Organic Process Research & Development **2006**, *10,* 417–422

Study of the Baylis–Hillman Reaction in a Microreactor Environment: First Continuous Production of Baylis–Hillman Adducts

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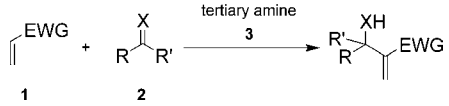
Abstract:

The Baylis–Hillman reaction has been optimized for use under microreactor conditions. After optimization, the reaction could be performed continuously and approximately 30% faster compared to batch conditions, however at a quite low flow rate.

Introduction

Baylis–Hillman Reaction. Recently, the Baylis–Hillman reaction has received a lot of attention because of the possibility of creating highly functionalized building blocks in a one-pot reaction. This reaction is a three-component reaction in which an activated alkene **1** couples to a carbon electrophile **2** with the aid of a tertiary amine **3** (mostly DABCO) as a catalyst. A carbon–carbon bond is formed at the α-position of the alkene (Scheme 1). Due to their high functionality, Baylis–Hillman adducts can be used for the formation of β- and γ-lactams,[1] antibiotics,[2] isoxazoles,[3] and several other classes of compounds.[4] In the context of industrial applications, in which the microreactor technology could play an important role, it should be mentioned that this reaction is a 100% atom-efficient conversion which is an important characteristic in the green chemistry concept. Usually, the Baylis–Hillman reaction is a slow reaction requiring days or weeks to go to completion. This depends mostly on the reactivity of the reagents, i.e., the activated alkene and the electrophile. A lot of work has been performed to improve the yield and the rate of the reaction,[5] using, e.g., ultrasound,[6] supercritical CO_2,[7] α-naphthylacrylates,[8] cyclodextrines,[9] lithium perchlorate as a cocatalyst of DABCO,[10]

Scheme 1. **General Baylis-Hillman reaction: EWG = COR, CN, CHO, COOR, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh; R= aryl, alkyl, heteroaryl; R′ = H, COOR, alkyl; X = O, NCOOR, NTs, NSO_2Ph**



$TiCl_4$,[11] hydroxylated compounds (as solvent[12] or as catalyst[13]), high pressure,[14] heterobimetallic complexes,[15] aprotic polar solvents.[16]

Microreactor. This rather new technology tries to couple miniaturization (see reactor in Figure 2) to optimal reaction conditions to produce chemical and pharmaceutical intermediates in a continuous way.[17] Several advantages are associated with the use of microreactor technology. The heat and mass transfer are improved due to a greater surface-to-volume ratio as well as the mixing of the reagents. This technology allows switching from batch to continuous processing using similar conditions without the expensive and time-consuming process of scale-up. Instead, the principle of numbering-up can be applied.[18,19] In this study, the CYTOS College System, a microreactor which is produced by CPC-Cellular Process Chemistry Systems GmbH, was used. Several reaction types such as exothermic reactions, reactions with unstable intermediates, toxic reactions,[19a] nitration reactions,[19d] pigment production[19g] were already successfully performed, using microreactor technology.

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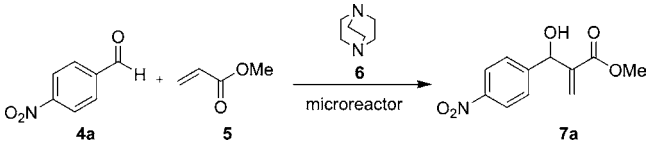
10.1021/op050228c CCC: $33.50
Published on Web 04/04/2006

Scheme 2. **Investigated Baylis−Hillman reaction**



Results and Discussion

The microreactor study was performed using a CYTOS College System (see Experimental Section).[20] The research was initiated using starting materials of which the reaction time for the Baylis−Hillman reaction was comparable to the maximum residence time of the microreactor used in this study. Because the maximal residence time in the microreactor (plus residence time unit, RTU) is approximately 2 h, a rather fast Baylis−Hillman reaction was evaluated first (longer residence times are possible, however not feasible, due to reproducibility problems). The reaction between 4-nitrobenzaldehyde **4a** and methyl acrylate **5** with DABCO **6** as catalyst (Scheme 2) seemed suitable, due to the short reaction time and the good yields of this particular Baylis−Hillman reaction.[6,12d,21] Since the goal was to study the impact of a switch from a batch process to the microreactor system, the same catalyst was used in both systems. It has to be mentioned that, next to DABCO, a lot of catalysts or cocatalysts are studied for this type of reaction.[4,10,22] Several of these catalysts give similar or better results, but DABCO was chosen from an economic as well as an industrial point of view.

