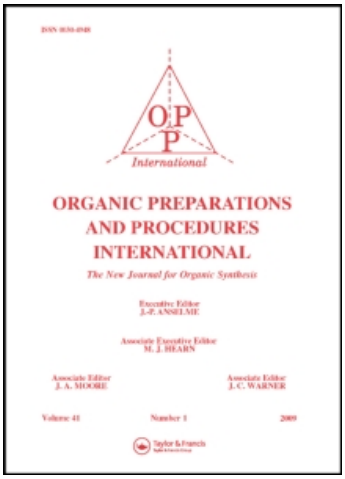
This article was downloaded by:
On: *26 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF 3-SUBSTITUTED-2-ACYLIMINO-4-THIAZOLIDONES UNDER MICROWAVE IRRADIATION

Yanqing Peng[a]; Gonghua Song[a]; Ling Liu[a]
[a] Shanghai Key Laboratory of Chemical Biology, Institute of Pesticides & Pharmaceuticals, East China University of Science & Technology, Shanghai, PR CHINA

To cite this Article Peng, Yanqing , Song, Gonghua and Liu, Ling(2004) 'SYNTHESIS OF 3-SUBSTITUTED-2-ACYLIMINO-4-THIAZOLIDONES UNDER MICROWAVE IRRADIATION', Organic Preparations and Procedures International, 36: 2, 151 — 155
To link to this Article: DOI: 10.1080/00304940409355386
URL: http://dx.doi.org/10.1080/00304940409355386

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

ORGANIC PREPARATIONS AND PROCEDURES INT., 36 (2), 151-199 (2004)

OPPI BRIEFS

SYNTHESIS OF 3-SUBSTITUTED-2-ACYLIMINO-4-THIAZOLIDONES UNDER MICROWAVE IRRADIATION

Submitted by (08/11/03)

Yanqing Peng, Gonghua Song * and Ling Liu

Shanghai Key Laboratory of Chemical Biology
Institute of Pesticides & Pharmaceuticals
East China University of Science & Technology
Shanghai 200237, P. R. CHINA

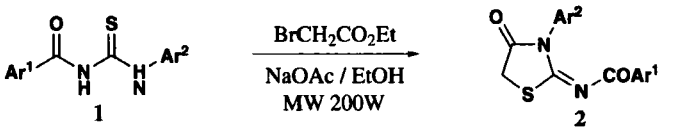
Downloaded At: 19:25 26 January 2011

Thiazolidones have generated much interest in the medical community and have prompted extensive research in the pharmaceutical and agrochemical industry for use as antiinflammatory agents,[1] anticonvulsant drugs,[2] fungicides,[3] herbicides[4] and acaricides.[5] However, since only a few attempts have been made to investigate methods for the synthesis of 3-substituted-2- acylimino-4-thiazolidones,[6] it was deemed useful to study the scope and improvement of these reactions.

The application of microwaves, as an efficient heating source for organic synthesis, was recognized in the mid-1980s. Since then, numerous reactions with dramatically enhanced reaction rates have been disclosed,[7] including the synthesis of thiazolidones.[8] In view of the importance of thiazolidones and the advantages of microwave-induced reactions, it was thought worthwhile to attempt to synthesize the title compounds using microwave technique. We report herein the rapid preparation of 3-substituted-2-acylimino-4-thiazolidones **2** and of 3-substituted-2-acylimino-5-carboxy- methyl-4-thiazolidones **3**, under microwave irradiation.

3-Phenyl-2-benzoylimino-4-thiazolidones **2** were previously synthesized in moderate yield (67%) by heating N-benzoyl-N'-phenylthiourea with ethyl chloroacetate for 3 h in KOH/DMF system.[6] Our initial goal was to study the use of microwave heating in the synthesis of **2**. In a model reaction, after 15 minutes of irradiation in microwave multimode cavity, **2a** was produced in 76% yield after purification. We then extended this method to other compounds **2b-2h** (*Table 1*). Reactions both under microwave irradiation and by conventional heating were performed and compared. Under microwave dielectric heating, the cyclization proceeded

© 2004 by Organic Preparations and Procedures Inc.



