Kinetic investigation of the heterogeneous synthesis of flavanone over MgO

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The synthesis of flavanone was studied over a magnesium oxide solid catalyst in a batch reactor. The reaction scheme consists of the Claisen–Schmidt condensation of 2′-hydroxyacetophenone with benzaldehyde towards the formation of a 2′-hydroxychalcone intermediate and the subsequent isomerization of this intermediate to flavanone. An initial parametric study yielded a range of values for key experimental parameters (*i.e.*, catalyst particle size and weight percentage and stirring rate) for which the batch reactor system operates in the kinetic regime. The kinetic investigation that followed indicates that over the MgO catalyst studied the Claisen–Schmidt condensation reaction follows first-order kinetics in 2-hydroxyacetophenone and half-order kinetics in benzaldehyde, while the 2′-hydroxychalcone isomerization follows first-order kinetics; activation energies of 40 and 48 kJ/mol were obtained for the two reactions, respectively.

KEY WORDS: fine chemicals; heterogeneous catalysis; flavanone; Claisen–Schmidt condensation; MgO.

1. Introduction

Currently, most fine chemicals and pharmaceuticals are produced *via* homogeneous catalytic routes. Replacement of the homogeneous catalysts with heterogeneous ones is expected to trivialize the separation and recycling processes for the catalyst, and to reduce the amount of waste generated [1–4]. Nevertheless, the number of available examples of successful transformations from homogeneous to heterogeneous syntheses is rather limited. The complexity of the surface chemistry involved in the heterogeneous syntheses, as well as the limited understanding of the kinetic and mass transfer effects incorporated liquid–solid reaction systems, are believed to represent major obstacles in such efforts [5].

In an attempt to demonstrate such a successful transformation, we have focused our efforts on the heterogeneous synthesis of flavanone [6,7], a common intermediate component for many fine chemical and pharmaceutical products [8–11]. Flavanone is routinely synthesized *via* homogeneous catalytic routes [12], and commonly utilizes a reaction scheme incorporating the Claisen–Schmidt condensation of benzaldehyde and 2-hydroxyacetophenone to form 2′-hydroxychalcone, and the subsequent isomerization of this intermediate to flavanone (figure 1). Both reactions are catalyzed by acid or base catalysts. The kinetics and the mechanisms of the two reactions involved in the homogeneous synthesis process have been studied in detail and, despite some minor disagreements on specific mechanistic points, are fairly well understood [13–17,20]. It has also been demonstrated that the same reaction scheme can be utilized to produce flavanone heterogeneously over solid catalysts at yields comparable to those obtained during homogeneous synthesis [19–21]. However, the available kinetic and mechanistic information for the heterogeneous synthesis is very limited, and only initial rates and overall yields have been reported.

The focus of the work presented in this paper is the study of the kinetics of the Claisen–Schmidt condensation between benzaldehyde and 2-hydroxyacetophenone and the isomerization of 2′-hydroxychalcone to flavanone over a MgO catalyst. MgO was chosen as the catalyst for this study because it exhibits strong Brønsted basicity [23,24], and a high initial rate for flavanone synthesis as compared to other bulk metal oxides [20,22]. Power law rate expressions and activation energies were determined for each reaction. In addition, studies were also conducted on the recovery and reuse of the MgO catalyst. A solvent was used to simplify the kinetic study, since in this case reactant concentrations can be varied independently of one another. The solvent used was dimethyl sulfoxide (DMSO), which was chosen because of its low volatility under the reaction conditions of interest.

2. Experimental

2.1. Catalyst preparation

Pure magnesium oxide (Aldrich; 99%+ purity) was used in the form of small particles. Prior to each experiment the catalyst was calcined at 475 °C for 5 h to remove any adsorbed impurities.

