Organic Process Research & Development **2007**, *11*, 865–869

Vanishing Microwave Effects: Influence of Heterogeneity

Mark H. C. L. Dressen,[†] Bastiaan H. P. van de Kruijs,[†] Jan Meuldijk,[‡] Jef A. J. M. Vekemans,[†] and Lumbertus A. Hulshof*[,†,§]

Eindhoven University of Technology, Department of Chemical Engineering and Chemistry, Laboratory of Macromolecular and Organic Chemistry, Applied Organic Chemistry, Den Dolech 2 5612 AZ Eindhoven, The Netherlands

Abstract:

A consistent setup of experiments has been conducted to demonstrate an enhanced reaction rate under microwave irradiation as compared to conventional heating, i.e. a real microwave effect. It was found that addition of a cosolvent, diminishing the heterogeneous character of the reaction mixture, greatly reduced the microwave effect. This was demonstrated by two examples; selective mono-urea formation and racemization of an N-acetylamino acid. Furthermore, formation of a Grignard reagent was accelerated under MW irradiation by electrostatic etching of the metal surface. The microwave effect observed in these reactions seems to rely on heterogeneity and specific interactions on the solid–liquid interface. Basic understanding of these findings is crucial for scaling up microwave assisted processes.

Introduction

Since its introduction in 1986,[1] microwave heating has been shown to offer a good alternative to conventional heating in many chemical transformations. It is safe to state that the results described in the second half of the past decade are obtained in dedicated microwave equipment operating either mono-mode or multi-mode to ensure reliability. Accurate temperature measurements from inside either by fiber optics or by a gas-pressure sensor strongly contribute to the reliability of the claimed microwave effects. The successes, but not necessarily the failures, have been reviewed extensively[2–4] and are undoubtedly real, albeit the origin of the microwave-induced accelerations remains unclear and thermal as well as nonthermal effects are invoked to rationalize it.[5–8] In an effort to implement microwave technology for scaling up organic reactions, we designed experiments to create insight into the essence of the microwave effect.[9] Microwave technology is, however, often not compatible with scaling up due to a penetration depth in the range of only centimeters, thus strongly limiting the size of batch reactors. Obviously mono-mode equipment is not suitable for scaling up, but even multi-mode equipment is not necessarily well-suited. The recent introduction of continuous-flow reactors may overcome this barrier and open the way to scale up microwave technology in organic chemistry.[10,11]

In this paper we focus on the fundamental insight into the microwave effect using exclusively multi-mode equipment to enable translation of the results to larger scales. Three heterogeneous processes have been investigated: (1) formation of a Grignard reagent, (2) racemization of an *N*-acetylamino acid and (3) selective mono-urea formation out of an amine and an isocyanate. Our main interest has been to reliably and directly compare microwave (MW) (multi-mode) heating with conventional heat (CH) transfer, e.g., using an oil bath. This comparison is crucial for scalability studies. Similar vessels and temperature control from inside the reaction vessels in both heating modes had to guarantee the reliability of the measurements.

Results and Discussion

In our setup a commercially available, automated multimode microwave oven, MicroSynth from Milestone s.r.l. (Italy), is used. This oven operates at 2.45 GHz and is temperature-controlled by a fiber-optic sensor. The maximum power input can be adjusted (0–1000 W). All presented results have been reproduced.

Formation of a Grignard Reagent. Reaction of Grignard reagents with alkyl and aryl halides enables creation of C–C bonds. Procedures to perform the insertion of magnesium in the C–X bond have been reported extensively.[12] Mostly an initiator (i.e., 1,2-dibromoethane) or a pretreatment of the magnesium is needed to facilitate the reaction. The combination of Grignard reagent formation with MW heating under pressurized conditions has also been reported.[13] Here we describe a method to perform a Grignard reagent formation at atmospheric pressure without pretreatment of the magnesium and

---

* To whom correspondence should be addressed: L.A.Hulshof@tue.nl.

[†] Laboratory of Macromolecular and Organic Chemistry, Applied Organic Chemistry.

[‡] Process Development Group.

[§] DSM Research, PO Box 18, 6160 MD, Geleen, The Netherlands.

(1) Gedye, R.; Smith, F.; Westaway, K. *Tetrahedron Lett.* **1986**, *27*, 279.

