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On the Magic of Microwave-assisted Organic Synthesis —1,5-Benzodiazepin-2-one from *o*-Phenylenediamine and Ethyl Acetoacetate—

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Microwave-assisted synthesis of 4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one by the condensation of 1,2-phenylenediamine and ethyl acetoacetate was examined. The yields were compared with those by classical heating under various conditions. The yield is mainly determined by the temperature of the reaction mixtures, and little affected by the difference in the heating methods. Nonthermal effects in microwave heating have not been observed.

There has been increased interest in microwave-assisted organic synthesis. Large number of paper has been published in this decade.[1,2] Microwave irradiation raises the temperature of the whole volume of the reaction mixture simultaneously, whereas the reaction mixture is heated through the vessel wall by conventional heating methods. This difference may cause effects on the yield and rate of reactions. Besides this thermal effect some authors have suggested nonthermal effects in microwave heating.[3,4] Binner et al.[5] explained microwave field might affect mutual orientation of polar molecules in reaction. It increases the collision frequency and thereby the reaction rate increases. Perreux and Loupy suggested that if the polarity of a system is enhanced from the ground state to the transition state, it can result in acceleration due to an increase in material-wave interactions during the course of the reaction.[4] However, considerable controversy exists about the nonthermal effects of microwave.[5–10]

In this paper, formation of 4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one from 1,2-phenylenediamine and ethyl acetoacetate under microwave irradiation and conventional heating is compared to clarify the effects of microwave irradiation. Bougrin et al. have reported a large effect of microwave irradiation on this reaction: the yield by 700-W microwave irradiation of the mixture of 10 mmol 1,2-phenylenediamine, 15 mmol of ethyl acetoacetate and 20 mL of xylene in a 100 mL Erlenmeyer flask for 10 min is 83%, whereas no product was obtained by classical heating at 136 °C during the same time.[11]

1,2-Phenylenediamine and ethyl acetoacetate were obtained from Tokyo Kasei, and were used without further purification. 0.4 mmol of biphenyl was added to all of the reaction mixtures as an internal standard. The yield of 4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one was measured with gas-chromatography (Hitachi 264-50) with FID. One meter stainless column filled with silicone SE-30 was used. The microwave oven used was a domestic Samsung KM-BP50J. A hole of 30 mm in diameter was made in the center of the top board of the oven. A quartz tube of 16.5 mm in inner diameter and 350 mm long, one end of which was sealed, was vertically inserted through the hole. Reaction mixtures were put in the tube and irradiated. The mixtures were not stirred. The temperatures after the irradiations were measured with a chromel-alumel thermocouple. The errors of the measurements are less than ±2 °C.

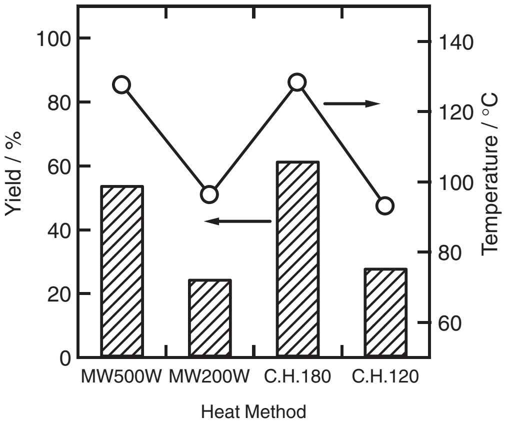

Figure 1. The yields of 4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one by the reaction of 1,2-phenylenediamine and ethyl acetoacetate and the temperatures just after the reaction heated for 10 min by 500-W (MW500 W), 200-W (MW200 W) microwave irradiation, and 180-°C (C.H.180) and 120-°C (C.H.120) oil baths.

The effects of heating method on the yield are compared in Figure 1. The mixture of 1 mmol 1,2-phenylenediamine, 1.5 mmol ethyl acetoacetate, and 2-mL xylene was heated at atmospheric pressure in an open vessel for 10 min by 500- and 200-W microwave irradiation and by 180- and 120-°C oil baths. The temperatures just after the reaction were measured. As was already pointed out by Gedye and Wei,[9] the product was obtained even by the conventional heating. It can be seen from Figure 1 that the yield mainly depends on the temperature rather than the heating methods. The low yield by Bougrin et al.[11] will be ascribed to a problem in evaluation of the temperature.

The reaction was performed in different solvents. The mixtures of the same amount of the reactants without solvent and with solvents of 2-mL hexane, toluene, and xylene were heated with 500-W microwave irradiation and 180-°C oil bath. The heating times were 10 min for both the methods. As shown in Figure 2, the yield increased in order of the temperatures after the reaction: it increased with the order of hexane, toluene, and xylene for both the heating methods. The yield was maximum without solvent by the oil bath, whereas it was less by microwave irradiation. The lower yield of the latter might arise from decomposition of the product due to the high temperature.

