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(4-Isobutyl-phenyl)-acetic acid (Ibufenac) Microwave-Assisted and Conventional Synthesis

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Abstract

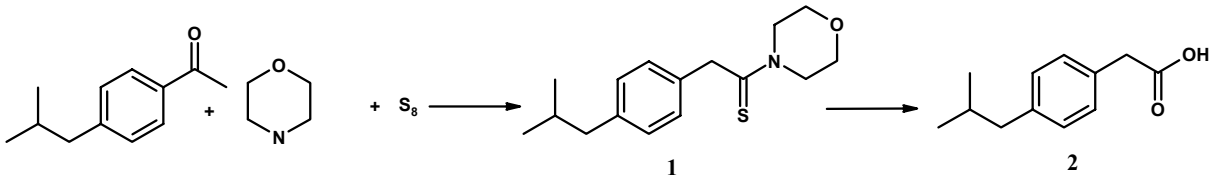
The multigrams synthesis of Ibufenac is reported and the results of conventional and microwave heating are compared.

Introduction

Ibufenac **2** was used as a non-steroidal anti-inflammatory drug (NSAID)[1] until it was taken off the market because of hepatotoxicity.[2] As the title compound is commercially available in mg quantities only we needed to prepare it in the context of joint collaboration in the chemo-genomics project DrugMatrix.[3]

Results and Discussion

In recent years, the use of microwave dielectric heating to assist chemical processes has attracted increasing attention in organic and medicinal chemistry community and the application of the Microwave-assisted Organic Synthesis (MAOS) protocols has been shown to significantly enhance the speed of reactions.[4] In particular, the use of dedicated microwave reactors that enable the rapid and safe heating of reaction mixtures in sealed vessels under controlled conditions with on-line temperature and pressure monitoring has greatly increased the general acceptance of the microwave heating method.



Scheme 1

It appeared to us that the use of microwave heating using sealed vessel (autoclave) would provide a rapid method to synthesize phenyl acetic acids.[5,6] It should be noted that the first reports on microwave-assisted Willgerodt-Kindler processes have appeared in the literature[7] these studies employed domestic microwave ovens that did not allow accurate temperature measurements and therefore, may prove difficult to reproduce.[4,5]

We report here a microwave enhanced Willgerodt-Kindler synthesis of the thiomorpholide and hydrolysis of this compound to Ibufenac with taking advantage of the sealed vessel capabilities of a dedicated single-mode microwave reactor, CEM Explorer™ [6] (a single mode automated microwave instrument (Fig. 1), the comparison with conventional heating with significant yield improvement.

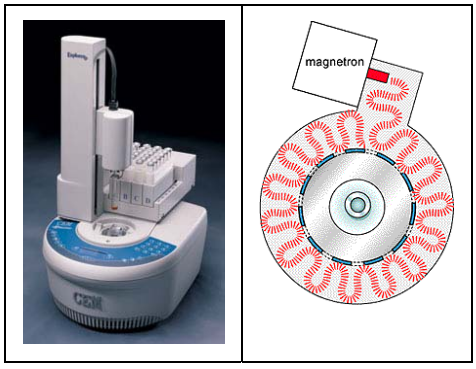


Fig. 1 CEM Explorer™ and Single-mode cavity design.

The reaction under solvent free conditions at different temperature and reaction time yielded 78-85% of the thiomorpholide **1** but using 1-methyl-2-pyrrolidone (NMP) as solvent the yield was increased to 94%. (Table 1) The hydrolysis with aq. NaOH solution at 150 °C for 20 min. applying microwave was not sufficient to complete reaction. However, the hydrolysis by adding alcoholic KOH (3N) to the reaction mixture and employing microwave heating for 20 min at 150°C resulted in 98% conversion. (HPLC)

Table 1- Optimization of the thiomorpholide **1** preparation.