(2) (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (b) Loupy, A *Microwave in Organic Chemistry*; Wiley-VCH: Weinheim, 2006.

(3) de la Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164.

(4) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.

(5) Jacob, J.; Chia, L. H. L.; Boey, F. Y. C. *J. Mater. Sci.* **1995**, *30*, 5321.

(6) Rejasse, B.; Besson, T.; Legoy, M. D.; Lamare, S. *Org. Biomol. Chem.* **2006**, *4*, 3703.

(7) Stuerga, D. A. C.; Gaillard, P. *J. Microwave Power Electromagn. Energy* **1996**, *31*, 87.

(8) Stuerga, D. A. C.; Gaillard, P. *J. Microwave Power Electromagn. Energy* **1996**, *31*, 101.

(9) (a) The claimed microwave effect accompanying Novozym 435-mediated esterifications and trans-esterifications was thoroughly investigated and could not be reproduced. CarrilloMunoz, J. R.; Bouvet, D.; GuibeJampel, E.; Loupy, A.; Petit, A. *J. Org. Chem.* **1996**, *61*, 7746. (b) Rejasse, B.; Lamare, S.; Legoy, M. D.; Besson, T. *Org. Biomol. Chem.* **2004**, *2*, 1086. (c) Lin, G. L.; Lin, W. Y. *Tetrahedron Lett.* **1998**, *39*, 4333.

(10) Cablewski, T.; Faux, A.F.; Strauss, C. R. *J. Org. Chem.* **2004**, *59*, 3408.

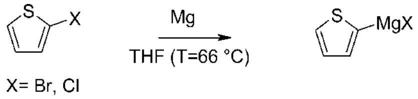
(11) Corradi, A.B.; Bondioli, F.; Ferrari, A. M.; Focher, B.; Leonelli, C. *Powder Technol.* **2006**, *167*, 45.

(12) Garst, J.; Soriaga, M. *Coord. Chem. Rev.* **2004**, *248*, 623.

(13) Gold, H.; Larhed, M.; Nilsson, P. *Synlett* **2005**, *10*, 1596.

10.1021/op700080t CCC: $37.00

Scheme 1. **Grignard reagent formation**



without the addition of an initiator in an inert gas atmosphere. 2-Bromothiophene and 2-chlorothiophene, precursors in the synthesis of α-terthienyl, are selected for this study; see Scheme 1.

The 2-halothiophene concentration is monitored as a function of time by taking small aliquots from the reaction mixture. As expected, the 2-bromothiophene reacts faster under CH than its chloro analogue. This was also observed in the MW oven; see Figure 1.

The combination of magnesium turnings and microwave irradiation causes violent arcing; see Figure 2.

The intensity of arcing decreases after the reaction has been initiated. The formation of Mg salts causes the liquid phase to interact with the microwaves more strongly. As a consequence the absorption of microwaves by the magnesium is simultaneously reduced. To acquire a proper insight into the positive effect of MW heating on the rate of the Grignard formation, we studied the reaction also in the presence of the initiator 1,2-dibromoethane. 1,2-Dibromoethane is often used to start up the Grignard formation reaction and could alter the initiation mechanism. Also the removal of the magnesium oxide layer on the Mg surface by an initiator could lead to a diffusion-controlled reaction-rate limit. Both thiophenes reacted in the presence of the initiator (see Figures 3 and 4) with similar initiation times in CH and MW. The positive effect on the conversion rate of both 2-halothiophenes, observed under microwave conditions, is desirable. However, the side effect of arcing limits its use upon scaling up. This issue of arcing can be overcome by adjusting the geometry of the magnesium particles. Smaller particles and a solid ribbon with similar mass prevent arcing under microwave irradiation. Also arcing can be suppressed by choosing other parameters[14] (choice of solvent, applied microwave power, density of metal, rate of stirring, pressure). Although these adaptations diminish the arcing, this phenomenon seems necessary for microwave irradiation to show a beneficial effect on the Grignard reagent formation. Analysis of the impact of the electrostatic discharges on the surface of the turnings by SEM showed dislodgement of the MgO layer. This layer is always present at the surface of the magnesium turnings. In contrast, microwave heating of Mg in THF under conditions where arcing was prevented, such as upon $MgBr_2$ addition and using a Mg ribbon instead of turnings, did not affect the initiation times.

