Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

Microwave-Assisted Bulk Synthesis and Polymerization of N-Benzenesulfonamide Maleimide

Mauro Iannelli[a]; Ella Bezdushna[a]; Helmut Ritter[a]
[a] Institut für Organische und Makromolekulare Chemie OCII, Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany

To cite this Article Iannelli, Mauro , Bezdushna, Ella and Ritter, Helmut(2007) 'Microwave-Assisted Bulk Synthesis and Polymerization of N-Benzenesulfonamide Maleimide', Journal of Macromolecular Science, Part A, 44: 1, 7 — 10
To link to this Article: DOI: 10.1080/10601320601041795
URL: http://dx.doi.org/10.1080/10601320601041795

Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry (2007) **44**, 7–10

ISSN: 1060-1325 print/1520-5738 online
DOI: 10.1080/10601320601041795

Microwave-Assisted Bulk Synthesis and Polymerization of N-Benzenesulfonamide Maleimide

MAURO IANNELLI, ELLA BEZDUSHNA, and HELMUT RITTER

Institut für Organische und Makromolekulare Chemie OCII, Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany

Received and accepted July, 2006

The synthesis of N-benzenesulfonamide maleimide was performed in bulk through the microwave-assisted reaction of maleic anhydride with 4-amino-benzenesulfonamide. The product was obtained in good yield in very short reaction time (2 min). The same reaction was also performed in an oil bath showing the superiority of the microwave-assisted approach. The monomer was polymerized in a N,N-dimethylformamide solution using benzopinacol as a free radical initiator. Qualitative investigation of the pH dependent solubility of the polymer was also performed.

Keywords: maleimide; sulfonamide; pH-responsive polymers; microwave irradiation; free radical polymerization

1 Introduction

Accelerations by applying of microwave (MW) energy have been discovered for a wide range of organic reactions (1–3). At the present time, the use of this relatively new technique is becoming widely accepted in organic and macromolecular chemistry because it allows us to obtain higher yields and higher selectivity in shorter reaction time compared with the syntheses performed under normal conditions. In our previous works, we showed the advantages of microwave-assisted synthesis in case, for example, of amides (4, 5) and polyoxazolines formation (6). We also investigated radical polymerization reactions (7) and polymer modifications (8).

Unsaturated imide derivatives are of a certain interest due to their biological properties, synthetic and industrial applications (9–11). The classical approach to the synthesis of N-substituted maleimides starts from maleic anhydride and the corresponding amine through a double step process that generally requires long reaction times. The easily obtained intermediate, maleamic acid, is converted in the maleimide by a ring-closure reaction using many different dehydrating agents as acetic anhydride, phosphorus pentoxide, acetyl chloride, thionyl chloride (12, 13). In this work, we used *4*-amino-benzenesulfonamide (**2**) as starting amine. It is well known that sulfonamides were the first substances used to prevent bacterial infections in human being and also to inhibit the growth of bacteria mainly by interfering with their enzymatic systems. The sulfonamide **2** can be considered a prominent predecessor of the sulfonamide drugs that are still widely used today in medicine despite the discovery of modern antibiotics (14, 15). In the past, we synthesized a number of (meth)acryl derivatives based on different sulfonamides by using activating agents (16). In this paper, we report the MW-assisted bulk synthesis of *4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-benzenesulfonamide* (**3**) starting directly from maleic anhydride and sulfanilamide.

Tawney et al. first polymerized maleimides by free-radical polymerization (17). We investigated the behavior of this monomer in the microwave-assisted polymerization using benzopinacol as a free radical initiator. The obtained polymers were characterized by ^{1}H-NMR, FT-IR, GPC and MALDI-TOF.

2 Experimental

2.1 Materials and Methods

All the reagents used in our experiments were commercially available. Maleic anhydride (Aldrich) was recrystallized from chloroform. Other reagents were used as received.