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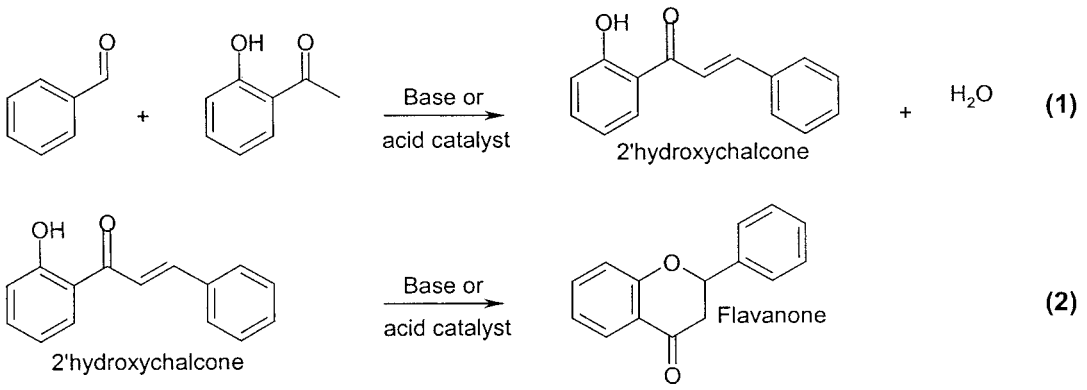

Figure 1. Reaction scheme for synthesis of flavanone via the Claisen–Schmidt condensation of benzaldehyde and 2-hydroxyacetophenone (1), and the subsequent isomerization of 2′-hydroxychalcone to flavanone (2).

2.2. Kinetic measurements

The batch reactor utilized in this study consisted of a four-port flat-bottom Pyrex flask. The four ports of the reactor were fitted with a stirring rod (attached to a motor), a reflux condenser, a thermocouple and a sampling apparatus (with a nitrogen purge line). The reactor was engulfed in a heating mantle, the operation of which was controlled by a temperature controller connected to the reactor thermocouple.

Prior to each experiment, the empty reactor was purged with nitrogen to remove oxygen from the system. Removal of oxygen is necessary to avoid the oxidation of benzaldehyde to benzoic acid [20]. Following this purging procedure, benzaldehyde (Aldrich; 99%+ purity), 2-hydroxyacetophenone (Aldrich; 99.0% purity) and the DMSO solvent (Aldrich; 99.9% purity) were placed in the reactor at the appropriate amounts (total volume of 150 ml). Nitrogen was continuously bubbled through the system. The reactor was then heated and the catalyst was added when the desired reaction temperature was reached ($t = 0$). Following this point the reactor was operated under total reflux.

Samples of 0.5 ml were taken intermittently with a specially designed sampling apparatus. Each sample was centrifuged (VWR Scientific Model V Micro centrifuge) at 10 000 rpm for 10 min to separate any solid catalyst particles that may have been trapped in the sample. Analysis was carried out offline using a SRI 8610 Gas Chromatograph equipped with a 5% phenyl methyl siloxane capillary column (Supelco) and a flame ionization detector. For the GC analysis, 5 and 50 μl aliquots of the samples obtained during the Claisen–Schmidt condensation and 2′-hydroxychalcone isomerization reactions respectively, were diluted in 1 ml of CH_2Cl_2. This dilution was necessary to obtain final sample concentrations in the range of optimum detector sensitivity. The general reproducibility of the analysis and concentration measurements was determined to be within 5% based on several repeat measurements.

Baseline experiments were conducted in the absence of the MgO catalyst and did not indicate any significant homogeneous activity in the benzaldehyde/2-hydroxyacetophenone/DMSO system for either the Claisen–Schmidt condensation or any other side reaction.

Initial reaction rates were calculated utilizing the concentration *versus* time data collected during the first few minutes of the reaction. During this initial time period, the concentration of the reactants decreases almost linearly with time, and hence the reaction rate (*i.e.*, the derivative of the reactant concentration with respect to time) could be calculated from the slope of a linear fit to these initial data. For the Claisen–Schmidt condensation reaction, where two reactants are involved, similar values for the initial rates were obtained whether the benzaldehyde or 2-hydroxyacetophenone concentrations were used, consistent with the absence of any side reactions and the 1:1 reaction stoichiometry. The values reported in this manuscript are averages of the values obtained with the two reactants.