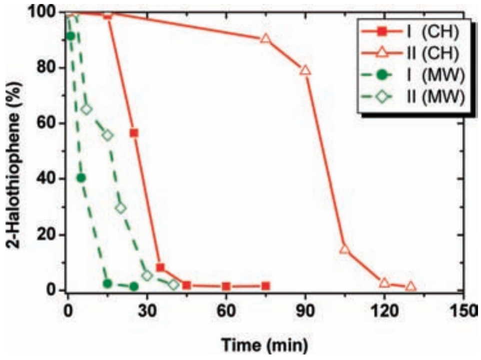


Figure 1. **Dimensionless concentration of 2-bromothiophene (I) and 2-chlorothiophene (II) as a function of time with conventional heating or MW heating in the presence of Mg turnings (C_0 = 1.4 mol/dm^3, T = 66 °C).**

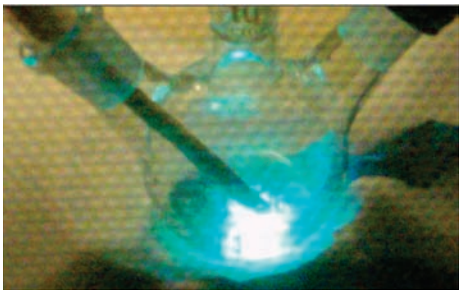


Figure 2. **Arcing of Mg turnings exposed to MW irradiation.**

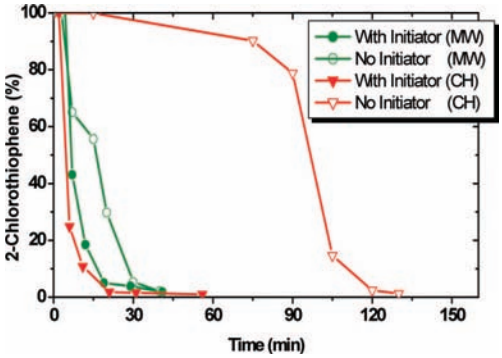


Figure 3. **Dimensionless concentration of 2-chlorothiophene as a function of time with conventional heating or MW heating in the presence of Mg turnings with and without initiator (C_0 = 1.4 mol/dm^3, T = 66 °C).**

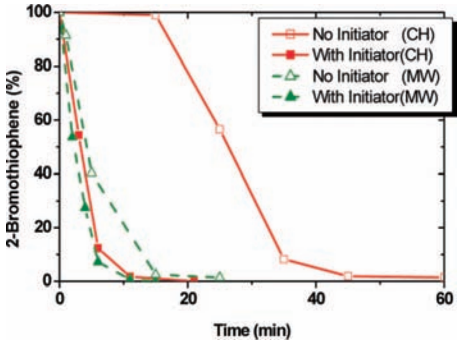


Figure 4. **Dimensionless concentration of 2-bromothiophene as a function of time with conventional heating or MW heating in the presence of Mg turnings with and without initiator (C_0 = 1.4 mol/dm^3, T = 66 °C).**

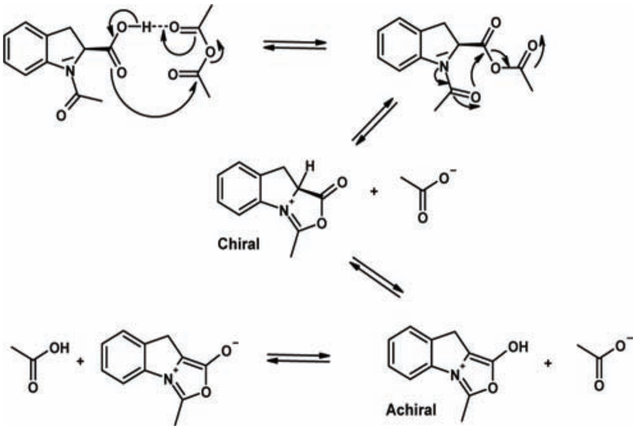
Racemization of an *N*-Acetylamino Acid. The racemization of scalemic 1-acetylindoline-2-carboxylic acid is performed in a highly boiling solvent: *p*-xylene catalyzed by the addition of acetic anhydride.[15] Acetic anhydride will reversibly form an oxazolium intermediate, which loses its chiral information. The mechanism is shown in Scheme 2. The catalyst is added after the reaction has been heated to 130 °C in the case of CH or MW heating to exclude rapid heating or overheating. The racemization is performed on a sample with 66 % enantiomeric

---

(14) Whittaker, A.; Mingos, D. *J. Chem. Soc., Dalton Trans.* **2000**, 1521.

