, max power 600 W), step 6: cool to 125 °C (15 min, not shown). The total microwave irradiation time was 82 min. Shown is the reaction temperature T1 measured with the IR sensor, the temperature at the distillation head T2 monitored by fiber-optic probe, and the microwave power P (pulsed microwave power).

As far as the energy balance for the three processes is concerned, we have employed a commercially available domestic electricity meter ('Watt-hour meter') to measure the consumed energy in all three processes.[12] As expected, the oil bath experiment not only required the longest time (26 h) but also consumed the most energy (17.59 kW h, Table 1). We were surprised to find that the heating mantle experiment required only 0.62 kW h and therefore proved to be the most energy efficient way to produce pyranoquinolone **2**. The microwave run involving the 1000 W multimode cavity consumed three times as much energy as the heating mantle experiment. This is even true if the energy used for magnetic stirring and the cooling fan in the reactor was taken into account (Table 1). It seems that the comparatively low efficiency of the magnetrons in converting electrical energy into electromagnetic radiation (70%)[13] and the amount of power inadvertently lost in a comparatively large multimode system are perhaps responsible for this outcome.

In addition to the microwave-assisted synthesis of pyrano[3,2-*c*]quinolone **2**, we also wanted to adapt the two-step degradation of **2** into *N*-methyl-4-hydroxy-2(1*H*)-quinolinone (**1**) to a microwave protocol. Traditionally, the ring-opening/decarboxylation of pyranoquinolone **2** to 3-acetylquinolone **3** is performed by heating of a solution of pyranoquinolone **2** with aqueous sodium hydroxide (5.0 equiv) in 1,2-ethanediol as solvent, furnishing the desired product in very high product yield within 1 h (after precipitation by acidification) (Scheme 2).[8] After some experimentation

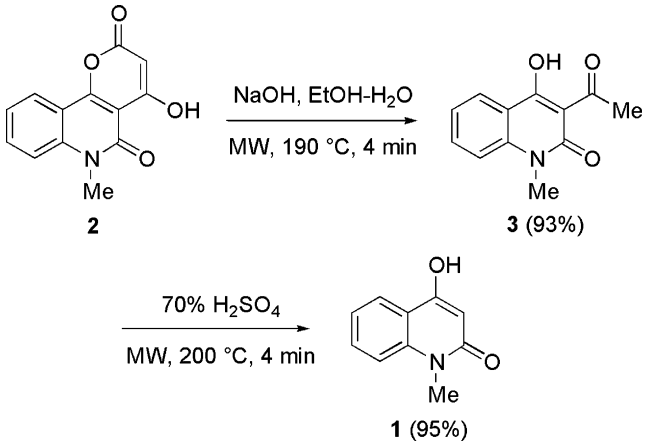
Table 1. Comparison of energy efficiency between three different heating modes in the synthesis of pyranoquinolone **2** (Scheme 1)

Heating method[a]	Reaction time (min)	Energy consumption[b] (kW h)
Oil bath	1560	17.59
Heating mantle	120	0.62
Microwave heating	82	1.67
Microwave heating[c]	82	1.29

[a] For a graphical representation of the employed heating apparatus, see the Supplementary data.

[b] An electricity meter (Energy Check 3000, Voltcraft) was set in serial between the power supply and the heating device. The power consumption of the computer terminal of the microwave instrument was not considered.

[c] After adjustment for the energy consumption for magnetic stirring and the cooling fan (0.38 kW h).



Scheme 2.

involving variation of the solvent, amount of base, reaction time, and temperature, we arrived at microwave-assisted conditions that allowed the ring-opening step to proceed within only 4 min (including a 3 min heating ramp) providing a similar high product yield. One of the best set of conditions was found to involve ethanol as solvent, 4.0 equiv of base and 190 °C reaction temperature. After successful optimization on a small scale in a sealed microwave vessel, the preparation of 3-acetylquinolone **3** was scaled to 100 mL reaction volume (0.04 mol) in a high-pressure microwave autoclave system (Milestone HPR 100 mL rotor), which tolerated the ca. 24 bar reaction pressure resulting from the superheated ethanol. Using these conditions, the desired 3-acetylquinolone **3** was produced in 93% isolated yield.

Finally, the deacetylation **3**→**1** was performed using 70% sulfuric acid at 200 °C in 4 min (including a 2 min heating ramp) on a 0.035 mol scale (20 mL). The isolated product yield of 95% compared well with the traditional thermal protocol employing 90% sulfuric acid at 140 °C for 15 min.[8]

In conclusion we have demonstrated that the combination of microwave heating under atmospheric pressure conditions with simultaneous product distillation is a very valuable—but underutilized—technology for organic synthesis. In the specific example provided herein, the cyclocondensation of *N*-methylaniline with diethyl malonate leading to pyrano[3,2-*c*]quinolone **2** must be carried out under these unusual reaction conditions. The conversion in this transformation can be conveniently monitored by the amount of the formed ethanol collected in the receiver and the rate of the reaction can be controlled by the level of the applied microwave power. Using more common sealed vessel microwave technology virtually no reaction takes place.

Acknowledgments

This work was supported by a grant from the Christian Doppler Society (CDG). T.R. thanks the Higher Education Commission of Pakistan for a Ph.D. scholarship. We are indebted to Professor W. Stadlbauer for helpful suggestions and comments and to Hana Prokopcová for experimental assistance.

Supplementary data

Supplementary data associated with this article (experimental procedures, images of equipment) can be found in the online version at doi:10.1016/j.tetlet.2007.02.052.

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