Yields and selectivities for the 2′-hydroxychalcone and flavanone products were calculated during catalyst recycle and regeneration experiments. In these cases, the yield towards a specific product is defined as the amount of this product formed divided by the initial amount of the limiting reactant. No stoichiometric adjustment is needed in this definition, due to the 1:1 stoichiometries for both reactions involved. The selectivity towards a specific product is defined as the amount of this product formed divided by the total amount of 2′-hydroxychalcone and flavanone formed. Once again, as a result of the 1:1 stoichiometries involved, a stoichiometric adjustment is not required in this definition.

3. Results and discussion

3.1. Investigation of potential mass transfer limitations

Initial rate measurements were conducted to determine a set of parameters for the operation of the batch reactor in the kinetic regime. These parametric studies were designed to assure the absence of any external or internal mass transfer limitations and the full suspension of the catalyst in the reactor. Consequently,

Table 1
Summary of results of parametric studies investigating potential mass transfer limitations

MgO (wt%)	MgO particle size range (μm)	Stirring rate (rpm)	Initial rate (mol/g · catalyst/s)
0.1	175–250	500	6.2×10^{-4}
0.1	175–250	50	4.3×10^{-4}
0.1	175–250	250	6.4×10^{-4}
0.1	175–250	400	6.1×10^{-4}
0.5	175–250	500	6.3×10^{-4}
1.0	175–250	500	4.6×10^{-4}
2.0	175–250	500	2.3×10^{-4}
0.1	75–85	500	6.2×10^{-4}
0.1	125–175	500	5.5×10^{-4}
0.1	500–840	500	4.2×10^{-4}

the parameters varied included the catalyst particle size and loading (*i.e.*, weight percentage of catalyst in the batch) and the stirring rate.

Rate measurements were conducted with the Claisen–Schmidt condensation reaction at 160 °C. Since this is the highest temperature examined in the kinetic studies, absence of any mass transfer limitations at this temperature also guarantees absence of mass transfer limitations at the lower temperatures, where the reaction is slower. Finally, given the similar diffusivities of the species involved, absence of mass transfer limitations for this reaction also guarantees absence of mass transfer limitations for the slower 2′-hydroxychalcone isomerization reaction.

The results of these studies are shown in table 1. The results indicate that for stirring rates above 100 rpm, catalyst particle diameters below 250 μm, and catalyst loadings below 1 wt%, the observed values of the initial reaction rates are not affected by the values of these parameters, and therefore they can be considered intrinsic reaction rates. Consequently, operating conditions safely within these ranges (*i.e.*, 500 rpm stirring rate, 175–250 μm catalyst particle diameter and 0.1 wt% catalyst loading) were chosen for the subsequent kinetic investigation.

3.2. Claisen–Schmidt condensation reaction

A typical set of concentration versus time data obtained for the benzaldehyde and 2-hydroxyacetophenone reactants is shown in figure 2. The concentrations of the 2′-hydroxychalcone and flavanone products (flavanone formed during the subsequent isomerization of 2′-hydroxychalcone over the same catalyst) are also shown in this figure. Finally, the lines shown represent the initial reaction rates for the reactants, estimated as described in section 2. An apparent delay is observed in the concentrations of the products as compared to the concentrations of the reactants (*i.e.*, initially the amounts of the products formed are lower than the amounts of the reactants consumed, leading to an apparent deficit in the overall mass balance). Elemental carbon analysis and extraction experiments conducted with catalyst samples withdrawn from the reactor at different stages during a kinetic experiment, indicate that a significant amount of organic species is weakly bonded to the catalyst and/or concentrates in its pore structure. The mass balances are eventually closed (within ±4%), however, towards the end of the experimental run. Consequently, the initial deficit in the overall mass balance and the observed delay in the product concentration profiles can be attributed to the strong adsorption of reactants and products on the catalyst surface and could be represented by a surface accumulation term in the overall mass balance.