(15) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417.

Scheme 2. **Racemization mechanism of *N*-acetylindoline carboxylic acid via oxazolium intermediates**



excess in favour of the (*R*)-enantiomer. The conversion has been measured by HPLC; see Figure 5.

The reaction rate is dramatically increased by microwave irradiation at atmospheric pressure. Solid 1-acetylindoline-2-carboxylic acid itself as well as *p*-xylene are poorly heated in the microwave oven. The application of a Weflon bar[16] was necessary to reach the desired temperature. The positive microwave effect vanished, however, upon addition of a cosolvent (acetic acid). Although acetic acid speeds up racemization with both heating techniques, it concomitantly decreases the difference between MW and CH. In the case of 20 wt % cosolvent the reaction mixture was homogeneous and no significant difference could be observed between microwave and conventionally heated reaction mixtures; see Figures 6 and 7. When the cosolvent was added, a Weflon bar was not required for efficient microwave heating. The beneficial effect of microwave heating that occurs in the absence of cosolvent will presumably last also during scaling up. Although the rate enhancement obtained by microwave irradiation could be diminished by cosolvent addition, the absence of cosolvent makes the subsequent workup less time-consuming and more energy-efficient.

Selective Mono-urea Formation. Selective mono-urea formation from hexane-1,6-diisocyanate (HDI) and 6-methylisocytosine gives access to supramolecular polymers after treatment with polymeric diamines.[17] HDI acts as a reactant as well as the solvent. Single addition per molecule of HDI is observed under the selected conditions; see Scheme 3.

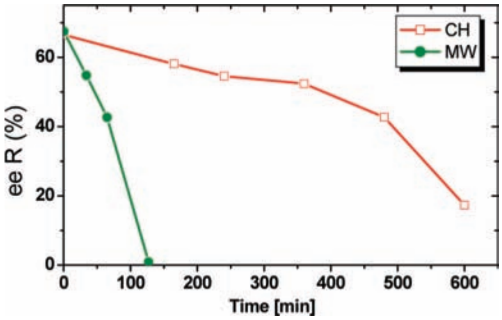


Figure 5. **Racemization of 1-acetylindoline-2-carboxylic acid in *p*-xylene at 130 °C.**

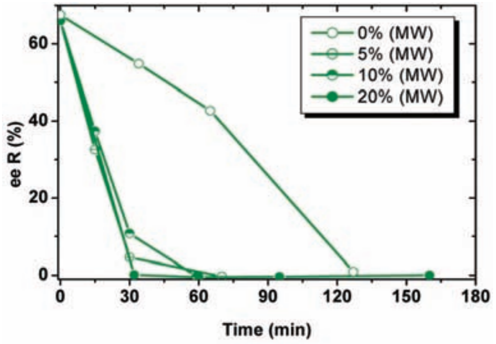


Figure 6. **Racemization of 1-acetylindoline-2-carboxylic acid with the addition of acetic acid as a cosolvent under microwave heating at 130 °C.**

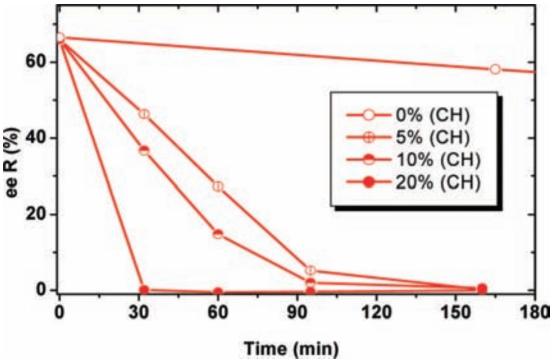
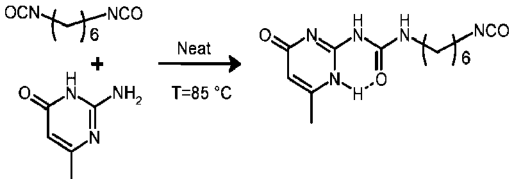


Figure 7. **Racemization of 1-acetylindoline-2-carboxylic acid with the addition of acetic acid as a cosolvent under conventional heating at 130 °C.**

Scheme 3. **Selective mono-urea formation (hexane-1,6-diisocyanate with methylisocytosine)**



The setup used is a closed vessel. The reaction was performed below the boiling point of HDI. This reaction also demonstrated a positive microwave effect. Similar to the approach to the racemization of 1-acetylindoline-2-carboxylic acid, we added *N*-methyl-2-pyrrolidinone (NMP) as a cosolvent to diminish or eliminate the difference between microwave and conventional heating; see Figure 8.