The identity of the synthesized compounds was determined by mass spectrometry, elemental analysis, and by NMR and FT-IR measurements. ^{1}H-NMR and ^{13}C-NMR were performed using a Brucker Advance DRX 500 spectrometer at 500.13 MHz for proton and 125.77 MHz for carbon, using $(CD_3)_2SO$ as solvent. The δ-scale relative to TMS was calibrated to the deuterium signal of the solvent as an internal

Address correspondence to: Helmut Ritter, Institut für Organische und Makromolekulare Chemie OCII, Heinrich Heine Universität Düsseldorf, Universitätsstraße 1, D-40225, Düsseldorf, Germany. Fax: +49 211 81 15 840; E-mail: h.ritter@uni-duesseldorf.de

standard. Infrared spectra were recorded on a Nicolet 5SXB FT-IR spectrometer. Gel permeation chromatography (GPC) was performed on a GPC-system consisting of a Viscotek VE 3580 differential refractometer and a Viscotek viscometer model 250, using DMF as eluent. The system was calibrated with polystyrene standards with a molecular weight ranging from 580 to 1 186 000 D. The flow rate was 1 mL · min^{-1}. 100 μL of a 0.125% (wt/wt) polymer solution was given to a SDVB based ViscoGEL column-combination consisting of a pre-column HHR-H and two main columns GMHHR-M. A monomode microwave (CEM-Discover) equipped with an infrared pyrometer and a fiber optic contact thermometer for the control of the temperature and operating at a maximum power of 300 W was used.

2.2 Synthesis of 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-benzenesulfonamide (3)

2.2.1 Synthesis by MW Irradiation

0.45 g (4.6 mmol) of maleic anhydride (**1**) and 0.80 g (4.6 mmol) of sulfanilamide (**2**) were mixed in a pressure-resistant test tube and sealed with a septum. The sample was subjected to MW irradiation under power control for a total time of 120 sec. The preset MW power was 50 W with a maximum preset temperature of 200°C. The maximum temperature reached was 100°C (IR pyrometer). The obtained product was purified by Soxhlet extraction with ethanol and dried under vacuum. The yield, after purification, was 50%. FT-IR (diamond): 3362 ($\nu_{N\text{-}H}$ *asymm*), 3265 ($\nu_{N\text{-}H}$ *symm*), 1782 ($\nu_{C=O}$ *asymm*), 1720 ($\nu_{C=O}$ *symm*), 1303 ($\nu_{O=S=O}$ *asymm*), 1156 ($\nu_{O=S=O}$ *symm*) cm^{-1}; ^{1}H-NMR (500.13 MHz, $(CD_3)_2SO$): $\delta = 7.94, 7.91, 7.57, 7.54$ (*Arom*), 7.24 (s, -CH═CH-), 7.46 (s, $-NH_2$) ppm; ^{13}C-NMR (125.77 MHz, $(CD_3)_2SO$): $\delta = 126.74$, 127.12, 134.81, 135.27 (*Arom*), 143.24 (*Vinyl*), 169.90 (Carbonyl) ppm.

Elemental analysis: $C_{10}H_8N_2O_4S$, Calc. C 47.61, H 3.17, N 11.11; Found. C 46.52, H 3.40, N 11.25.

2.2.2 Synthesis by Conventional Thermal Heating in Oil Bath

An equimolar mixture of the reagents (**1** and **2**) was heated for 15 min in a preheated oil bath at a temperature that made it possible to have 100, 130, 150 and 170°C inside the reaction vessel. The products were characterized as reported for the synthesis by MW irradiation.