Experiments were conducted at different initial concentrations of the two reactants to obtain the kinetic

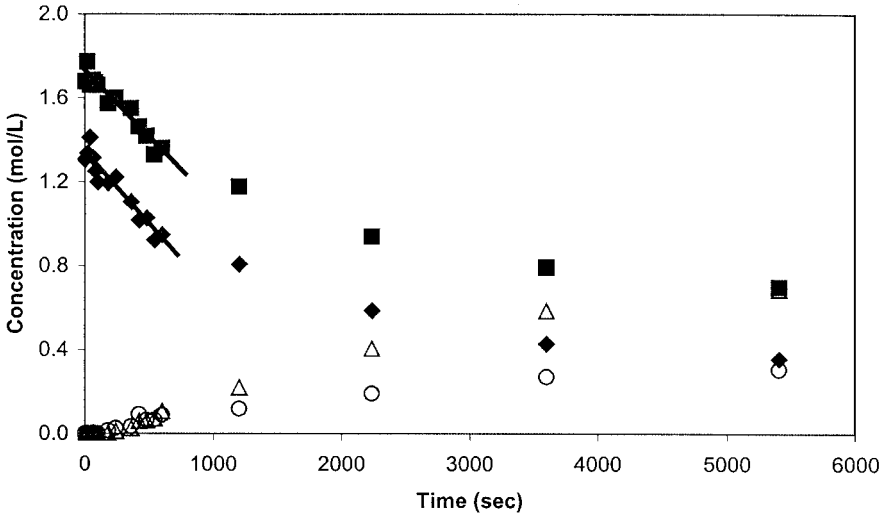

Figure 2. Concentration versus time profiles for the reactants (◆, 2-hydroxyacetophenone; ■, benzaldehyde) and products (△, flavanone; ○, 2′-hydroxychalcone) during the synthesis of flavanone over MgO at 150 °C (initial concentrations: 2-hydroxyacetophenone 1.35 mol/l; benzaldehyde 1.72 mol/l).

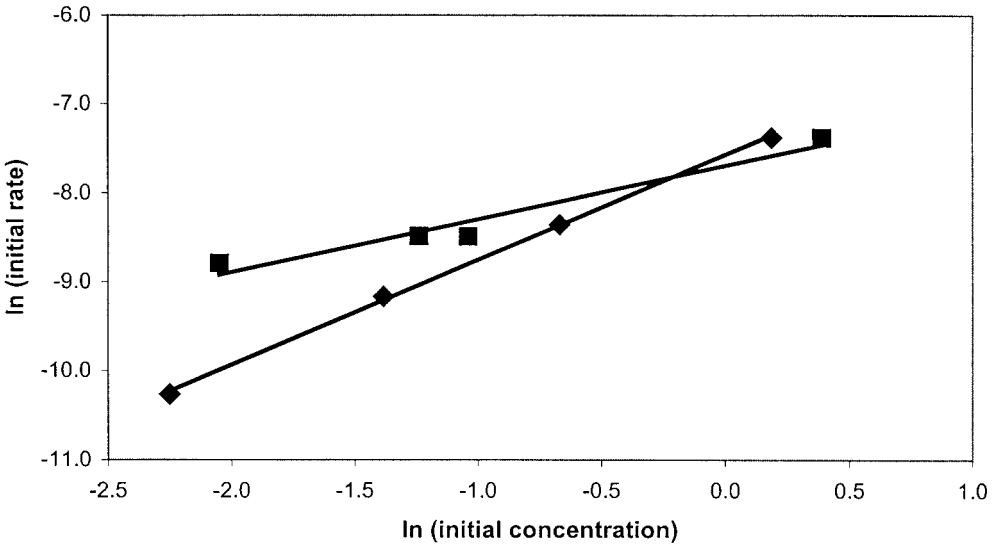

Figure 3. Initial rate of the Claisen–Schmidt condensation reaction as a function of the initial reactant concentrations at 130 °C. (◆, 2-hydroxyacetophenone; ■, benzaldehyde).

