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Scaling Up of Dihydropyridine Ester Synthesis by Using Aqueous Hydrotrope Solutions in a Continuous Microwave Reactor

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Abstract:

We report here the scaling up of clinically important dihydropyridine by using a continuous microwave reactor (CMR). We also report the use of aqueous hydrotrope solution as a cheap, safe and "green" alternative to organic solvent to carry out homogeneous reactions under microwave heating. We have studied different aqueous hydrotrope solutions for the reaction in batch as well as continuous-flow process.

Introduction

The utility of microwave irradiation to carry out organic reactions has now become a regular feature. This is evident from the number of reviews[1−8] published on the use of microwave technology for carrying out organic reactions. From the future point of view of microwave technology the question that now needs to be answered is how to carry out large-scale reactions by employing microwaves and to understand the nature of the microwave effect. In 1994, Strauss[9] and co-workers demonstrated the use of a continuous microwave reactor for scaling up organic reactions in homogeneous conditions. However, later on, the reports were very scanty. Now attention is focused on the aspect of scaling up of reactions using microwave technology. The research groups of Kabza et al.,[10] Loupy et al.,[11] E. Esveld et al.,[12] and Hamelin et al.[13] have published promising results.

Keeping this in mind we have developed a continuous microwave reactor (CMR) for carrying out reactions on a larger scale using a domestic microwave oven. By using this reactor, about 500 mL of the reaction mixture can be processed within a short time. We are developing new technology by making use of an aqueous hydrotrope solution[14,15] as an homogeneous reaction medium, which is a reliable, cheap, and safe alternative to organic solvents to carry out reactions under microwave exposure in a continuous flow using CMR. By this we are avoiding the use of costly and hazardous organic solvent systems by replacing them with a reusable aqueous hydrotrope solution as a new generation "green" solvent system.

We describe here the Hantzsch ester synthesis[16] using the hydrotrope solution. The mixture of benzaldehyde, methyl 3-aminocrotonate, and ethyl/methyl acetoacetate was solubilized in the aqueous hydrotrope solution of sodium *p*-toluene sulphonate and circulated through the microwave oven cavity to obtain dihydropyridines in high yield and of excellent quality. Dihydropyridines[17−19] are an important class of calcium channel blocker and have extensive clinical use.

Results and Discussion

We have used for the first time an aromatic hydrotrope solution system such as 50% sodium *p*-toluene sulphonate aqueous solution (NaPTSA), 40% sodium cumene sulphonate aqueous solution (NaCuS), and 20% sodium *p*-xylene sulphonate (NaXS) aqueous solution to carry out Hantzsch ester synthesis to give 4-aryl-1,4-dihydropyridines under microwave exposure.

We studied two routes for Hantzsch ester synthesis of 4-aryl-1,4-dihydropyridines under microwave exposure. Initially each route was studied and optimized for a batch process in 50% NaPTSA under microwave exposure (Figure 1). We also studied the reaction in 40% NaCuS and 20% NaXS hydrotrope solution. We found that the yields of DHPs were higher in 50% NaPTSA than in the other two hydrotrope solution.

Development and Application of Continuous Microwave Reactor

The promising results obtained from the batch reaction for DHP's synthesis encouraged us to develop a continuous microwave reactor (CMR) to carry out DHP synthesis reaction at a larger scale. We have used 50% NaPTSA hydrotrope solution to carry out reaction under CMR.

Description of the Reactor

An omega-shaped circular glass reactor was constructed for CMR study. The omega shaped reactor was found to be

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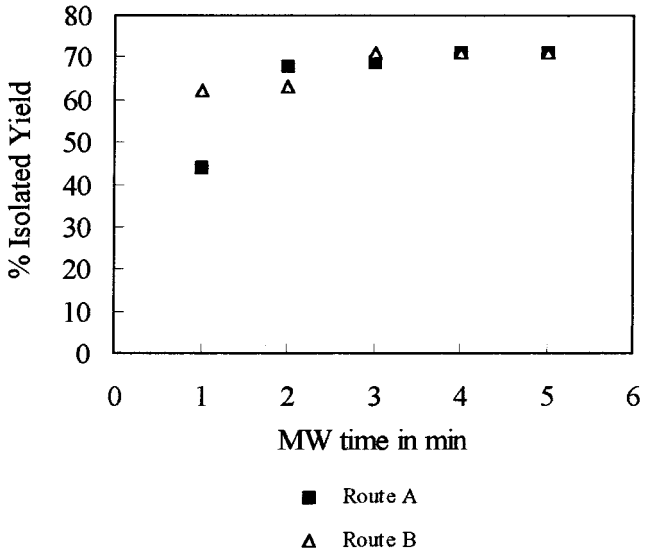


