

Microwave-Assisted Three Component Cyclocondensation Reaction: A Facile Synthesis of Highly Functionalized Cyclohexene Derivatives

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ABSTRACT: Microwave-assisted three component cyclocondensation reactions of aldehydes, amides and dienophiles in the presence of acetic anhydride and para-toluenesulfonic acid as a catalyst to afford the highly substituted cyclohexene derivatives, in relatively good yields after several minutes are reported.

KEY WORDS: Aldehyde, Amide, Cycloaddition, Three-component reaction, Microwave-irradiation.

INTRODUCTION

Very recently, Beller and his co-workers devised an one-pot three-component tandem Diels-Alder cycloaddition reactions in which an aldehyde, amide and a dienophile are combined to produce an amino functionalized cyclohexene or cyclohexadiene derivatives [1]. In this procedure product yields are relatively good (65-92%), but reaction times necessary for these yields are very long, for example 20-68 hours at 80-120 °C in *N*-methylpyrrolidinone (NMP), which because of high boiling point (202 °C) of solvent, it has to be removed by oil pump.

Microwave activation as a non-conventional energy source has become an important method that can be used to carry out a wide range of reactions within short reaction times, which usually occur at high temperatures and within very long reaction times [2-6]. In addition, due to short reaction times associated with microwave irradiation and rapid heating, the decomposition or polymerization of the reactants and the reversibility of the

reaction have been avoided, a situation not accessible in most classical methods.

EXPERIMENTAL

Aldehyde (1.5 mmol), amide (1.5 mmol), dienophile (1 mmol), acetic anhydride (1.5 mmol) and para-toluenesulfonic acid monohydrate (0.052 mmol) were combined in a screw-capped vial, and solvent was added (1 ml, as showed in table 1).

Then, the reaction mixture is irradiated in a microwave oven for a period as indicated in the table 1. After completion of the reaction, the solvent and other volatile compounds were evaporated to give an orange or red residue. Silica gel column chromatography (hexane:ethyl acetate=1:2) afforded product (**4**) as a white solid. All of the products are known compounds and were identified by comparison of their physical and spectral data with those authentic samples.

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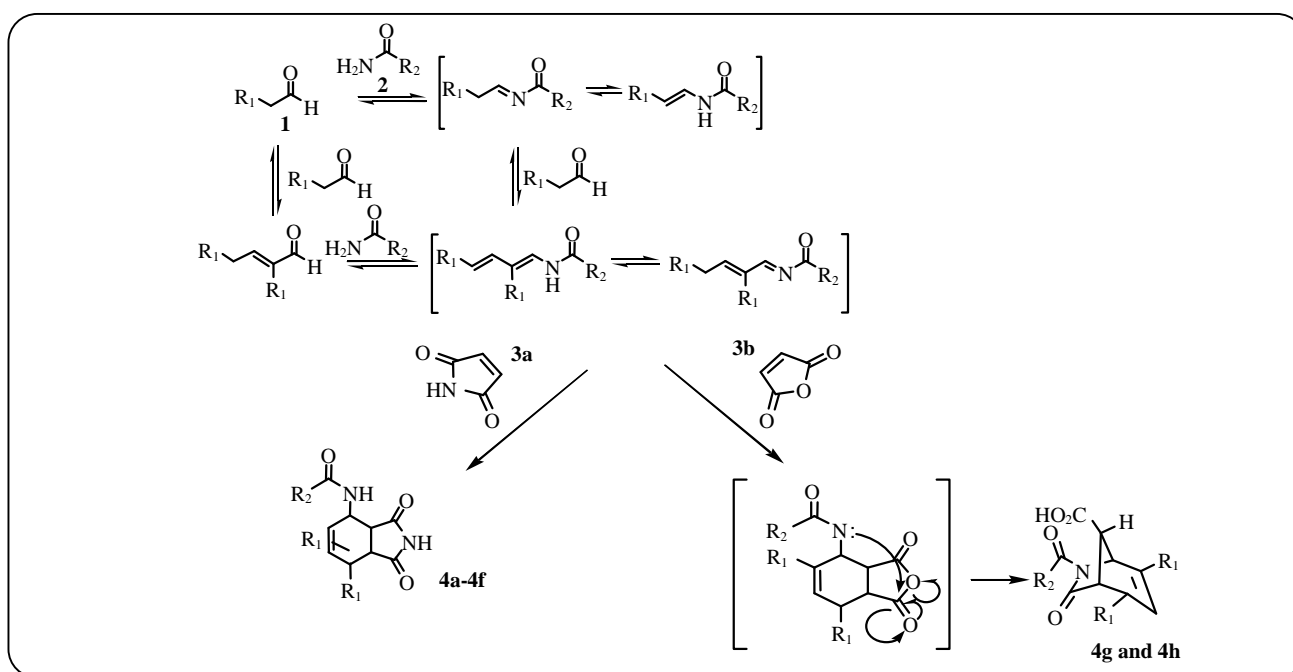
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Table 1: Synthesis of 4a-4h under microwave irradiation or conventional heating conditions.