dependencies of the initial reaction rate on the reactant concentrations. The results of these studies at 130 °C are shown in a graphical form in figure 3. From the slopes of the two lines in the logarithmic plot of initial reaction rate *versus* reactant concentrations, it becomes evident that the Claisen–Schmidt condensation reaction over the MgO catalyst follows first-order kinetics with respect to 2-hydroxyacetophenone and half-order kinetics with respect to benzaldehyde. Similar results were obtained when the same experiments were conducted at 160 °C, suggesting that there are no significant changes in the reaction mechanism or the relative significance of the different reaction steps over the temperature range of interest in this study. Csuros *et al.* [25] have reported that the Claisen–Schmidt condensation of benzaldehyde and acetophenone follows first-order kinetics in both reactants over a base anion exchange resin. Similar results were also obtained by Coombs and Evans [26] for the homogeneously catalyzed reaction. The observed half-order dependence on benzaldehyde in our case suggests that the benzaldehyde molecule is strongly, and possibly dissociatively, adsorbed on the MgO catalyst.

Initial rate calculations were also conducted at different temperatures in the 120–160 °C range. Values of the reaction rate constant (per catalyst mass) were then extracted from these rates utilizing the first- and half-order kinetic dependences on the two reactants, obtained as described in the previous paragraph. An Arrhenius plot of these reaction rate constants is shown in figure 4. From the slope of the $\ln r$ *versus* $1/T$ line, an activation energy of 40 kJ/mole is obtained for the Claisen–Schmidt condensation reaction over MgO. This value is very similar to activation energy values of 38 kJ/mole reported by

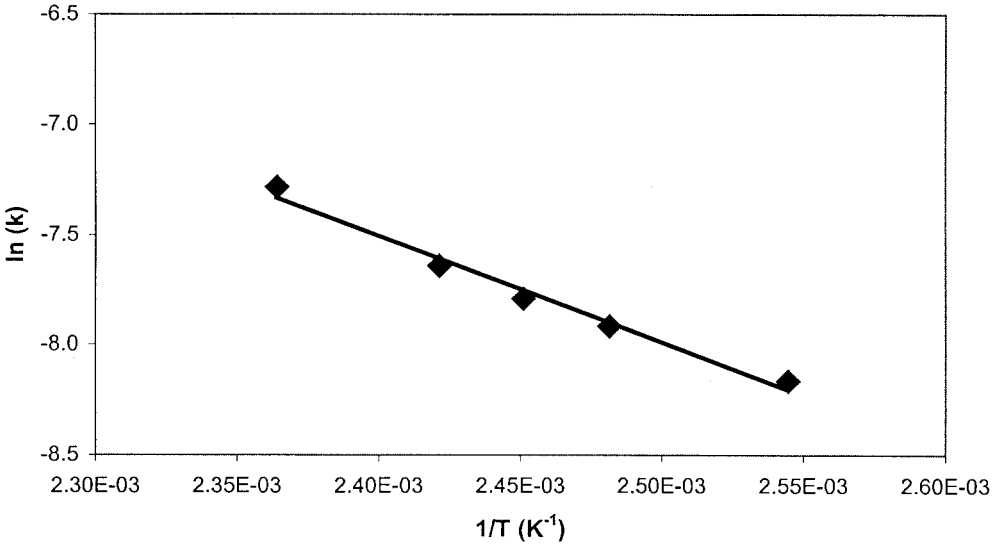

Figure 4. Arrhenius plot for the Claisen–Schmidt condensation of benzaldehyde and 2-hydroxyacetophenone.