Although with the addition of 5 wt % NMP as cosolvent a homogeneous solution could not be obtained, the microwave effect almost vanished. Increasing the amount of cosolvent even led to a decreasing difference between MW heating and CH but the loss of selectivity (double addition) made this approach undesirable. The urea formation reactions were magnetically stirred in both heating methods, but the same results were obtained by mechanical stirring (pitched-blade impeller (down flow), 850 rpm). We demonstrated that the reaction obeys intrinsic kinetics at temperatures below 100 °C. In the urea

---

(16) A Weflon bar is a non-magnetic teflon bar with a carbon amount of ±25 wt %.

(17) Janssen, H. M. U.S. Pat. Appl. Publ. 2004, USXXCO US 2004034190 A1 20040219.

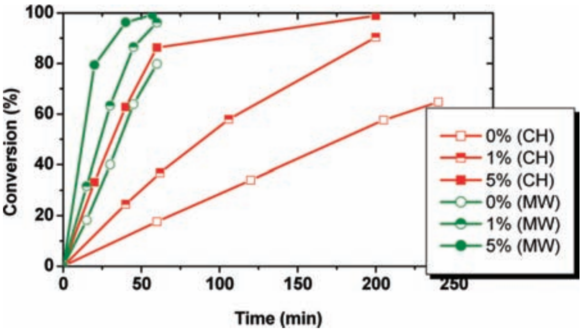


Figure 8. **Urea formation with cosolvent at 85 °C.**

formation experiments the microwave effect is advantageous and the occurrence of this phenomenon during scaling up in the continuous-flow reactor is likely.

Conclusions

In conclusion, it was possible to decrease the difference between conventional and microwave heating for the formation of a Grignard reagent, the racemization of an *N*-acetylamino acid and a selective mono-urea formation. In all three reactions we demonstrated that the solids themselves are poor microwave absorbers. The heating rate of solvent with or without the solid is similar in all three cases. Also, thermographic imaging showed that selective heating of the Grignard turnings did not occur. The addition of a cosolvent, diminishing the heterogeneous character of the system, causes a decrease in the microwave effect (conversion plots of CH and MW approach or overlap). Our hypothesis is that the accelerating phenomena observed in the studied systems occur at the interface of solid and liquid. Although the heterogeneity in our systems is a striking factor, it is not a sufficient condition: the degree of insolubility of the solids or metal determines the effects observed. Conversely, it must be stressed that beneficial effects on homogeneous systems can not be excluded. However, the origin of those effects is most likely different in nature. The effects observed by our group are affected by the heterogeneity of the system for the racemization and urea formation. The experiments involving the Grignard reagent formation indicate also a surface effect by electrostatic etching of the upper layer. The overlap of time conversion history graphs of these experiments indicates that the influence of microwave irradiation on the magnesium surface produces an equally accessible surface as is obtained by the use of an initiator. At these interfaces between solid and liquid, mass-transport and/or kinetics are influenced beneficially by microwave irradiation.

Our future research will be focused on further rationalizing the microwave effects and to develop a setup to integrate microwave heating, in a continuous-flow setup, with other unit operations in the synthesis of fine chemicals.

