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Solventless Organic Reactive Crystallization at Mild Conditions

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Abstract

Solid state mixtures of two reactants, 2-hydroxy-1-naphthaldehyde and 2-aminobenzonitrile, were melted at a temperature even lower than both the melting points. And dehydration condensation reaction occurred in the melt to give reaction product N-(2-cyanophenyl)-2-hydroxy-1-naphthadimine. Since the melting point of the product was higher than the reactants, self-crystallization of the product occurred. Usefulness of this one-pot synthesis and crystallization method for industrial application was described.

Keywords

Reaction, Crystallization, Polymorphism, Dehydration Condensation

1. Introduction

Condensation reaction of 2-hydroxy-1-naphthaldehyde (**napht**) and 2-aminobenzonitrile (**abn**) produces N-(2-cyanophenyl)-2-hydroxy-1-naphthaldimine (**1**, see **Figure 1** for reaction scheme). This dehydration condensation reaction has been reported occur in variety of phases [1]. One is solution method using organic solvent such as tetrahydrofuran and toluene. In this conventional method, product **1** is synthesized in homogeneous phase and must be purified by crystallization. Four crystal polymorphisms have been reported for product **1** [1].

It is interesting to note that the reaction in **Figure 1** can occurs in solvent-free conditions. Manual grinding of stoichiometric amount of **napht** and **abn** yielded product **1** as crystalline state [1]. The chemical reaction of **Figure 1** in melt was also reported [1], however, details had not been described. The most interesting point in the literature is that crystal polymorphism control is possible by modifying the solvent-less crystallization method [1]. Although, solvent-free method has been widely applied for various reaction system [2] [3], we are very interested in the system in which both the reaction and crystallization occur in one-pot.

Grinding of the materials generate heat by friction and the temperature of the friction surface must be in-

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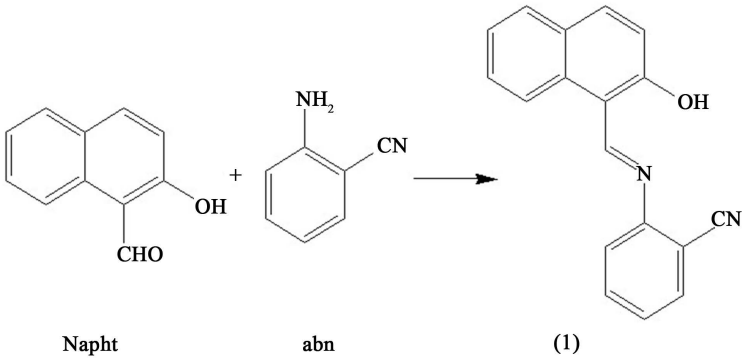

Figure 1. General scheme for synthesis of N-(2-cyanophenyl)-2hydroxy-1-naphthaldimine.

creased. This causes partial melting at the friction interface and the reaction (**Figure 1**) must occur at the local site. We believe essential point of the reaction is heat to cause melting rather than mechanical shock given by grinding. If it is true, only heat is enough to cause the reaction and/or crystallization. Although heterogeneous system (grinding method) was focused on in the literature, reaction/crystallization in homogeneous system (melt) has been studied in this paper.

2. Experimental Section

2.1. Materials

Two reactants, 2-aminobenzonitrile (**abn**, >98%) and 2-hydroxy-1-naphthaldehyde (**napht**, >98%), were purchased from Tokyo Kasei Kogyo Co., Ltd. (reagent grade) and were used without purification.Melting point of the two reactants were measured by thermal analysis method and were estimated as **abn** = 50˚C, **napht** = 81˚C.

2.2. Method

Before contacting **napht** and **abn** crystals for reaction, the crystalline samples were grinded for about one minute separately. This manual grinding was performed for increase reaction interface and the care was taken kindly so as not to destroy crystal structures. The two crystalline reactants were mixed in a small bottle by manual shaking for ten second. The mixed reactants were put on the hot stage and the reaction was commenced by applying heat. During the experiment, temperature of the hot stage was kept constant and change in the solid mixture was observed.