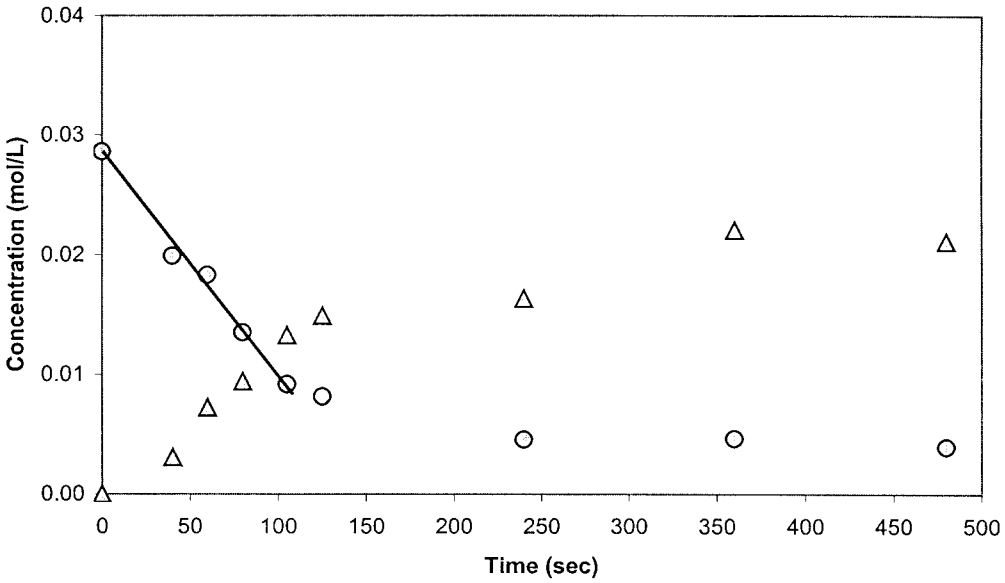

Figure 5. Concentration versus time profiles during the isomerization of 2′-hydroxychalcone (●) to flavanone (▲) at 140 °C. (Initial concentrations: 2′-hydroxychalcone 0.029 mol/l).

Csuros *et al.* [25] and 41 kJ/mole reported by Coombs and Evans [26] for the benzaldehyde–acetophenone condensation over an anion-exchanged resin and in a sodium ethoxide homogenenously catalyzed system, respectively. It does, however, represent a significant decrease from the 98 kJ/mol activation energy value we observed previously for the same reaction and MgO catalyst system in the absence of the DMSO solvent [27]. The origins of this difference and solvent effect in general, are investigated in detail in a separate study [28].

Based on the above, the following rate expression can be written for the Claisen–Schmidt condensation of benzaldehyde with 2-hydroxyacetophenone in the 120–160 °C temperature range over MgO:

$$\begin{aligned}\text{rate}(\text{mol/g}\cdot\text{cat/s}) = {} & 5.9\times10^{1}(L^{1.5}/\text{g}\cdot\text{cat/mol}^{0.5}/\text{s}) \\ & \times\exp\left(\frac{40\,\text{kJ/mol}}{RT}\right) \\ & \times(C_B(\text{mol/l}))^{0.5}C_{hA}(\text{mol/l}) \qquad (1)\end{aligned}$$

3.3. Isomerization of 2′-hydroxychalcone to flavanone

A typical set of concentration *versus* time data obtained for the 2′-hydroxychalcone reactant and the flavanone product is shown in figure 5. The line shown represents the initial reaction rate for 2′-hydroxychalcone, estimated as described in the experimental section. This isomerization is known to be reversible and the flavanone produced can be isomerized back to 2′-hydroxychalcone. In the temperature range studied, however, the equilibrium constant for this reaction is of the order of 5. Consequently, at the initial stages, when the ratio of the 2′-hydroxychalcone to flavanone concentration is high, the reverse reaction can be considered negligible. Closure of overall mass balances from the bulk concentrations does not represent a problem for this reaction, indicating that no significant accumulation of either 2′-hydroxychalcone or flavanone takes place on the MgO catalyst.

Experiments conducted at different initial concentrations of 2′-hydroxychalcone at 160 °C indicate a first-order dependence of the initial reaction rate on the concentration of 2′-hydroxychalcone (figure 6). This result is consistent with a low coverage of 2′-hydroxychalcone on the MgO catalyst and the absence of any significant accumulation, as discussed in the previous paragraph. A similar first-order dependence on 2′-hydroxychalcone was reported by Furlong and Nudelman [15,29] for the homogeneously catalyzed isomerization.