Initially, a suitable solvent for the microreactor setup was needed. The best results were obtained using a mixture of water and 1,4-dioxane (v/v 1:1).[21] Some initial experiments in a batch setup showed a considerable concentration effect with a higher concentration of the reagents leading to better conversions (Table 1, entries 1, 4, and 6). However, a concentration limit needs to be determined when solid reagents (such as DABCO and 4-nitrobenzaldehyde) are used, because of the risk of clogging the capillaries of the microreactor (width approximately 100 μm) when reagents or the product precipitates from the reaction medium. Moreover, the supply medium of the reactor needs to be double concentrated for each storage solution compared to the reactive concentration inside the reaction cell, provided that both pumps are operated at the same flow rate. Therefore, the maximum concentration that could be investigated in the microreactor was 0.1 M of 4-nitrobenzaldehyde, since concentrations higher than 0.2 M became insoluble in the case that water/1,4-dioxane (v/v 1:1) was used. Even for a concentration of 0.2 M, warming of the medium up to 35 °C at the inlet was required to prevent precipitation in the supply medium.

Table 1. **Baylis−Hillman reaction of 4-nitrobenzaldehyde and methyl acrylate in batch mode using DABCO as a catalyst in water/1,4-dioxane (v/v 1:1) as solvent[a]**

entry	4-nitro-benzaldehyde (M)	DABCO (M)	methyl acrylate (M)	degree of conversion (mol %)[b]	yield (%)[c]
1	0.1	0.1	0.3	81	74
2[d]	0.1	0.1	0.3	−	83
3[e]	0.1	0.1	0.3	75	69
4	0.05	0.05	0.15	51	43
5[f]	0.05	0.05	0.15	49	44
6	0.033	0.033	0.1	21	22

[a] Reaction time: 3 h; a solution of 1 equiv of 4-nitrobenzaldehyde and 3 equiv of methyl acrylate in 10 mL of water/1,4-dioxane (v/v 1:1) was stirred at room temperature in the presence of 100 mol % DABCO.[21] [b] Based on the integration signals in the ^{1}H NMR spectrum. [c] Based on total mass of end product collected in the rough mixture and degree of conversion. [d] Reference 21. [e] Reaction time: 2 h. [f] Without stirring the mixture.

To optimize the reaction in the microreactor, several conditions were tested by altering the residence time, the initial concentration of the substrates, the ratio between the substrates, the temperature, and the mixing of the substrates. Table 2 summarizes these results. First, the order of mixing of the substrates was investigated. Considering the mechanism, which has recently been revised,[23] the Baylis−Hillman reaction consists of an addition−elimination sequence which involves the tertiary amine. The tertiary amine **6** attacks the double bond of the activated alkene **5** with the formation of a zwitterion **8**, which then reacts with the aldehyde **4**. The intermediate **9** attacks a second equivalent of the aldehyde, and after proton transfer, the catalyst is eliminated. This last step is the rate-determining step. Scheme 3 illustrates the mechanism of the reaction between an aldehyde, methyl acrylate, and DABCO as catalyst. In view of the mechanism, the mixing of methyl acrylate and the catalyst prior to the entrance of the microreactor seems advantageous. However, this resulted in a very low conversion and yield (results not shown). This is in accordance with the results obtained by Yu et al.[21] who stated that preincubation of 100 mol %

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Table 2. **Baylis−Hillman reaction[a] of 4-nitrobenzaldehyde and methyl acrylate in continuous mode using DABCO as a catalyst in water/1,4-dioxane (v/v 1:1) as solvent**