4	R ₁	R ₂	Dienophile	Solvent	Yield ^a (%)/Time (min)	Yield ^b (%)/Time (h)
a	CH ₃	Ph	3a	THF	92/ 28	83/20
b	CH ₃	CH ₃	3a	THF	78/10	80/24
c	CH ₃ CH ₂	CH ₃	3a	CH ₃ CN	80/12	92/24
d	CH ₃ CH ₂	Ph	3a	THF	85/20	90/20
e	CH ₃ (CH ₂) ₅	CH ₃	3a	THF	87/16	86/24
f	PhCH ₂	CH ₃	3a	THF	85/15	84/68
g	CH ₃	CH ₃	3b	EtOAc	65/10	68/24
h	CH ₃ CH ₂	CH ₃	3b	EtOAc	67/10	63/24

a) Microwave-assisted reaction conditions.

b) Literature yields based on conventional heating conditions at 120-180 °C [1].



Scheme 1.

In connection with our previous work on multi-component condensation reactions [7-11] and using microwave irradiation as an efficient tool for enhancing reaction rates, [12-15] we describe here a rapid one-pot cyclocondensation reactions of aliphatic aldehydes (**1**), amides (**2**) with maleimide (**3a**) or maleic anhydride (**3b**) as a dienophile in the presence of acetic anhydride and *para*-toluenesulfonic acid using microwave irradiation (Scheme 1). The procedure not only gives products in relatively good yields, but also avoids problem connected with using high boiling point solvent, and moreover, the

reaction times are reduced from a few days to a several minutes.

As can be seen from the results reported in table 1, application of microwave irradiation in these reactions decreases the time required to obtain good yields by a factor of about 40. For example the required time to synthesis of (**4a**) in 83% yield, 20 h at 120 °C in NMP [1], is reduced to 28 min when microwave irradiation is used. Product formation under microwave irradiation showed a significant solvent dependence and appropriate solvent for each of the reactions is reported in table 1.

To explore the scope and limitations of this reaction under microwave irradiation, we extended the procedure to other dienophiles. We found that the reaction proceeds with maleic anhydride, affording rearranged products (4g) and (4h), as previously reported [1], but it did not proceed when dimethyl acetylenedicarboxylate and acrylonitrile were used.

We have also investigated the possibility of reaction of propionaldehyde, benzamide and maleimide or maleic anhydride in the presence of *para*-toluenesulfonic acid on the surface of various supports such as montmorillonite K10 and silica sulfuric acid [16], under microwave irradiation. However these reactions did not occur.

CONCLUSION

In conclusion, we have demonstrated that the microwave-assisted procedure described here can replace classical methods, allowing easy and rapid access to the synthesis of highly substituted cyclohexene derivatives. Thus, the short reaction times associated with microwave activation avoid the decomposition of reagents and products, and prevents polymerization of the dienes well.

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