As shown above, melting points of **abn** and **napht** are 50˚C and 81˚C, while that of the product **1** were reported as 190˚C - 197˚C depending on the crystal polymorphism [1]. Thus if temperature is kept constant between melting points of the reactants and the product, it could be expected that the solid-state reactants mixture melt and reaction occur in melt, followed by spontaneous crystallization of the product. Achievement of this isothermal one-pot synthesis/crystallization is our purpose.

We selected the experimental temperature lower than melting temperature of product **1** and, basically, higher than the melting temperature of reactants. Selected temperatures were 35˚C, 55˚C, 100˚C and 150˚C.

3. Results and Discussion

Figure 2 shows a typical example of a series of melting, reaction and recrystallization processes observed at 35˚C. Initially **Figure 2(a)**, the reactant mixture is pale yellow color. Though the temperature is lower than melting points of two reactants, **abn** = 50˚C, **napht** = 81˚C, partial melting of the solid mixtures is occurred. For example, melting of the solid can be seen at the bottom right of the **Figure 2(b)**. This is well-known melting point depression effect. After 2 min 45 s (**Figure 2(c)**), the whole of the crystals were melted. After a while the color of the melt changed to orange from pale yellow. This color change may be clearly seen by comparing **Figure 2(c)** and **Figure 2(d)**. This melt color change suggests us occurrence of the chemical reaction (**Figure 1**). In **Figure 2(d)**, crystalline like particles were formed in the melt as indicated by arrows in **Figure 2(d)**. With the progress of the time, crystalline parts were developed and almost all the melt changed to crystals **Figure 2(h)**.

Crystalline samples were collected when solidification was completed as **Figure 2(h)** and its powder X-ray diffraction patterns were measured. Though, two types of crystals, yellow and orange, are existed as recognized in **Figure 2(h)**. Characterization of the each crystals were difficult in this study.

In **Figure 3**, PXRD patterns of the reaction product at 35˚C is shown. Cinčić *et al*. reported four crystal polymorphisms of compound **1** [1]. For comparison, XRD of four crystal polymorphisms of compound **1** was calculated using the literature crystallographic data [1] in addition to measured XRD of two reactants (**abn** and **napht**). As can be seen in **Figure 3**, the product crystals is not a single phase. However, appearance of Form I may be identified from the three peaks appeared at 6.5˚, 7.6˚, 9.5˚. NMR measurements also show existence of solid compound **1**. Other components included in the product must be Form II and unreacted **napht**. Anyway, reaction and crystallization of compound **1** was achieved by this mild condition. To improve the reaction rate, operational temperature was increased (**Figure 4**). At 55˚C, almost the same results were obtained with the case