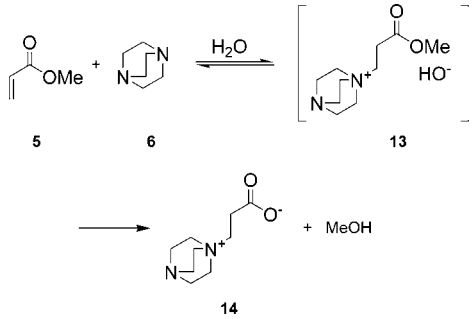
entry	4-nitro-benzaldehyde (M)	DABCO (M)	methyl acrylate (M)	*T* (°C)	degree of conversion (mol %)[b]	yield (%)[c]
1	**0.1**	**0.1**	0.3	**RT**	83	64
2	**0.05**	**0.05**	0.15	**RT**	57	48
3	**0.05**	**0.05**	0.05	**RT**	17	17
4	**0.05**	**0.1**	0.05	**RT**	26	40
5	**0.05**	**0.1**	0.1	**RT**	48	69
6	**0.05**	**0.025**	0.025	**RT**	10	7
7	**0.05**	**0.05**	0.15	**40**	33	31
8	**0.033**	**0.033**	0.1	**RT**	29	27
9	**0.033**	**0.067**	0.1	**RT**	46	66
10	**0.017**	**0.017**	0.05	**RT**	7	11
11	**0.05**	**0.05**[d]	0.15	**RT**	64	35
12[e]	**0.2**	**0.2**	0.6	**RT**	93	82

[a] Residence time: 1 h 58 min; products in bold are mixed together before they enter the microreactor system; concentration of the reagents as in the reactor; reaction quenched with HCl (1 N). [b] Based on the integration signals in the ^{1}H NMR spectrum. [c] Based on total mass of end product collected in the rough mixture and degree of conversion. [d] Quinuclidine as catalyst instead of DABCO. [e] 4-Nitrobenzaldehyde and DABCO dissolved into a 3:7 (v/v) water/1,4-dioxane mixture; methyl acrylate stirred into a 7:3 (v/v) water/1,4-dioxane mixture.

DABCO with 3 equiv of methyl acrylate in a water/1,4-dioxane (v/v 1:1) mixture before the addition of aldehyde resulted in a 9-fold decrease of the product yield due to a side reaction. In this side reaction the hydrolysis of the Michael adduct leads to a stable betaine **14** which consumes both the catalyst and the methyl acrylate (Scheme 4). Mixing 4-nitrobenzaldehyde and DABCO indeed proved to be the best option for the continuous reaction.

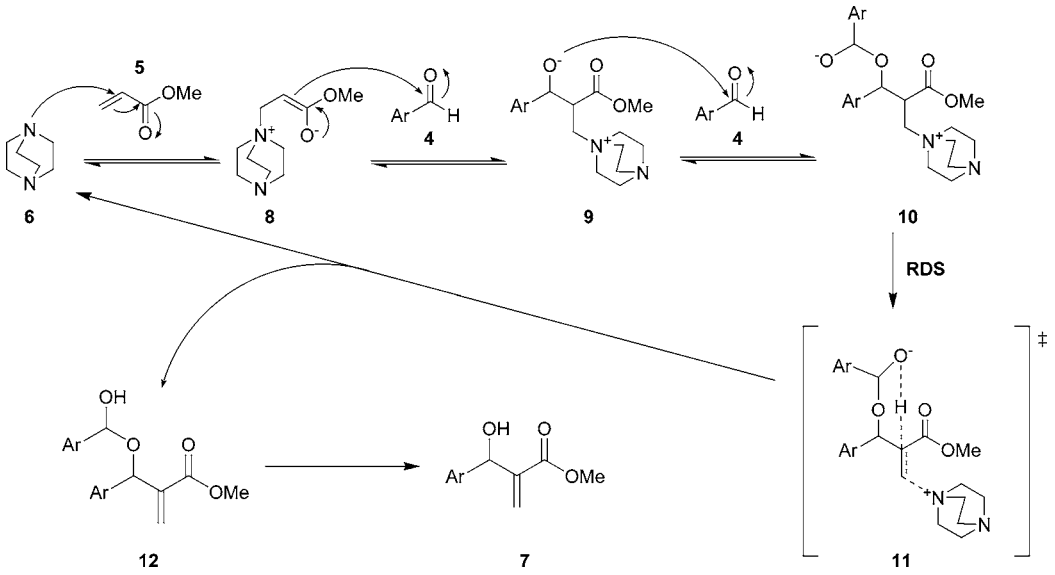
Second, different concentrations were tested. As can be seen from entries 1, 2, 8, and 10 the same concentration effect appears as in a batch setup. Moreover, the conversions and yields in the batch reaction after 3 h appear to be more or less the same as these in the microreactor with a residence time of 2 h (Table 1, entry 1 and Table 2, entry 1). Since the reaction profile under batch conditions at the highest concentration (for the continuous reaction i.e., 0.1 M