Figure 1. **Optimization of DHP synthesis (for entry no. 6) under microwave exposure in 50% NaPTSA by routes A and B.**

suitable for our study as the reaction solution moved smoothly and also because the chances of clogging by DHP formed during the final stages of reaction was avoided by this kind of reactor design. The glass reactor was placed in such a way that it traversed along the circumference of the turntable (glass plate without a rotor) inside the microwave cavity. As it was placed along the periphery of the turntable, more uniform heating of the reaction mixture could be achieved easily using a simple modified kitchen oven (Figure 2). At the rear wall of the domestic microwave oven two holes of 1 cm diameter and 5 cm apart from each other were drilled for inlet and outlet ports for the two ends of the glass reactor to come out. To these ends Teflon tubes were connected. The tubes were cooled to control the temperature during microwave irradiation.

The reactor volume was 65 mL, and that of the connecting Teflon tubes was 35 mL (dead volume). Therefore, the total volume for CMR was 100 mL, and the reaction was carried out in a closed-loop mode. The reaction mixture was placed in a three-necked round-bottom flask of 500 mL capacity, and the mixture was stirred using magnetic stirrer. A condenser was fitted to one of the central necks, while the remaining two were used as inlet and outlet ports.

Chemicals and Materials

Hydrotrope solutions were provided by Industrial General Products Pvt. Ltd., Mumbai, India, and were used as such. Aldehydes, ethyl acetoacetate, methyl acetoacetate, and liquid ammonia (sp. gravity 0.91) were supplied by S.D. Fine-Chem Ltd., Mumbai, India. The continuous microwave reactor and sampling assembly was made up of Borosil glass. Peristaltic pump of Electrolab model PP-VT 100 series was used. A domestic microwave oven of IFB Neutron having 750 W output working at 2450 MHz was modified to suit the reaction.

Experimental Section

The Hantzsch dihydropyridine ester synthesis was carried out in an aqueous hydrotrope solution using two different routes.

Route A. In a round-bottom flask an aldehyde (5 mmol) was added to the hydrotrope solution (7 mL) and solubilized (by warming to 40 °C if necessary); to this solution were added alkyl acetoacetate (10 mmol) and 2 mL of ammonia (sp. gravity 0.91) solution. The reaction mixture was then irradiated at full power in a modified domestic microwave oven provided with a reflux and stirring facility.[20] Immediately after the irradiation, the reaction temperature was noted. The reaction was then cooled to room temperature or in ice as needed, to give 4-aryl-1,4-dihydropyridine ester as the solid product. The solid product obtained after filtration was washed with 10 mL of water and 5 mL of methanol. The product was air-dried which showed the correct melting point (Scheme 1, Table 1).

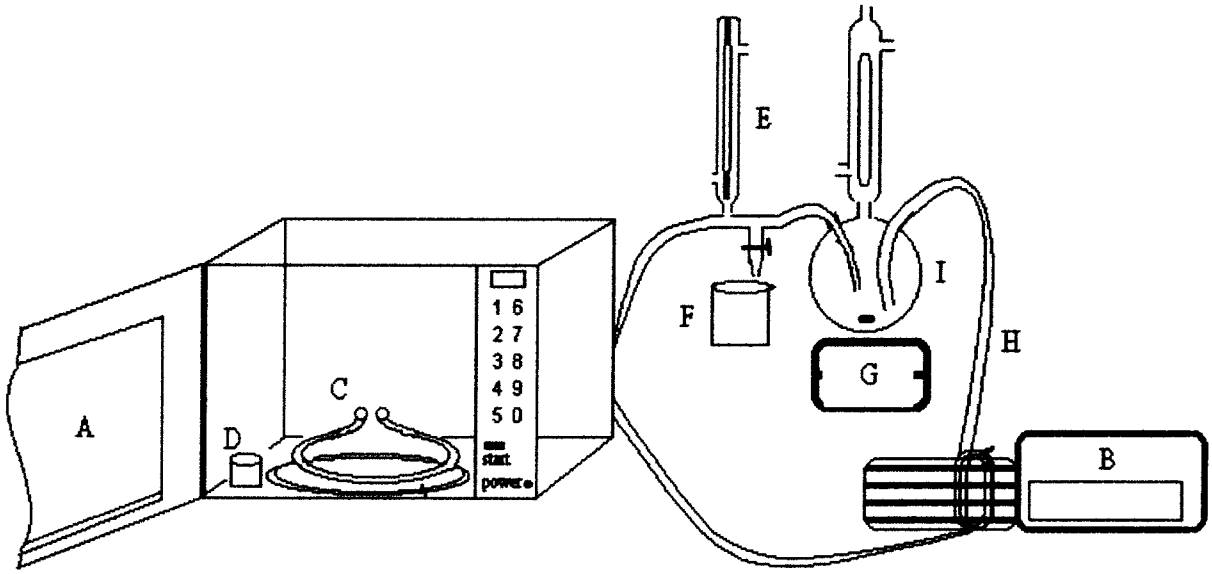
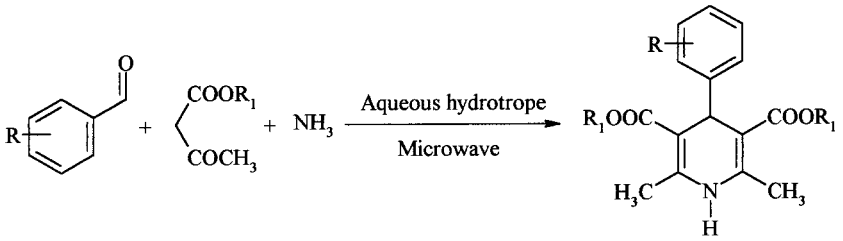