Entry	µw	solvent	Temperature (°C)	Time (min.)	HPLC yield (%)
1	+	Neat	140	10	82
2	+	Neat	160	10	84
3	+	Neat	200	10	78
4	+	Neat	160	20	85
5	+	NMP	160	10	85
6	+	NMP	160	15	90
7	+	NMP	160	20	94
8	-	Neat	120	480 (8h)	77
9	-	Neat	125	600 (10h)	95

The three-component condensation of 4-isobutylacetophenone, morpholine and elemental sulfur using NMP as solvent also was carried out employing microwave flash heating at 160 °C for 20 min. Then alcoholic solution of KOH (3N) was added to the reaction mixture and irradiation continued for 20 min. at 150 °C.

Although microwave irradiation allowed a significant reduction in the reaction time, conditions for preparation of 30 g of Ibufenac were inconvenient from a practical point of view. This would be convenient just using scale up microwave instrument (e.g. Synthos 3000™).[6,9] However for quick preparation of smaller scale and diverse libraries MAOS protocol would be an ideal opportunity. (See Table 1,2)

Table 2- Optimization of the hydrolysis, Ibufenac preparation.

Entry	µw	Base	Temperature (°C)	Time (min.)	HPLC yield (%)
a	+	NaOH (aq., 2N)	120	10	12
b	+	NaOH (aq., 2N)	150	10	23
c	+	KOH (EtOH, 3N)	150	10	90
d	+	KOH (EtOH, 3N)	150	20	98[a]
e	-	KOH (EtOH, 3N)	110	720 (12h)	99[a]

[a]Isolated yield is 95%, >99% HPLC purity.

EXPERIMENTAL

Melting points were measured on a Kofler micro hot stage. NMR-spectra were recorded on a Bruker AC-200 in CDCl3. Thin layer chromatography (TLC) was performed on pre-coated plates (Merck TLC aluminum sheets silica 60 F254) with detection by UV light or with phosphomolybdic acid in aqueous EtOH by heating. For reaction monitoring and quality (purity) control of the product a Waters 996 HPLC system, that included Waters 600-MS pumps, an autosampler (Waters 712 WISP), and Waters 996 photodiode array UV detector was used. The separations were carried out using a Chromolith Performance reversed phase analytical column (E. Merck, 100 × 4.6 mm) at 25 °C and a mobile phase from (A) 0.1% TFA in 97:3 water/MeCN and (B) 0.1% TFA in MeCN (all solvents were HPLC grade, Fisher and Merck; TFA was analytical reagent grade, ROTH). The following gradients were applied at a flow rate of 3 mL/min: linear increase from solution 3% B to 60% solution B in 8 min, hold at 60% solution B for 2 min.

General microwave assisted procedure

Step 1

Preparation of 2-(4-Isobutyl-phenyl)-1-morpholin-4-yl-ethanethione (1)

The process vial was charged with 4-isobutylacetophenone (353 mg, 2 mmol), morpholine (516 mg, 6 mmol) and elemental sulfur (128 mg, 4 mmol) neat or NMP (2 mL) was added then capped with Teflon septa and aluminum crimper. After microwave irradiation according to table 1, the reaction mixture was monitored by HPLC and directly used for step 2. An analytical sample for structure verification was prepared. Mp 69 °C (Lit.[10] 62°C), ^{1}H-NMR in $CDCl_3$ δ ppm, 7.17 (dd, 4 H), 4.25 (t, 4H), 3.72 (t, 2H), 3.58 (t, 2H), 3.30 (t, 2H), 2.35 (d, 2H), 1.79 (m, 1H), 0.82 (d, 6H), ^{13}C-NMR in $CDCl_3$ δ ppm, 200.3, 140.5, 132.9, 129.8, 127.4, 66.3, 66.0, 50.3, 50.2, 44.9, 30.1, 22.3.

Step 2

Preparation of Ibufenac (2)

To the reaction mixture of the step 1 according to table 2, aq. NaOH (3 mL, 3N) or alcoholic KOH (3 mL, 3N) was added and then capped with Teflon septa and aluminum crimper. The vial was heated employing microwave irradiation. (See Table 2) After cooling, reaction was monitored by HPLC and filtered, the filtrate was acidified with HCl to pH 6 and then filtered off and washed with ethyl acetate (5 × 20 mL), separated the organic layer, and the aqueous layer was acidified with dilute HCl, to yield the pure Ibufenac as solid. (Entry **7d** : 365 mg of overall yield 95% with HPLC purity >99%) Mp 88 °C (lit.[11] 85-87.5°C), ^{1}H-NMR in $CDCl_3$ δ ppm, 10.45 (b, 1H), 7.19 (dd, 4 H), 3.63 (s, 2H), 2.48 (d, 2H), 1.91 (m, 1H), 0.98 (d, 6H), ^{13}C-NMR in $CDCl_3$ δ ppm, 178.3, 148.4, 130.5, 129.4, 129.2, 45.1, 40.7, 30.1, 22.4.