The effects of the volume of the solvent were compared in Figure 3. The mixtures of the same amount of the reactants and the different volumes of xylene were heated with 500 W of microwave irradiation and 180-°C oil bath. The heating times

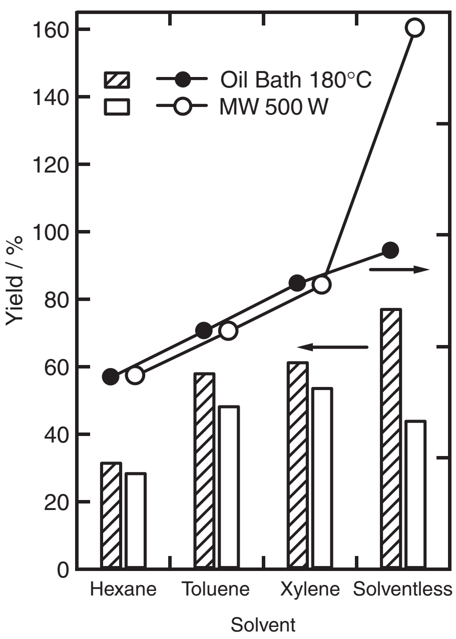

Figure 2. The yields of 4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one by the reaction of 1,2-phenylenediamine and ethyl acetoacetate and the temperatures just after the reactions in different solvents. The heating times are 10 min.

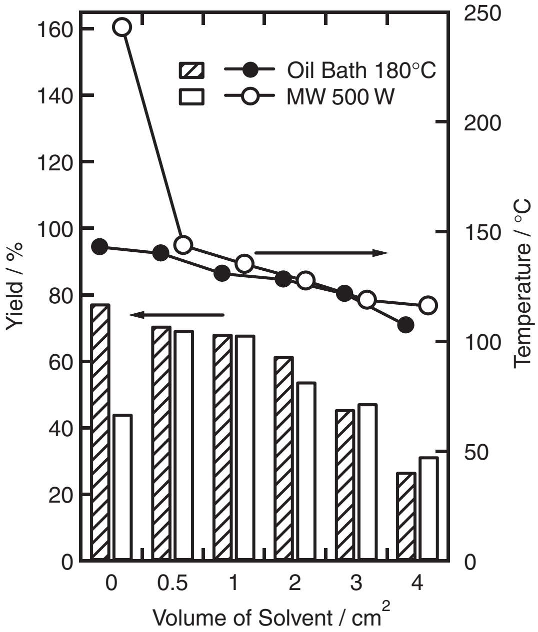

Figure 3. The yield of 4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one by the reaction of 1,2-phenylenediamine and ethyl acetoacetate and the temperatures just after the reactions in different volume of the solvent of xylene. The heating times are 10 min.

were 10 min for both the methods. Except for the solventless mixture heated with the microwave irradiation, the yield and the temperature of the mixtures decrease with increasing the volume of the solvent. The differences in the temperatures arise from those in the boiling points of the mixtures.

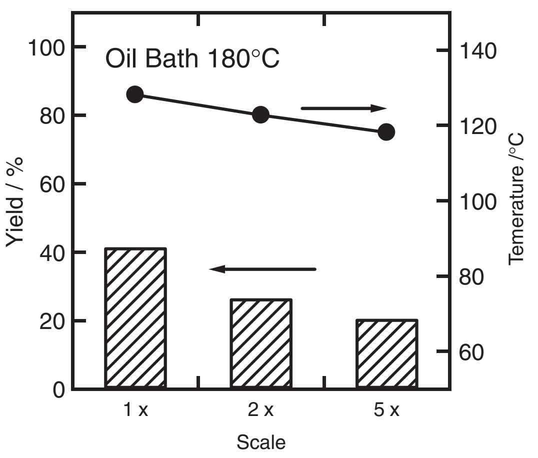

Figure 4. The yields of 4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one by the reaction of 1,2-phenylenediamine and ethyl acetoacetate and the temperatures just after the reaction in different scales. The heating times are 2 min.

The effects of the scale of the reaction mixtures were compared in Figure 4. The mixture of 1× consists of 1.0 mmol of 1,2-phenylenediamine, 1.5 mmol ethyl acetoacetate, 0.4 mmol biphenyl, and 2.0-mL xylene. The mixtures of 2× and 5× contains two and five times of the same materials with the same ratio. The reaction time was 2 min heated with 180-°C oil bath. The yield and the temperature increases with decreasing the scale. The changes in the temperatures will arise from the evaporation of the solvent. The part of the solvent evaporates and attached to the wall of the reaction vessel. The fraction of the attached solvent and the concentration of the reactants in the mixtures increase with decreasing the scale. It raises the boiling point, and accelerates the reaction. Microwave heating in organic syntheses are often performed in smaller scale than conventional heating. The rate enhancement by microwaves will arise from the difference in the scale in many cases.

In conclusion, the yield of 4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one from 1,2-phenylenediamine and ethyl acetoacetate is determined by the temperature of the reaction mixture regardless of the difference in the heating methods. Nonthermal effects of microwave have not been found.

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