Scheme 4. **Side reaction with formation of a betaine**



aldehyde) proved that the reaction is still not completed after 2 h (Figure 1), it can be concluded that this Baylis−Hillman reaction is faster under microreactor conditions. Table 1, entry 3, shows also the conversion after 2 h, which is lower compared to the microreactor reaction at the same time (Table 2, entry 1). Although better results were expected using this technology, no important improvement was achieved; however, in this particular case a rate enhancement of 30% was observed. A possible explanation for this rather small enhancement, compared to some classical examples of rate enhancement in microreactors,[19a,b,24] is shown in Table 1, entries 4 and 5. These results show that the intensity of mixing of the reagents is not important in achieving higher conversions and yields. This means that the mass transfer advantage of the microreactor technology is minimalised for the Baylis−Hillman reaction. Since the conversion was not complete at the highest concentration of the substrates, no higher flow rates (resulting in smaller residence times) were tested. Also no higher residence times were tested with continuous flow since the applied flow rate was the lowest reproducible one the piston pumps could handle. To increase the residence time, the stopped-flow technique was evaluated (see further). Since the initial concentration of the reagents was of great importance (Table 2), attempts were made to further increase the concentrations. It was possible to make a 0.4 M solution of 4-nitrobenzaldehyde and 0.4 M DABCO if the solvent mixture was changed to 3:7 (v/v) water/1,4-

Scheme 3. **Mechanism of the Baylis−Hillman reaction[23]**



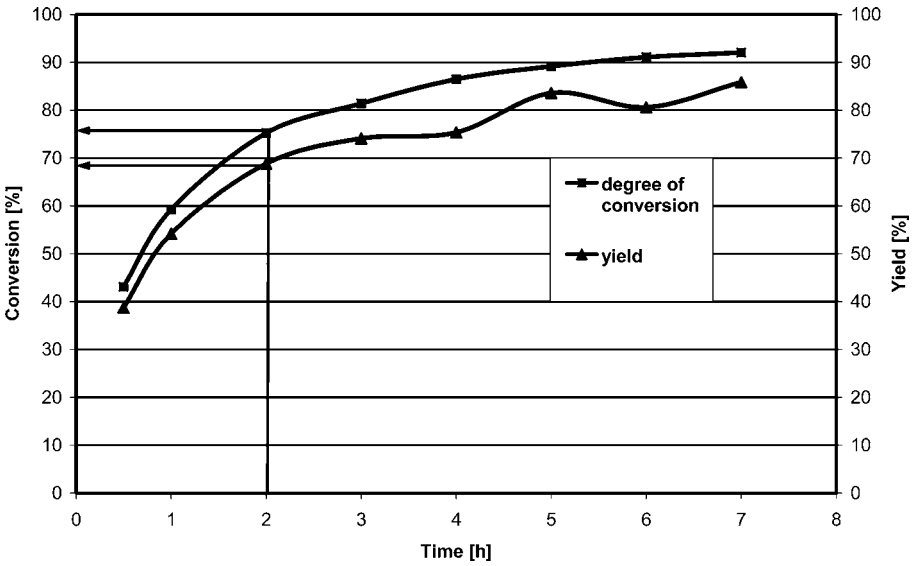


Figure 1. **Reaction profile of the batch reaction in water/1,4-dioxane (v/v 1:1) at room temperature.**

dioxane. Because a 1:1 (v/v) mixture proved to give the highest yields,[21] the methyl acrylate was dissolved in a 7:3 (v/v) mixture of water and 1,4-dioxane to have a 1:1 (v/v) mixture in the microreactor. Table 2, entry 12, shows that the conversion and yield were further improved.