Conventional procedure

Step 1

Preparation of 2-(4-Isobutyl-phenyl)-1-morpholin-4-yl-ethanethione (1)

The 500 mL round bottom flask was charged with 4-isobutylacetophenone (26.4 g, 150 mmol), morpholine (45mL, 0.5 mol), elemental sulfur (9.6 g, 0.3 mol) and *p*-toluene sulfonic acid (0.4 g, 2 mmol). The reaction mixture was stirred at 125 °C for 10 h. The reaction was analyzed monitored by HPLC and directly used for step 2.

Step 2

Preparation of Ibufenac (2)

To the reaction mixture of the step 1 alcoholic KOH (250 mL, 3N) was added and stirred at 110°C for 12 h. After cooling, 200 mL water was added to the reaction mixture and washed with Et_2O (3×mL) then acidified by HCl 2N (pH=2) and extracted to dichloromethane. The organic phase was dried over Na_2SO_4, decolorized with activated carbon, filtered and evaporated under vacuum to yield the product as a yellow solid. The product was recrystallized from EtOH: water (1:1, 250 mL) to yield **2** (27.3 g, 95%) with >99% HPLC purity.

CONCLUSION

This report summarizes a convenient approach to the synthesis of Ibufenac. The reaction time has been decreased from 22 hours conventional to 30 min. microwave dielectric heating with total yield 95%.

References & Notes

1. Nicholson, J. S. (1982). *Ibuprofen.* In J.S. Bindra & D. Lednicer (Eds.), Chronicles of Drug Discovery (pp. 149), J. Wiley (New York).

2. (a) Herxheimer, A., **1968**. *Drug Ther. Bull.* 6, 48. (b) Adams, S. S. *Chemistry in Britain*, 1987, 1193. (c) Pohl, L. R., **1993**. *Chem. Res. Toxicol.* 6, 786-793.

3. Iconix Pharmaceuticals, Inc. USA. http://www.iconixpharm.com/products/products_drugmatrix.html

4. (a) Hayes, B. L. Microwave Synthesis: Chemistry at the Speed of Light; CEM Publishing: Matthews, NC, 2002. (b) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: New York; 2002. (c) C. Oliver Kappe *Angew. Chem. Int. Ed*. **2004**, *43*, 6250. (d) For more information on microwave-assisted organic synthesis, see: http://www.maos.net.

5. Zbruyev, O. I.; Stiasni, N.; Kappe, C. O. *J. Comb. Chem.* **2003,** *5,* 145-148.

6. Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N.; Kappe, C. O. *Organic Process Research & Development* **2003**, *7,* 707-716.

7. (a) Moghaddam, F. M.; Ghaffarzadeh, M. *Synth. Commun.* **2001**, *31*, 317-321. (b) Gupta, M.; Paul, S.; Gupta, R. *Synth. Commun.* **2001**, *31*, 53-59. (c) Nooshabadi, M.; Aghapoor, K.; Reza Darabi, H.; Majid Mojtahedi, M. *Tetrahedron Lett.* **1999**, *40*, 7549-7552.

8. All microwave assisted synthesis was performed using *CEM-Explorer* which is an automated reaction handling module for maximum throughput and flexibility in a microwave-enhanced synthesis workstation. For more information see: http://www.cemsynthesis.com.

9. Anton Paar GmbH, Austria. Scale up microwave instrument Synthos 3000. For more information see: http://www.anton-paar.com.

10. Dolby, L. J.; Riddle, G. N. *J. Org. Chem.* **1967**, *32*, 3481-5.

11. Hamajima, R. *Yuki Gosei Kagaku Kyokaishi* **1978**, *36*, 875.