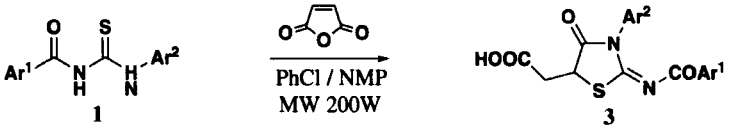
1 2

a) $Ar^1 = C_6H_5$, $Ar^2 = 2\text{-}MeC_6H_4$; b) $Ar^1 = C_6H_5$, $Ar^2 = 2\text{-}MeOC_6H_4$; c) $Ar^1 = C_6H_5$, $Ar^2 = 4\text{-}NO_2C_6H_4$; d) $Ar^1 = C_6H_5$, $Ar^2 = 2\text{-}FC_6H_4$; e) $Ar^1 = C_6H_5$, $Ar^2 = 4\text{-}FC_6H_4$; f) $Ar^1 = 4\text{-}MeOC_6H_4$, $Ar^2 = 4\text{-}MeC_6H_4$; g) $Ar^1 = 4\text{-}MeOC_6H_4$, $Ar^2 = 4\text{-}ClC_6H_4$; h) $Ar^1 = 4\text{-}MeOC_6H_4$, $Ar^2 = C_6H_5$

Scheme 1

smoothly in ethanol in the presence of NaOAc within 18 min or less to afford 72–86% isolated yields of **2**. An 8-12-fold of reaction rate enhancement, albeit with very slightly improved (1-7%) yields, was encountered with all substrates tested.

Encouraged by these initial findings, we explored the synthesis of 3-aryl-2- acylimino-5-carboxymethyl-4-thiazolidone **3** both under conventional and microwave condition. Up to now, there is only one report concerning the synthesis of **3** by treatment of N-aroyl-N'-arylureas with maleic anhydride in refluxing toluene. Only three compounds were prepared and the reaction time was not given.[9]



1 3

a) $Ar^1 = C_6H_5$, $Ar^2 = 2\text{-}MeC_6H_4$; b) $Ar^1 = C_6H_5$, $Ar^2 = 2\text{-}MeOC_6H_4$; c) Ar $Ar^2 = 4\text{-}MeC_6H_4$; d) $Ar^1 = 4\text{-}MeOC_6H_4$, $Ar^2 = 4\text{-}ClC_6H_4$; e) $Ar^1 = 4\text{-}MeOC_6$

Scheme 2

Table 1. Yields, mps and Combustion Data of Compounds **2** and **3**

Cmpd	mp (°C)	Time oil bath (h)	Time mw (min)	Yield (%) oil bath	Yield (%) mw	Elemental Analysis (Found) C	H	N
2a	201-203	3	15	71	76	65.79(65.91)	4.55(4.50)	9.03(9.16)
2b	202-204	3	18	73	77	62.57(62.43)	4.32(4.37)	8.58(8.55)
2c	205-207	3	15	68	72	56.30(56.44)	3.25 (3.28)	12.31(12.42)
2d	156-157	3	18	71	73	61.15(61.23)	3.53(3.54)	8.91(8.88)
2e	148-149	3	15	70	77	61.15(61.12)	3.53(3.55)	8.91(8.94)
2f	167-168	2	15	82	84	63.52(63.63)	4.74(4.70)	8.23(8.25)
2g	190-191	2	15	77	83	56.60(56.67)	3.63(3.65)	7.77(7.82)
2h	169-170	2	15	80	86	62.57(62.59)	4.32(4.37)	8.58(8.54)
3a	184-185	36	40	79	80	61.94(61.92)	4.38(4.44)	7.60(7.69)
3b	136-137	30	40	73	74	59.38(59.43)	4.20(4.24)	7.29(7.31)
3c	218-219	5	25	78	82	60.30(60.32)	4.55(4.59)	7.03(7.08)
3d	199-200	18	35	72	75	54.50(54.46)	6.69(6.78)	7.03(7.06)
3e	169-170	8	30	78	81	59.38(59.43)	4.20(4.29)	7.29(7.36)

Downloaded At: 19:25 26 January 2011

To investigate the efficiency of microwave irradiation in this transformation, several solvents were examined. Chlorobenzene / N-methylpyrrolidone (5:1 in volume) was found to be the most effective for the microwave-induced cyclization. Attempts to use DMSO, DMF or ionic liquid [bmim][PF_6] (1-*n*-butyl-3-methylimidazolium hexafluophosphate) to assist as microwave-absorption failed to give desired product, leading instead to tarry mixtures.