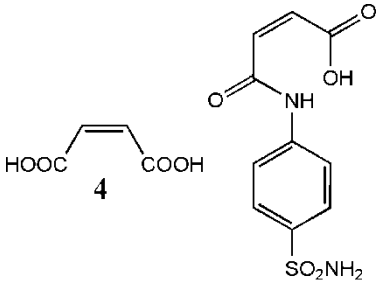
2.2.3 Polymerization of 3

2.05 g (8.13 mmol) of **3** and 0,15 g of benzopinacol (5.0 mol% in respect to the monomer) in 10 ml DMF were charged in a polymerization vial and purged with argon for 20 min. The solution was then subjected for 120 min to MW irradiation under temperature control with a preset power of 80 W and a maximum temperature of 100°C (fiber optic). The crude product was purified by precipitation in boiling isopropanol from DMF solution and dried under vacuum. The yield was 62%. FT-IR (diamond): 3358 ($\nu_{N\text{-}H}$ *symm.*), 3269 ($\nu_{N\text{-}H}$ *symm*), 1784 ($\nu_{C=O}$ *symm*), 1706 ($\nu_{C=O}$ *symm*), 1332 ($\nu_{O=S=O}$ *symm*), 1158 ($\nu_{O=S=O}$ *symm*) cm^{-1}; ^{1}H-NMR (500.13 MHz, $(CD_3)_2SO$): $\delta = 7.98$ ($-SO_2NH_2$), 7.51 (-N-*Arom*), 3.40 (*Aliphatic*) ppm.

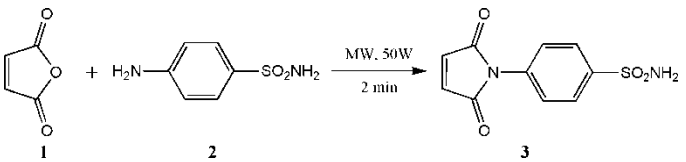
3 Results and Discussion

In a recent work, (18) we showed that the application of MW energy enhances the formation of N-phenylmaleimide. Here, we realized a one-pot bulk synthesis of the imide **3** starting from maleic anhydride (**1**) and sulfanilamide (**2**) without any chemical activation of the reagents and bypassing the ring-closure step normally needed by the classical synthetic approach. This reaction takes place under the applied MW conditions with a yield (after purification) up to 50% after only 2 min of irradiation (Scheme 1). Longer reaction times did not afford any yield improvement and resulted in partial decomposition of the samples.

^{1}H-NMR spectroscopy was used to confirm the structure of all obtained products. In analyzing the side products, it was possible to recognize, among others unidentified, the maleic acid ((*Z*)-but-2-enedioic acid, **4)** due to the hydrolysis of the starting maleic anhydride and the intermediate maleamic acid (3-(4-sulfamoyl-phenylcarbamoyl)-acrylic acid, **5**).



The maximum reached temperature was 100°C, according to the IR-pyrometer equipped with the MW reactor. It is well known that this temperature does not correspond to the real temperature inside the reaction vessel. Considering that the reaction takes place between two solids in conditions far below the melting temperature and in a heterogeneous system, using a fiber-optic contact thermometer to evaluate the temperature seemed to be of lesser significance. To qualify the benefit of the MW dielectric heating, the same



Sch. 1. Microwave-assisted synthesis of 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-benzenesulfonamide.

synthesis was also performed by conventional thermal heating in oil bath. Without having accurate temperature measurements in the MW and knowing that the real temperature is still higher than the one observed outside of the reaction vessel, we carried out the comparison in oil bath working with temperatures ranging from 100°C to 170°C for 15 min. Performing the reaction for 2 min (as in the MW case), it only afforded unreacted educts. The relative conversions (evaluated by ^{1}H-NMR), referred to the identified products considering them as the only ones present in the raw mixture, are plotted against the reaction temperature (Figure 1).

According to Figure 1, it is possible to conclude that for temperatures below 150°C there was no imide formation and the main product was maleamic acid (**5**) accompanied by minor percentages of maleic acid (**4**). Upon increasing the temperature, the percentage of maleimide **3** increased progressively up to 19% (170°C) with the corresponding decrease of both acids **4** and **5**. These results are in good accordance with the accepted two steps mechanism that leads to the maleimide through dehydration of maleamic acid certainly enabled by the high reaction temperature. Starting from 150°C, the partial decomposition of the samples with formation of unidentified side products also occurred.