A third aspect was the evaluation of the optimal reaction temperature. Due to the small capillaries (width approximately 100 μm) the microreactor provides a narrower temperature profile than that in batch systems. At higher temperatures no improvement was noticed (Table 2, entry 7). Lower temperatures (significantly below room temperature) could not be investigated due to the melting point of 1,4-dioxane. Although no solidification occurred at 10 to 15 °C in the batch reaction, partial clogging already occurred at these temperatures in the microreactor, probably due to the capillaries, the high concentration of the substrates in a low-temperature environment, and the considerably low flow rate. In the batch system, a high turbulence prevents solidification. Since lower temperatures have a positive effect on the reaction rate,[25] other solvents were evaluated. Using dichloromethane, no Baylis−Hillman adduct was formed using the same conditions described in Table 2, entry 2. Even a decrease to −15 °C gave no adduct.

A final aspect that was investigated was the ratio of the substrates. Table 2, entry 3 shows that lowering the concentration of the methyl acrylate to 1 equiv gave less favorable results compared to the excess of 3 equiv. This was expected since in most procedures an excess of the activated alkene is used.[22g,26] An excess of catalyst (Table 2, entry 4) instead of an excess of methyl acrylate also increased the yield; however, it was not a breakthrough in the optimization process. Since the Baylis−Hillman reaction proved to be a second-order reaction in the aldehyde,[23] an experiment with an excess of aldehyde was also evaluated. Entry 6 shows the very low conversion and yield in this case. It was found in the literature that quinuclidine was more active than DABCO in the Baylis−Hillman reaction,[13] so an experiment was performed under the same conditions. The degree of conversion was somewhat higher than in the case of DABCO. Further optimization with quinuclidine was not done because DABCO is a much cheaper catalyst.

Since the reagents also react upon standing (without stirring), the reaction mixture was quenched immediately with an equal amount of hydrochloric acid (1 N) so that further conversion was prevented after leaving the RTU of the microreactor. The study revealed that under continuous conditions comparable results can be obtained compared to those from batch procedures (Table 1, entry 1 and Table 2, entry 1). The best conditions were obtained using water/1,4-dioxane (v/v 1:1) as a solvent at room temperature using a 1:1:3 ratio of aldehyde, DABCO, and methyl acrylate and a concentration of 0.2 M of 4-nitrobenzaldehyde (Table 2, entry 12).

The main advantages of the continuous procedure using the microreactor are the continuous processing and the reduction of the reaction time by approximately 30% compared to the batch reaction in the case of 4-nitrobenzaldehyde.

Since the reaction was not completed after the maximal residence time of the microreactor and the reaction profile of the batch process shows that the conversion still increases after 3 h (Figure 1), the residence time of the microreactor was increased using the stopped-flow technique. The rationale is to increase the residence time, and thus the reaction time, by pausing the pumping at regular time intervals. Recently, other research groups have also successfully applied this technique.[19b,24b,27] To make a decent comparison without making the experiment unnecessarily long, a 5-fold

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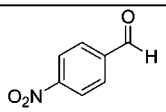
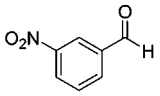
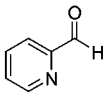
Table 3. **Comparison between continuous Baylis−Hillman reaction with or without stopped flow for different aldehydes[d]**

Entry	*Aldehyde*	*Product*	*Concentration (M)*	*Without stopped flow* Degree of conversion (mol%)[a]	*Without stopped flow* Yield (%)[b]	*With stopped flow* Degree of conversion (mol%)[a]	*With stopped flow* Yield (%)[b]
1		**7a**	0,2[c]	93	82	99	95
			0,05	57	48	83	87
2		**7b**	0,2[c]	76	66	80	76
			0,05	23	21	45	35
3		**7c**	0,01	97	47	100	51