Table 2. IR and ^1H NMR Spectroscopic Data of Compounds **2** and **3**

Cmpd.	FTIR (ν_{max}, cm^{-1})	^1H NMR (δ_H, ppm)
2a	1725, 1625, 1600, 1580, 1500, 1380, 1320, 1200, 1175, 1100	2.20 (s, 3H, CH_3), 4.20 (q, J = 8.12, 2H, CH_2), 7.36-7.53 (m, 7H, ArH), 7.91(d, J = 2.19, 2H, ArH)
2b	1725, 1625, 1600, 1580, 1500, 1450, 1380, 1320, 1200, 1175, 1100	3.81(s, 3H, OCH_3), 4.14 (q, J = 18.3, 2H, CH_2), 7.12-7.52 (m, 7H, ArH), 7.93 (d, J = 7.90, 2H, ArH)
2c	1725, 1625, 1600, 1580, 1500, 1380, 1320, 1200, 1175, 1080, 1060, 1000	4.20 (s, 2H, CH_2), 7.43-8.02 (m, 7H, ArH), 8.50 (d, J = 9.04, 2H, ArH)
2d	1750, 1630, 1600, 1580, 1500, 1450, 1380, 1320, 1200, 1175, 1100	4.20 (s, 2H, CH_2), 7.25-7.66(m, 7H, ArH), 7.97 (m, 2H, ArH).
2e	1750, 1640, 1620, 1500, 1380, 1320, 1280, 1200, 1180, 1100	4.20 (q, J = 8.31, 2H, CH_2), 7.37-7.58 (m, 7H, ArH), 8.00 (d, J = 12.09, 2H, ArH)
2f	1725, 1625, 1600, 1580, 1500, 1450, 1380, 1320, 1260, 1200, 1175, 1100	2.44 (s, 3H, Me), 3.85 (s, 3H, MeO), 4.10 (s, 2H, CH_2), 6.95 (d, J = 8.60, 2H, ArH), 7.38 (m, 4H, ArH), 8.10 (d, J = 8.60, 2H, ArH)
2g	1725, 1625, 1600, 1580, 1500, 1380, 1320, 1260, 1200, 1175, 1100	3.88 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2), 6.9 (d, J = 8.76, 2H, ArH), 7.55 (d, J = 8.76, 2H, ArH), 7.65 (d, J = 8.78, 2H, ArH), 7.90 (d, J = 8.94, 2H, ArH)
2h	1725, 1625, 1600, 1580, 1500, 1450, 1370, 1330, 1250, 1200, 1160, 1100	3.82 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 6.91 (d, J = 8.90, 2H, ArH), 7.45-7.57 (m, 5H, ArH), 7.91 (d, J = 8.71, 2H, ArH)
3a	3150, 1730, 1700, 1635, 1600, 1580, 1500, 1460, 1450, 1380, 1320, 1210	2.28 (s, 2H, CH_3), 3.20 (d, 2H, CH_2COOH), 4.40 (t, J = 3.76, 1H, CH), 7.05-7.60 (m, 7H, ArH), 7.90 (m, 2H, ArH)
3b	3150, 1730, 1700, 1635, 1600, 1580, 1500, 1450, 1380, 1200, 1180	3.30 (d, 2H, CH_2COOH), 3.80 (s, 3H, OCH_3), 4.55 (t, J = 3.91, 1H, CH), 7.12-7.52 (m, 7H, ArH), 7.93 (m, 2H, ArH)
3c	3150, 1730, 1700, 1635, 1600, 1580, 1500, 1380, 1325, 1250, 1210, 1160	2.42 (s, 3H, CH_3), 3.25 (m, 2H, CH_2COOH), 3.82 (s, 3H, OCH_3), 4.51 (t, J = 4.02, 1H, CH), 6.90 (d, J = 8.96, 2H, ArH), 7.35(d, J = 8.23, 4H, ArH), 7.92 (d, J = 8.97, 2H, ArH)
3d	3150, 1730, 1700, 1635, 1600, 1580, 1500, 1450, 1380, 1325, 1260, 1210	3.28 (d, J = 10.24, 2H, CH_2COOH), 3.85 (s, 3H, OCH_3), 4.51 (t, J = 4.36, 1H, CH), 6.90 (d, J = 8.98, 2H, ArH), 7.50 (d, J = 8.60, 2H, ArH), 7.61 (d, J = 8.71, 2H, ArH), 7.90 (d, J = 8.98, 2H, ArH)
3e	3150, 1730, 1700, 1635, 1580, 1520, 1450, 1380, 1325, 1210	3.15 (d, J = 7.80, 2H, CH_2COOH), 3.85 (s, 3H, OCH_3), 4.15 (t, J = 5.78, 1H, CH), 6.93 (d, J = 8.78, 2H, ArH), 7.48~7.60 (m, 5H, ArH), 7.93 (d, J = 8.79, 2H, ArH)