Initial rate calculations were also conducted at different temperatures in the 120–160 °C range. Values of the reaction rate constant (per catalyst mass) were then extracted from these rates utilizing the first-order kinetic dependence on 2′-hydroxychalcone, obtained as described in the previous paragraph. An Arrhenius plot of these reaction rate constants is shown in figure 7. From the slope of the $\ln r$ *versus* $1/T$ line an activation energy of 48 kJ/mole is obtained for the 2′-hydroxychalcone isomerization reaction over MgO. This value is significantly lower than what has been previously observed by Furlong *et al.* [15] for the same reaction in a homogeneously catalyzed system in water (62.8 kJ/mole) and methanol (81.6 kJ/mole) solvents. It is also lower than the 69 kJ/mol activation energy value we observed previously for the same reaction and MgO catalyst system in the absence of the DMSO solvent [27]. Since this reaction is known to be affected by pH and solvent polarity (effects related to the ease of a proton transfer from 2′-hydroxychalcone), the observed

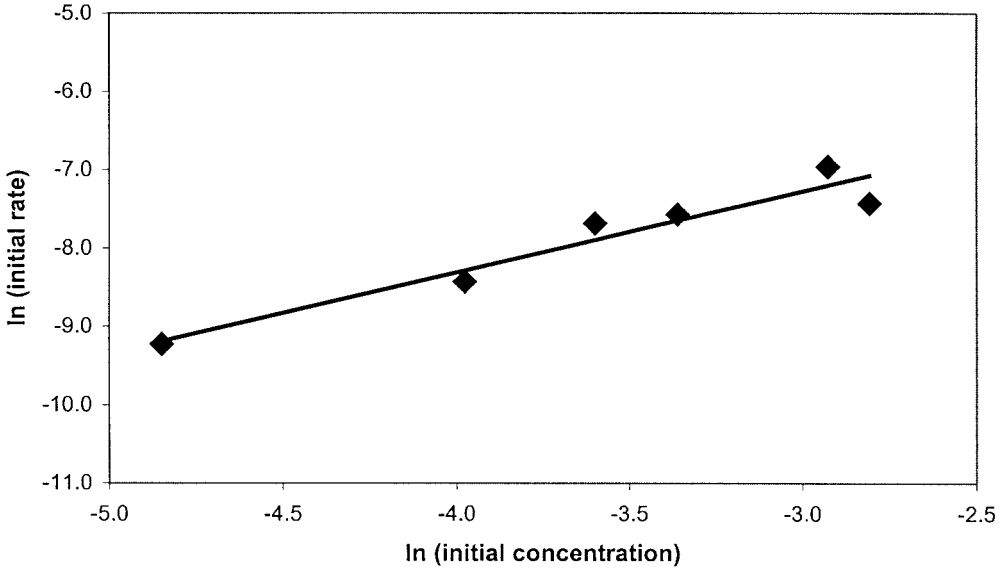

Figure 6. Initial rate of the isomerization of 2′-hydroxychalcone as a function of the 2′-hydroxychalcone initial concentration at 160 °C.

differences can be attributed to the polarity of the sulfoxide group in the DMSO solvent and are further investigated in a separate study [28].

Based on the above the following rate expression can be written for the isomerization of 2′-hydroxychalcone in the 130–160 °C temperature range over MgO:

$$\text{rate}(\text{mol/g}\cdot\text{cat/s}) = 6.3 \times 10^3 (L/\text{g}\cdot\text{cat/s}) \times \exp\left(\frac{48\,\text{kJ/mol}}{RT}\right) C_{hC}(\text{mol/l}) \quad (2)$$

3.4. Catalyst recovery, regeneration, and reuse

Following a typical 1.5 h run, catalyst recovery and reuse was attempted in an effort to determine if any deactivation is taking place as the result of exposure to reaction conditions. Catalyst recovery was accomplished *via* vacuum filtration. Subsequently, the recovered catalyst was washed with acetone to extract any remaining organic species, and dried overnight at 120 °C in a vacuum oven prior to its next use in the reaction. Elemental analysis performed by Galbraith Laboratories, Inc. indicates that after the acetone extraction the recovered catalyst contains approximately 10% carbon by weight. Alternatively, and in a separate experiment, the catalyst was also further calcined in air for 5 h at 500 °C in an attempt to regenerate any lost activity by removal of the accumulated carbon. Activity results obtained with this regenerated sample, as well as the fresh and recovered (*i.e.*, acetone-extracted) samples are shown in table 2.