[a] Based on the integration signals in the ^{1}H NMR spectrum. [b] Based on total mass of end product collected in the rough mixture and degree of conversion. [c] Aldehyde and DABCO dissolved into a 3:7 (v/v) water/1,4-dioxane mixture; methyl acrylate stirred into a 7:3 (v/v) water/1,4-dioxane mixture. [d] Reaction conditions: ratio aldehyde/DABCO/methyl acrylate is 1:1:3; residence time is 1 h 58 min without stopped flow and 9 h 50 min with stopped flow; reaction quenched with HCl (1 N).

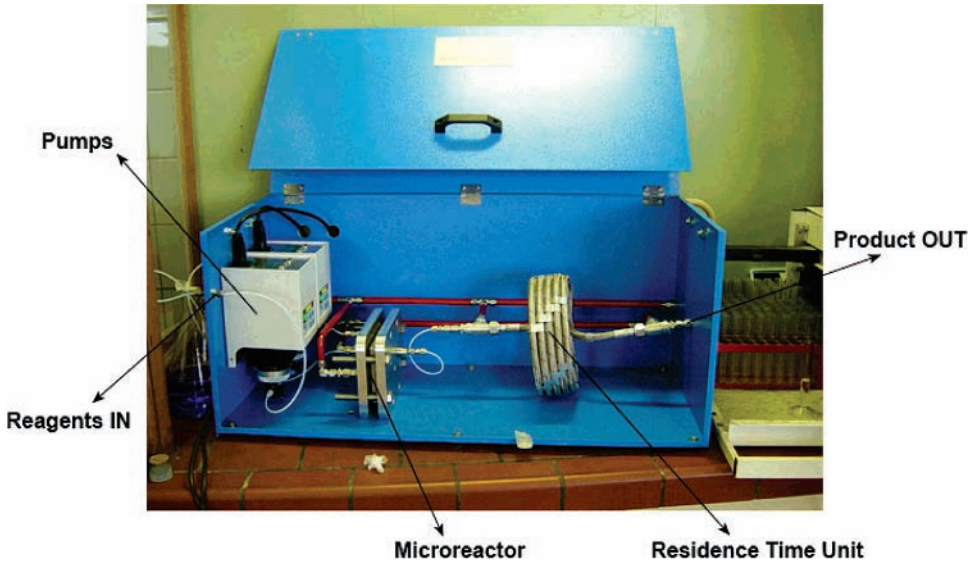


Figure 2. **CYTOS College System.[20]**

increase of the residence time was chosen, so that the ratio of pumping time to pause time had to be 1:4. Also, the pumping interval had to be long enough to ensure a reproducible residence time since the pump does not reach the maximum flow rate immediately. By using a pumping interval of 1 s the influence of the start-up of the pump was too big, and a longer residence time occurred. On the other hand, long pause times are disadvantageous because of more diffusion in longitudinal direction. As a compromise, a pumping interval of 1 min was chosen, to minimize the effect of the start-up and to minimize the pause time which was 4 min in this case. Since problems with the reactivity of the methyl acrylate (lower conversions were obtained after 9 h 50 min residence time compared to 1 h 58 min residence time, results not shown) occurred when the acrylate−solvent mixture was standing too long before reaction, the mixture was refreshed on a regular basis. The results of the stopped-flow study are shown in Table 3.

The data prove that the reactions are still not completed after 2 h of reaction time, since considerable enhancement of conversion and yield can still be achieved. In the case of 3-nitrobenzaldehyde (entry 2) the conversion to the Baylis−Hillman adduct is doubled at a concentration of 0.05 M. If 2-pyridinecarboxaldehyde is used (entry 3), even a complete conversion is achieved. Thus, by regulating the residence time using the stopped-flow technique, it is possible to drive the Baylis−Hillman reaction to completion in a continuous way. The lower yields are associated with a more difficult workup of the reaction.

(27) (a) Phan, N. T. S.; Khan, J.; Styring, P. *Tetrahedron* **2005**, *61*, 12065. (b) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2002**, *2*, 62.