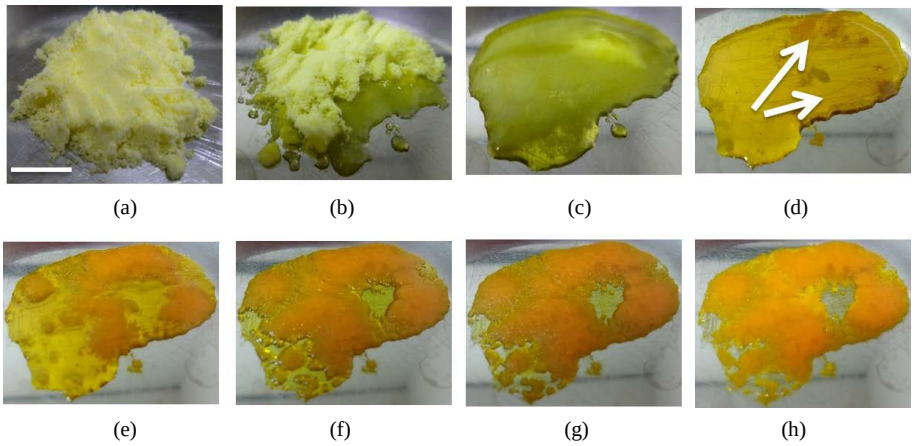

Figure 2. A series of photographic pictures showing one-pot synthesis of N-(2-cyanophenyl)-2hydroxy-1-naphthaldimine at 35˚C. (a) initial mixture of two components (**abn** and **napht**); (b) partial melting of the reactants crystals; (c) melting; (d) appearance of solid in the melt; (e)-(g) progress of crystallization in melt; (h) completion of crystallization. Bar in (a) = 1 cm. (a) start; (b) 45 s; (c) 2 min 45 s; (d) 1 h 57 min; (e) 2 h 16 min; (f) 2 h 32 min; (g) 2 h 47 min; (h) 3 h 57 min.

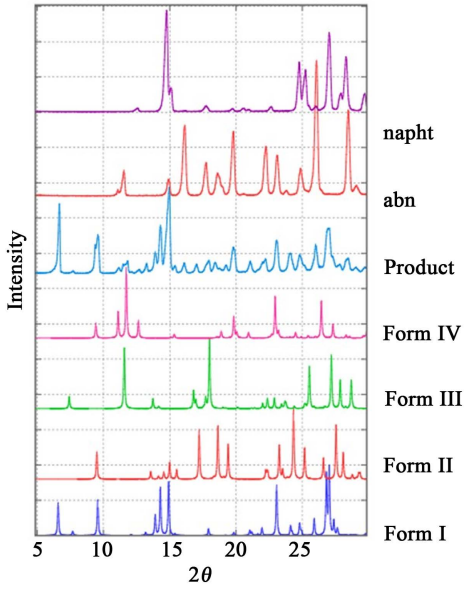

Figure 3. Comparison of powder XRD pattern of the synthesis product (35˚C) with calculated patterns of four polymorphism of the product and two reactants (**abn**, **napht**).

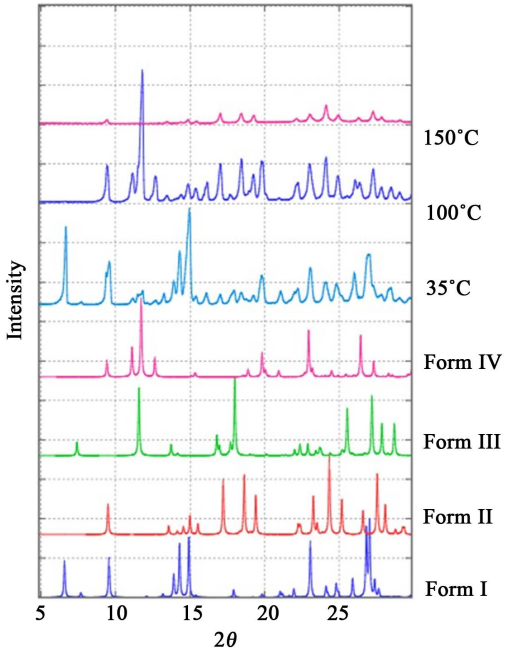

Figure 4. Temperature dependence of powder XRD pattern of the synthesis product.

of 35˚C. Polymorphic mixtures of Forms II and III were obtained at 100˚C in addition to small amount of reactant. At 150˚C, peak of **napht** was not recognized and only a single phase (Form II) was detected. It is interesting that different temperature results in different crystal polymorphism. This suggests possibility of polymorphism control.

Product **1** has been successfully obtained by using solventless one-pot organic reactive crystallization proposed in this study. Characteristic point of this method proposed in this study is (external) solvent-free and energy saving. For application purpose, however, some problems are remains. 1) How to remove water molecule efficiently produced by the dehydration condensation reaction. In addition, how the water molecule influences the reaction and/or crystallization including polymorphism formation. 2) How to control the polymorphism in this method. We have been studying about these topics now.

4. Conclusion

Efficient way to crystallize reaction product in one-pot is proposed. Features of this method, solventless one-potorganic reactive crystallization, are easy-to-operate, solvent-free and energy saving. Thus application of this method for industrial purpose is very interesting.

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