Experimental Section

Typical Procedure of Grignard Reagent Formation. A slurry of magnesium (0.22 g, 9 mmol) in dry THF (1 mL, distilled) was prepared in a round-bottomed flask. 2-Halothiophene (7 mmol, 0.83 g (chloro)/1.14 g (bromo)) was dissolved in dry THF (4 mL, distilled). From this solution 1 mL was added to the Mg slurry under an argon atmosphere (the presence of oxygen must be avoided for safety reasons) and irradiated with microwave energy (maximum power input 350 W) to a temperature of 66 °C. As soon as initiation took place the remaining halothiophene solution was added dropwise over 60 s and additional irradiation with microwave energy (maximum power input 200 W) was applied for 30–60 min to maintain a temperature of 66 °C. The solution of Grignard reagent was separated from the remaining Mg with a syringe and was added dropwise to an excess of freshly prepared dry solid CO_2. After acidification with 10 wt % HCl, the aqueous layer was extracted with toluene. The organic layer was dried with $MgSO_4$, filtered and evaporated. The crude residue was dissolved in toluene, and the solution was extracted with 1.0 M KOH. The aqueous layer was acidified with concentrated HCl and extracted with toluene. The toluene layer was dried with $MgSO_4$, filtered and evaporated yielding the pure product. Yield after workup: bromo; 0.66 g (73 %); chloro; 0.66 g (73 %); ^1H NMR ($CDCl_3$, 200 MHz) δ 9.78 (s, 1H, OH), δ 7.91 (dd, 1H, 5-H), δ 7.66 (dd, 1H 3-H), δ 7.15 (dd, 1H, 4-H).

The same procedure was executed for the conventionally heated experiment substituting microwave irradiation with oil bath heating. Yield after workup: bromo; 0.76 g (86 %) and chloro; 0.74 g (82 %).

Typical Procedure for the Racemization of 1-Acetylindoline-2-carboxylic Acid (MW). A round-bottomed flask was charged with wet 1-acetylindoline-2-carboxylic acid (1.78 g, 8.7 mmol, 66 % ee *R*) and *p*-xylene (5.5 g). This mixture was heated in a Dean–Stark distillation setup to azeotropically remove water (~1.5 mL distillate). The total mass of the reaction mixture was adjusted at 7.0 g with solvent, and the mixture was heated to 130 °C in a Milestone microwave oven. (A Weflon[16] bar was added during MW heating at 0 wt % cosolvent). Then acetic anhydride (100 μL, 1.1 mmol) was added. After 2 h water (100 μL) was added, and via a Dean–Stark distillation setup *p*-xylene/water/acetic acid was distilled from the reaction mixture (~2.5 mL distillate). After cooling the solid was filtered and washed twice with *p*-xylene (2 mL) and dried under reduced pressure at 50 °C. The reaction was monitored by quenching a sample (~50 mg) with water (25 μL) to neutralize the anhydride. The samples were generously dissolved in a mixture of formic acid (3 mL), isopropanol (25 mL) and *n*-hexane (72 mL) and analyzed by HPLC, chiral column (Daicel, Chiracel OD) with an eluent composed of formic acid (1 v%), isopropanol (10 v%) and *n*-hexane (89 v%). Yield after workup: 1.35 g (76 %).

The same procedure was executed for the conventionally heated experiment substituting microwave irradiation with oil bath heating, except for the usage of a Weflon bar at 0 wt % cosolvent. Yield after workup: 1.62 g (91 %).

Typical Procedure for the Mono-urea Formation. A 50-mL reaction tube was charged with 6-methylisocytosine (0.75 g, 6.0 mmol) and hexane-1,6-diisocyanate (7.5 g, 44.6 mmol). The tube was flushed with argon and closed. Temperature was measured via an insert. The reaction mixture was heated at 85 °C with stirring for 2 h in a Milestone microwave oven. Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed twice with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed. Yield after workup: 1.39 g (79 %); ^{1}H NMR (400 MHz) in $CDCl_3$/*d*-TFA (1/1 vol %) δ 6.3 (s, 1H, C*H*=C-CH_3), 3.3 (t, 2H, NH-C*H*$_2$, 3.2 (t, 2H, C*H*$_2$-NCO), 2.5 (s, 3H, C*H*$_3$-C=CH), 1.8 (m, 2H, NH-CH_2-C*H*$_2$), 1.6 (m, 2H, C*H*$_2$-CH_2-NCO), 1.5 (m, 4H, (C*H*$_2$)$_2$-(CH_2)$_2$-NCO).

The same procedure was executed for the conventionally heated experiment substituting microwave irradiation with oil bath heating, except the duration of the reaction is 4 h. Yield after workup: 1.55 g (88%) mono-selective product.

Acknowledgment

We gratefully thank SenterNovem for funding this research. We thank DSM Pharma Chemicals, Geleen, The Netherlands and Syncom B.V., Groningen, The Netherlands for their support.

Received for review April 10, 2007.

OP700080T