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STEREOSPECIFIC SYNTHESIS OF TETRAHYDROISOQUINOLINE VIA MICROWAVE-INDUCED REACTION

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Abstract: A highly stereosepcific synthesis of tetrahydroisoquinoline via microwave-induced reaction has been developed. This reaction has been successfully performed in a one-pot operation using clay.

Keywords: Microwave, Tetrahydroisoquinoline, One-pot reaction

Introduction:

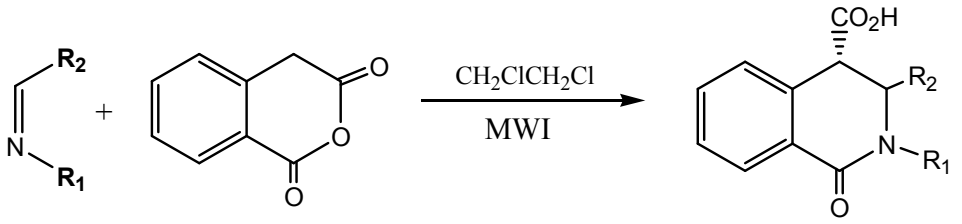
Conducting organic reactions in an eco-friendly way is challenging for synthetic chemists. Many conventional organic reactions involve excess use of solvents and chemicals waste that could pollute our environment. The microwave-mediated organic synthesis[1,2] is one of the well-suited methodology to serve this purpose.

We have developed "Microwave-Induced Organic Reaction Enhancement (MORE) Chemistry Techniques.[2] These techniques allow many organic reactions to be conducted in a few minutes in open glass vessels using reagents or reaction media that are dipolar. The key feature of MORE chemistry is to use a high boiling polar solvent as the microwave energy transfer agent and adjust the oven to reach a desirable reaction temperature with little vaporization; no reflux condenser is therefore needed. The open system also eliminates the risk of explosion. Energy reaches the reactants directly without first heating the vessel, stirrers are not necessary. Reaction in a few grams to several hundred grams scale can be completed in 1-10 min. in domestic microwave ovens. Stereoselective reactions and reduction in the formation of byproducts lowers the need for purification steps. In our ongoing project of exploring various reactions by MORE chemistry, we report an efficient one-pot synthesis of isoquinoline derivatives.

Results: At the beginning of the synthesis, the required starting materials were prepared by following the method developed by Cushman and Madaj.[3] Refluxing a dichloromethane solution of the imine **1** with homophthalic anhydride **2** for 1h produced the acid **3** as a single stereoisomer as evident from the coupling constant of the adjacent protons on the isoquinoline ring. We simplified the preparation of the acid by using microwave irradiation in a one-pot operation. The

reaction was completed after 5-8 min of microwave irradiation. Recently, Varma *et al.*[4] reported a solventless method of preparing imines in microwave in millimolar quantities. Applying this methodology, we prepared the imine in the presence of montmorrillonite KSF clay, in the microwave in quantitative yield. The crude imine prepared was used for the next step. Microwave irradiation of the crude imine with homophthalic anhydride for 6-8 min in the presence of dichloroethane as solvent, provided the acid in 85-90% yield (**Scheme 1** and **Scheme 2**). A variety of imines can be used with equal success.

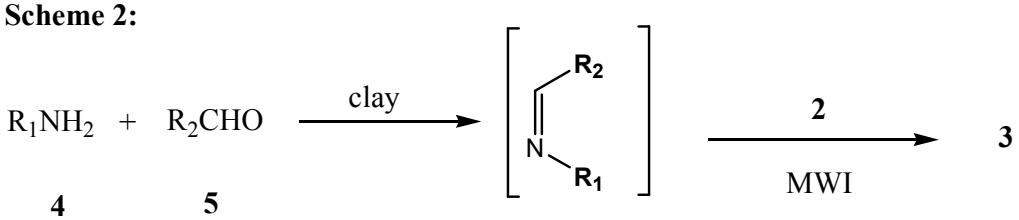
Scheme 1:



1 **2** **3**

a : $R_1 = R_2$ = Ph (90%)
b: R_1 = p-methoxyphenyl, R_2 = Ph (90%)
c: R_1 = Ph, R_2= p-methoxyphenyl (90%)
d: R_1 = -$CH_2CH{=}CH_2$, R_2 = Ph (85%)
e: R_1 = -$CH_2CH{=}CH_2$, R_2 = 2-Bromophenyl (85%)

Scheme 2:



4 **5** **1**

Conclusion: We have shown the versatility of the present work by carrying out the reactions in microwave oven in a one-pot operation. The acceleration of the reaction rates under microwave irradiation and stereoselctivity may be entirely due to the rapid attainment of temperature. The information reported in the paper should also be useful for the synthesis of polycyclic benzphenanthridine and protoberberine group of alkaloids and various other natural products.

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