Conclusions

In summary, the Baylis−Hillman reaction could be performed in a continuous way using the CYTOS College System with yields comparable to those of a batch reaction and with a reduction of the reaction time of approximately 30%. Using the stopped-flow technique, complete conversion can be achieved.

Experimental Section

Materials and Methods. The microreactor used in this study is a CYTOS College System[20] (Figure 2). The CYTOS College System microreactor consists of several stacked plates with microstructures in the submillimeter range (width approximately 100 μm). The volume of the microreactor itself is 2 mL, and that of the RTU 45 mL, so the total volume (V_{total}) of the system is 47 mL. The pumps were calibrated at the desired flow rate. The temperature was controlled using an external circuit (Huber Tango thermostat).

The reagents were used without prior purification before use. ^{1}H NMR spectra (300 MHz) were recorded in $CDCl_3$ with a JEOL Eclipse FT 300 NMR spectrometer.

General Procedure in Batch (Table 1, entry 1). For the Baylis−Hillman reaction in batch mode, the procedure of Yu et al.[21] was followed. In a round-bottom flask 4-nitrobenzaldehyde (151 mg, 1 mmol), DABCO (112 mg, 1 equiv), and methyl acrylate (272 μL, 3 equiv) were mixed in 10 mL of water/1,4-dioxane (v/v 1:1). The solution was stirred for different time intervals (see Figure 1) after which the mixture was partitioned with 150 mL of *tert*-butyl methyl ether and 80 mL of water. The organic phase was washed with 2 × 50 mL of brine, dried with $MgSO_4$ and filtered, and the solvent was evaporated. A ^{1}H NMR spectrum of the crude mixture was recorded. The degree of conversion was calculated using the integration of the signals in the ^{1}H NMR spectrum. The yield of the reaction was calculated from the total mass of end product collected and the degree of conversion. The other results were obtained in the same way, except for minor changes such as concentration and the lack of stirring the mixture.

General Procedure in the Microreactor (Table 2, entry 1). In the continuous mode, a solution of 0.2 M 4-nitrobenzaldehyde and 0.2 M DABCO in a water/1,4-dioxane (v/v 1:1) mixture was prepared and transferred in a measuring cup. Another solution of 0.6 M methyl acrylate was prepared in the same solvent mixture and transferred to a second measuring cup. Both measuring cups were connected to the CYTOS College System. The flow rate was controlled by measuring the ingoing and outgoing volumes. Both pumps were set up to the same flow rate. The residence time was calculated by the following formula:

$$\tau = \frac{V_{total}}{r_{total}} \quad \text{with} \quad r_{total} = 0.4 \text{ mL/min}$$

At the outlet, the end product was collected at steady-state conditions, i.e., after 1.6 τ. About 10 mL was collected for analysis. The workup of the reaction mixture was performed using the procedure of Yu et al.[21] The degree of conversion and the yield were calculated in the same way. This procedure has been used to obtain the results of Table 2, entry 1. The other results were obtained in the same way, except for minor changes such as concentration, temperature. and flow rate, as stated with the experiments. In the case of higher concentrations, 4-nitrobenzaldehyde and DABCO were dissolved in a 3:7 (v/v) mixture of water and 1,4-dioxane. Methyl acrylate was added to a 7:3 (v/v) water/1,4-dioxane mixture and was continuously stirred to have a homogeneous emulsion.

Additional Experiment. In the experiment with the stopped flow, the same conditions were used as in the general microreactor procedure. The goal was a 5-fold increase in residence time. A flow time of 1 min was chosen, so the stop time was 4 min. With a total volume of 47 mL and a flow rate of 0.2 mL/min/pump, this meant the total residence time increased from 1 h 58 min to 9 h 50 min.

Compounds **7a**,[28] **7b**,[21] and **7c**[21] are known compounds, and their spectroscopic data matched those reported in the literature.

Acknowledgment

We thank the National Fund for Research-Flanders and Ghent University for financial support (BOF) and CPC - Cellular Process Chemistry Systems GmbH for their collaboration.

Received for review November 23, 2005.

OP050228C

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