The monomer **3** was polymerized in DMF solution using benzopinacol as a free radical initiator. MW irradiation under temperature control was used. The maximum temperature, checked internally using a fiber optic thermometer, was 100°C. Even the preset power was 80 W, the irradiation power was ranging between 5 and 25 W due to reaching the maximum temperature. The most commonly used radical initiators, such as peroxides or aliphatic azo compounds, do not seem to be very efficient for MW-assisted polymerization due to their relatively low decomposition temperature. Using a good MW absorber solvent such as DMF (tan $\delta = 0.161$), even irradiating with a quite low power, it can be difficult to maintain suitable temperatures for these initiators. High reaction temperatures result in a fast consumption of the radicals and finally in low yield even after long reaction times. Moreover, in this particular case, the polymerization at 60°C using AIBN as a free radical initiator yielded only a few percentages of the polymer. The use of C-C-bond splitting initiators offers the possibility to polymerize at relatively high temperature due to their improved thermal stability. Benzopinacol is the most used among this class of initiators and can be handled up to 160°C without danger as it does not decompose under explosion in this temperature range. The diarylhydroxy radicals formed from its decomposition do not react directly with the monomer under addition, but in a secondary reaction by hydrogen transfer forming monomer radicals that initiate the polymerization. Using this kind of initiator, it is possible to get polymers with hydrogen atoms at the end of the chain, i.e. "end-group free polymers" (19).

The structure of the obtained polymer was confirmed by ^{1}H-NMR and FT-IR spectroscopy. The IR-spectra exhibited the characteristic absorptions for the imide ring at 1706 and 1784 cm^{-1} attributed to the symmetrical and asymmetrical carbonyl stretching vibration. MALDI-TOF analyses indicated that the mass signals of polymeric ions are distributed approximately between 1000 and 4200 m/z corresponding to chain lengths of about 4 up to 17 repeating units. The maximum of intensity at about m/z 1283 corresponds to 5 repeating units. The low molecular weight obtained and the relative low isolated yield (62%) could be attributed to the low homopolymerization tendency typical of N-phenyl maleimide derivatives. GPC analyses showed an average molecular weight (*M*w) of 5 017 Da, corresponding to about 20 repeating units with a polydispersity index of 1,3. However, a calibration with polystyrene leads to higher values compared to MALDI-TOF analyses because of coil extension due to the more rigid main chain of the polyimide.

The presence of the —SO_2NH_2 group provides the polymer with a pH dependent solubility behavior. A qualitative analysis showed that the polymer is insoluble for pH values below 12 and becomes highly soluble at pH above 13 (Scheme 2).

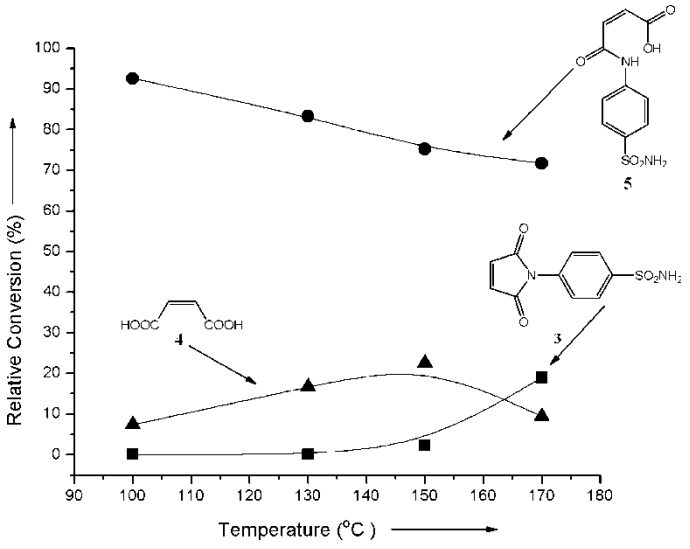
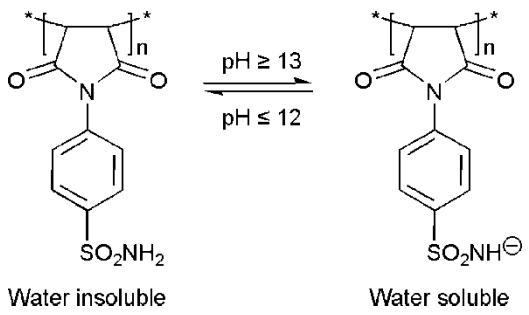


Fig. 1. Relative products distribution for the reaction between **1** and **2** in oil bath at different temperatures.



