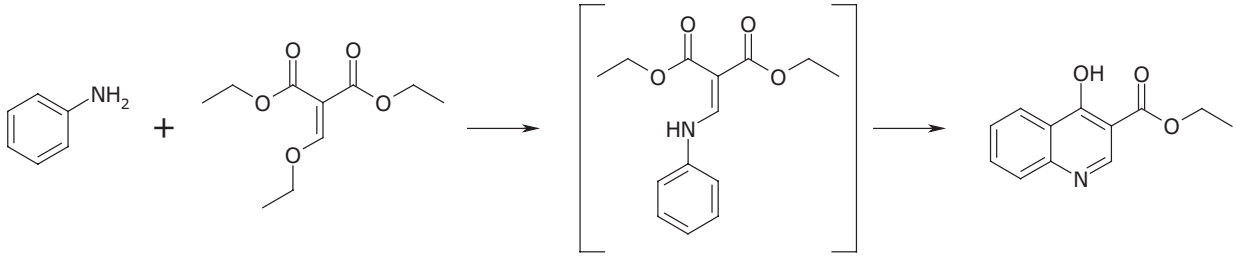
Gould-Jacobs Quinoline-forming Reaction: A Comparison of Heating using Microwave Irradiation to 250 °C and 300 °C

Application Note

Introduction

Quinolines are an important class of broad-spectrum antibiotics[1] that were traditionally obtained by refluxing an aniline and diethyl ethoxymethylemalonate (**Scheme 1**) for several hours often in low yield.[2] Heating the reaction mixture by microwaves to temperatures above the boiling points, with or without solvents, improves the yields and shortens the reaction time dramatically.[3-6]



1 **2** **3** **4**

Scheme 1

Experimental

Materials

All materials were obtained from commercial suppliers; Sigma-Aldrich (aniline and diethylethoxymethylenemalonate); Fisher Scientific for acetonitrile. Milli-Q (Millipore) water was used for HPLC-MS analysis.

Synthesis

Aniline (**1**) (0.16 mL, 2.0 mmol) and diethyl ethoxymethylenemalonate (**2**) (1.21 mL, 6.0 mmol) was added to a 2.5 mL mw-vial equipped with a magnetic stirring bar. The mixture was heated to 250 ºC or 300 ºC on Biotage® Initiator^{+}[7] microwave synthesis system for the reaction times stated in *Table 1*. The mixture was cooled to room temperature and the precipitated product was filtered off and washed with ice-cold acetonitrile (3 mL). The resulting solid was dried under vacuum and analyzed on HPLC-MS along with the corresponding mother-liquor. In all reactions starting material (**1**) had reacted completely, and the product isolated was >95% purity. Analytical HPLC was performed on an Agilent 1100 system. The samples were analyzed on an ACE 3 AQ C18 column (2.1 × 50 mm). Identification was carried out by APCI-MS (Agilent 6120 Quadrupole) both on positive and negative mode.

Entry	Temp (ºC)	Reaction Time (min)	Isolated yield (%)	Pressure (bar)
1	250	7.5	1	2 to 5
2	300	7.5	37	4 to 15
3	250	15	9	3 to 6
4	300	15	28	5 to 24
5	300	5	47	4 to 13

Table 1

Results and Discussion

The Gould-Jacobs quinoline synthesis between an aniline (**1**) and ethoxymethylene-malonate (**2**) starts with a fast Michael-addition followed by elimination of the allylic ethoxy-group. The intermediate formed (**3**), undergoes a thermal high temperature intra-molecular cyclization yielding the product (**4**). This is confirmed in Entry 1, where all (**1**) has been consumed and only 1 % product can be isolated. Only intermediate (**3**) along with the excess starting material (**2**) was left in the mother-liquor according to HPLC analysis. Increasing the reaction time (Entry 3) does not, dramatically increase the conversion of intermediate (**3**) to quinoline (**4**). However, increasing the temperature to 300 ºC (Entry 2) gives product (**4**) in 37% yield but only 5% (**3**) is left in the mother-liquor. Increasing both the temperature and the reaction time gives less product isolated (28 %, Entry 4). Considering the high pressure generated (24 bar), decarboxylation occurs. No intermediate (**3**) is left in the mother-liquor. By increasing the temperature but also decreasing the reaction time to 5 minutes, a higher yield of the product (**4**) was isolated (47%, Entry 5).

Conclusion

Generally, most organic reactions benefit from a higher reaction temperature, in terms of decreasing the reaction times dramatically and, often, increasing the purities and yields of the products formed. The Gould-Jacob reaction is a reaction that needs higher temperature in order to achieve the intra-molecular cyclization. However, the reaction time must be adjusted in order to minimize the degradation of the product. A thorough time-temperature examination must be performed in order to optimize the yield of the reaction.

References and Notes

1) Ball, P., *J. Antimicrob. Chemother.* **2000**, 46, 17.
2) Gould, R.G and Jacobs, W.A., *J. Am. Chem. Soc.* **1939**, 61 (10), 2890.
3) Smith, R.B., Faki, H and Leslie, R., Synthetic Communications, **2011**, 41, 1492.
4) Lange, J.H.M, Verveer, P.C., Osnabrug, S.J.N. and Visser, G.W., *Tetrahedron Lett.* **2001**, 7, 1367.
5) Zhang, M. Q., Haemers, A., Vanden Berghe, D., Pattyn, S. R., Bollaert, W. and Levshin, I. *J. Heterocyclic Chem.* **1991**, 28 (3), 685.
6) Biotage Pathfinder.
7) Advanced Mode, see Getting Started Guide.

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