The observed initial rates indicate that some catalyst deactivation is taking place, and only part of the original

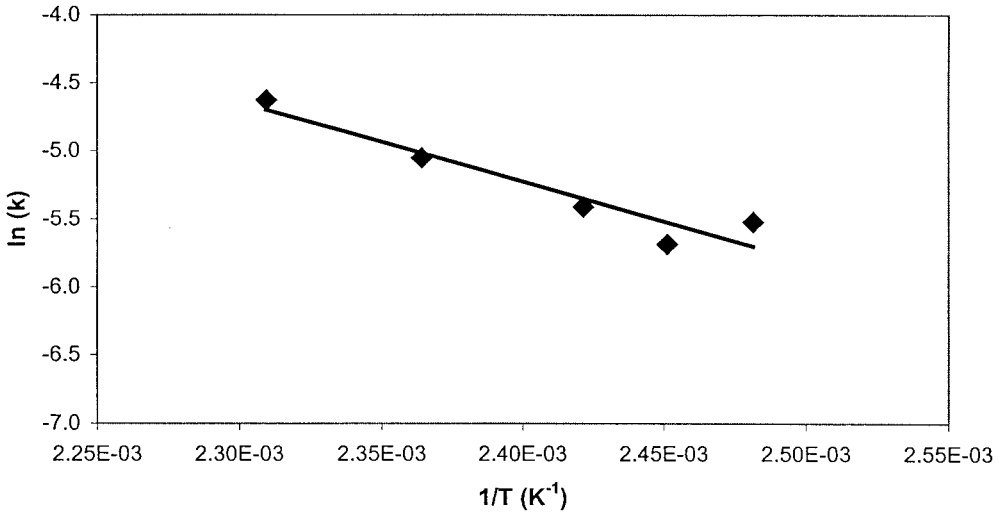

Figure 7. Arrhenius plot for the isomerization of 2′-hydroxychalcone.

Table 2
Summary of results of catalyst recycle and regeneration studies

Catalyst	Yield flavanone (%)		Yield 2′-hydroxychalcone (%)		Selectivity to flavanone (%)		Initial rate (mol/g · catalyst/s)
	0.5 h	1.5 h	0.5 h	1.5 h	0.5 h	1.5 h	
Fresh	36	54	11	24	77	70	6.2×10^{-4}
Recovered	23	48	9	23	76	68	3.2×10^{-4}
Regenerated	25	51	8	23	77	69	4.1×10^{-4}

activity can be recovered by the high temperature calcination treatment. However, the same end-point and final product yields can be reached with the fresh, recovered, and regenerated catalyst after a sufficiently long reaction time.

4. Conclusions

Flavanone was successfully synthesized heterogeneously from benzaldehyde and 2-hydroxyacetophenone over a solid MgO catalyst. The two reaction steps involved in this process (*i.e.*, the Claisen–Schmidt condensation of 2-hydroxyacetophenone with benzaldehyde and the subsequent isomerization of the 2′-hydroxychalcone intermediate to flavanone) were investigated separately, and their kinetic dependencies on temperature and reactant concentrations were determined. The kinetic results suggest a strong adsorption of benzaldehyde on the MgO catalyst and low surface coverages for 2-hydroxyacetophenone and 2′-hydroxychalcone. Furthermore, some differences were observed in the activation energy values obtained in this and the limited number of other kinetic studies available for this reaction scheme, which may be related to the choice of the DMSO solvent for this study.

Acknowledgments

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