Sch. 2. pH dependent solubility behavior of poly (N-benzenesulfonamide maleimide).

We previously reported similar behavior in a work concerning polymeric sulfonamides as potential carriers for anti-tumor agents (16).

4 Conclusions

We have shown that it is possible to synthesize *4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-benzenesulfonamide* (**3**) by MW irradiation of a solid mixture of maleic anhydride and sulfanilamide. The one step reaction proceeds with good yield in only 2 min of reaction time. The oil-bath reaction, investigated as a comparison, results in lower yield even after 15 min. The polymerization of **3**, performed in MW using benzopinacol as a free radical initiator, afforded a pH-sensitive polymer that could find applications in pharmaceutical areas, such as site-specific targeting, and sensors.

5 References

1. Perreux, L. and Loupy, A. (2001) *Tetrahedron*, **57**, 9199–9223.
2. De la Hoz, A., Dıaz-Ortiz, A. and Moreno, A. (2005) *Chem. Soc. Rev.*, **34**, 164–178.
3. Lidström, P., Tierney, J., Wathey, B. and Westmam, J. (2001) *Tetrahedron*, **57**, 9225–9283.
4. Goretzki, Ch., Krlej, A., Steffens, C. and Ritter, H. (2004) *Macromol. Rapid. Commun.*, **25**, 513.
5. Iannelli, M., Alupei, V. and Ritter, H. (2005) *Tetrahedron*, **61**, 1509.
6. Sinnwell, S. and Ritter, H. (2004) *Macromol. Rapid. Commun.*, **26**, 160.
7. Iannelli, M. and Ritter, H. (2005) *Macromol. Chem. Phys.*, **206**, 349.
8. Bezdushna, E., Troev, K. and Ritter, H. (2005) *Macromol. Rapid. Commun.*, **26**, 471.
9. Filho, V.C., de Campos, F., Correa, R., Yunes, R.A. and Nunes, R.J. (2003) *Quim. Nova*, **2**, 230.
10. Torgenson, D.C., Hensley, W.H. and Lambrech, J.A. (1983) *Contrib. Boyce Thompson Inst.*, **22**, 67.
11. Fujinami, A., Ozaki, K., Nodera, T. and Tanaka, K. (1972) *Agr. Biol. Chem.*, **36**, 318.
12. Baumgarten, E. *Organic Synthesis Collective*; Baumgarten, E. (ed.); Wiley: New York; Vol. 5, 1973.
13. Kretov, A.E. and Kul'chitskaya, N.E. (1956) *J. Gen. Chem.*, **26**, 221.
14. Bjelakovic, G., Stojanovic, I., Pavlovic, D., Kocic, G. and Dakovic-Milic, A. (2002) *Medicine and Biology*, **9**, 201.
15. Colak, S. and Korkmaz, M. (2003) *International Journal of Pharmaceutics*, **267**, 49–58.
16. Hofmann, V., Przybylski, M., Ringsdorf, H. and Ritter, H. (1976) *Makromol. Chem.*, **177**, 1791–1811.
17. Tawney, P.O., Snyder, R.H., Conger, R.P., Leibbrand, K.A., Stiteler, C.H. and Williams, A.R. (1961) *J. Org. Chem.*, **26**, 15.
18. Bezdushna, E. and Ritter, H. (2005) *Macromol. Rapid. Commun.*, **26**, 1087.
19. Braun, D. and Becker, K.H. (1971) *Ind. Eng. Chem. Prod. Res. Develop.*, **10**, 386.