Figure 2. **Schematic diagram for CMR. (A) IFB microwave oven (760-W, 2450-Hz), (B) peristaltic pump, (C) omega-shaped glass coil, (D) alumina 110-g load, (E) double surface condenser, (F) sampling assembly, (G) magnetic stirrer, (H) Teflon tubing, (I) round-bottom flask.**

Scheme 1. **Route A for DHP synthesis**



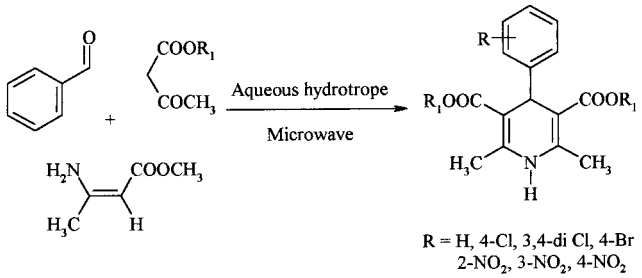
R = H, 4-Cl, 3,4-di Cl, 4-Br
2-NO_2, 3-NO_2, 4-NO_2

Table 1. **Optimized Percent yields for the synthesis of DHPs by route A**

entry	R[a]	MW (min)	50% NaPTSA[b]	40% NaCuS[b]	20% NaXS[b]	lit[19]	mp (°C)[19] [c] obsd.
1	H	4	81	45	45	35	198
2	4-Cl	4	52	30	34	55	195−196
3	3,4-di-Cl	6	50	41	41	−	163−164
4	4-Br	6	70	51	29	66	193−194
5	2-NO_2	1	28	−	−	−	172−173
6	3-NO_2	5	71	45	20	65	209−210
7	4-NO_2	4	64	45	38	66	197−198
8	3-NO_2	6	39	45	34	−	160−161

[a] Entries 1−7 structure R_1 = Me; entry 8 structure R_1 = Et. [b] Yield of pure, isolated product. [c] The melting point and spectral data of products were identical with those of authentic samples.

Scheme 2. **Route B for DHP synthesis**



R = H, 4-Cl, 3,4-di Cl, 4-Br
2-NO_2, 3-NO_2, 4-NO_2

A small amount of the product was recovered as a second crop. Yields reported are combined yields. The completion of reaction was monitored by TLC (toluene−ethyl acetate 8:2 v/v).

Route B. Aldehyde (5 mmol) was added to the hydrotrope solution (7 mL) and was solubilized by warming when necessary. To this solution were added alkyl acetoacetate (5 mmol) and methyl 3-aminocrotonate (5 mmol), and the reaction mixture was irradiated as per the above procedure. The results are summarized in (Scheme 2,Table 2).

For all of the substrates in the above routes the amount of hydrotrope was sufficient to solubilize the reactant. The solubility of reactants (solid aldehydes) in aqueous hydrotrope solution was found by loss-in-weight method.[21] The alkyl acetoacetate and methyl 3-aminocrotonate were completely soluble in the hydrotrope solutions. In both methods it was noted that when the same reactions were performed in water bath at microwave irradiation end temperature 86 °C, they failed to give significant yields for the comparable time. This supports the utility of microwave assistance to carry out the reactions.

Table 2. **Optimized Percent yields for the synthesis of DHPs by route B**

entry	R[a]	MW (min)	50% NaPTSA[b]	40 %NaCuS[b]	20 %NaXS[b]	lit.[19]	mp (°C)[19] [c] obsd.
1	H	5	81	53	50	35	198
2	4-Cl	5	34	29	33	55	195−196
3	3,4-di-Cl	6	67	75	60	-	163−164
4	4-Br	6	49	48	35	66	193−194
5	2-NO_2	1	11	-	-		172−174
6	3-NO_2	3	71	38	52	65	209−210
7	4-NO_2	6	83	35	44	66	197−198
8	3-NO_2	6	76	46	18		158−159

[a] Entries 1−7 structure R_1 = Me; entry 8 structure R_1 = Et. For entry 3: ^{1}H NMR ($CDCl_3$/TMS) δ 2.3−2.5 (s 6H, 2× $-CH_3$); δ 3.6−3.8 (s 6H, 2× $-OCH_3$); δ 5 (s 1H, NH); δ 5.7−5.8 (s 1H, CH); δ 7.1−7.5 (m 3H, Ar−H). [b] Yield of pure, isolated product. [c] The melting point and spectral data of products were identical with those of authentic samples.

Experimental Section for CMR study (for Nitrendipine Preparation)

In a 500-mL three-necked round-bottom flask (I) 125 mL of 50% NaPTSA solution was placed. To it was added *m*-nitrobenzaldehyde (0.15 mol, 22.68 g). The solution was stirred for 15 min to solublize the aldehyde completely. To this clear solution ethyl acetoacetate (0.15 mol, 19.52 g) and methyl 3-aminocrotonate (0.15 mol, 17.25 g) was added. This homogeneous solution was then pumped through an omega-shaped glass reactor via Teflon tubing using a peristaltic pump (Electrolab, model PP-VT 100 series). The flow rate was optimized to 100 mL/min. The reaction mixture was circulated through the microwave cavity in four cycles of 6 min each. A 2 min interval between each cycle (only to avoid excessive heating) was taken. The reaction mixture was cooled to room temperature and then placed in crushed ice for 10 min. The solid product obtained after cooling was filtered, washed two times with 25 mL of water and then by 15 mL of methanol, and air-dried to give 94% (50.76 g) yield. The hydrotrope solution can be reused. Similarly, other DHPs were also synthesized in CMR (Table 3).

Nifedipine was obtained in relatively low yields, as the reaction time was not increased due to the development of brown coloration of the reaction mixture. We have observed that development of such color affects the quality of the product, moreover ortho-substituted nitro DHPs are known to form lower yields.

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Table 3. **Optimized results for the synthesis of DHPs by route B in CMR**

entry	R[a]	MW (min)	% isolated yield[b]	mp (°C) obsd. (lit[19])
1	3-NO_2 (nitrendipine)	24 (6 × 4 cycles)	94	158−159
2	2-NO_2 (nifedipine)	18 (6 × 3 cycles)	42	172−174
3	3-NO_2	18 (6 × 3 cycles)	98	209−210
4	4-NO_2	8 (6 + 2)	88	197−198
5	2-Cl	24 (6 × 3 cycles)	86	184−185

[a] Route B: equimolar amount of aldehyde, alkyl acetoacetate and methyl 3-amino crotonate in 50% NaPTSA solution. Entry 1: structure R_1 = Et; entries 2−5: structure R_1 = Me. [b] Yield of pure isolated product. The melting point and spectral data of products were identical with those of authentic samples.

Conclusions

Scale up of DHPs is easily possible using a CMR. The construction of the reactor using a domestic microwave oven and a peristaltic pump is simple. The reactor is easy to handle and just by alterating the coil size, it would be possible to scale up the reaction to liters. As compared to batch process, a significant increase in the yields of DHPs was observed when reaction was carried out in CMR. Many of Hantzsch products (e.g., 4-aryl-1,4-dihydropyridines such as nitrendipine, nifedipine) synthesized in our laboratory have extensive clinical use as calcium channel blockers. Therefore, such continuous processes can be commercially important.

By carrying out Hantzsch ester synthesis in aqueous aromatic hydrotrope solution we have found a cheap, safe and "green" alternative to organic solvent to carry out homogeneous reactions under microwave heating. The easy recovery of products from the hydrotrope solutions and most significantly little or no foaming unlike the surfactants makes the use of hydrotrope possible at the industrial scale also. Not surprisingly, we expect this area to continue to be focus of extensive activity in near future.

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