Downloaded At: 19:25 26 January 2011

HPLC was used to optimize the microwave-induced reaction time. For example, the reaction between N-benzoyl-N'-(*o*-tolyl)-thiourea (**1a**) and maleic anhydride was monitored by HPLC by sampling every 10 min. After *ca* 40 min, the conversion of **1a** reached a plateau (94%). In contrast, by using conventional heating, as long as 36 h were needed to afford the desired compound in comparable yield. A 54-fold enhancement in reaction rate was observed. The same procedure led to five 3-aryl-2-acylimino-5-carboxymethyl-4- thiazolidones (**3a-3e**, *Table 1*).

EXPERIMENTAL SECTION

All reactions were performed with the apparatus described previously.[10] The microwave unit consists of microwave source, waveguide, circulator, water load, power detector and multimode cavity. Microwave power generated with magnetron (operating frequency: 2450 MHz) is regulated from 0–1000 W by an infinitely variable power supply. The reagents and solvents are commercially available except for **1**, which was prepared according to the literature procedure and was obtained in satisfactory yields.[11] Melting points were determined on a X-4 micro-melting point apparatus and are uncorrected. IR spectra (KBr pellets) were recorded on a Nicolet Nexus 470 spectrophotometer. ^{1}H NMR spectra were recorded on Bruker AM 500 (500MHz) spectrometer in $CDCl_3$ or acetone-d_6 with TMS as an internal standard. Elemental analysis was performed on an Italian Mod. 1106 analyzer.

Downloaded At: 19:25 26 January 2011

MW-Assisted Synthesis of 3-Substituted-2-acylimino-4-thiazolidones (2). General Procedure.- A mixture of N-aroyl-N'-arylureas (2 mmol), ethyl bromoacetate (0.40 g, 2.4 mmol) and anhydrous NaOAc (0.20g, 2.4 mmol) in 5 mL of absolute ethanol was irradiated (200 W) for an optimized time (*Table 1*). On completion of the reaction (monitored by TLC), the mixture was cooled in an ice bath and precipitates thus obtained were collected by filtration. The filtrate was then diluted with 5 mL of cold water to obtain another portion of product. The combined crude products were washed with cold water, dried and recrystallized from 95% ethanol to give pure products as white solids.

MW-Assisted Synthesis of 3-Substituted-2-acylimino-5-carboxymethyl-4-thiazolidones (3). General Procedure.- A suspension of a mixture of N-aroyl-N'-arylureas (2 mmol) and maleic anhydride (0.39 g, 4 mmol) in chlorobenzene (5 mL) containing NMP (1 mL) was subjected to microwave irradiation (200 W). The suspension became homogeneous after a few minutes and the product separated out subsequently as the reaction progressed. After the reaction time indicated in *Table 2* (determined by HPLC), the slurry thus obtained was wished with water and the chlorobenzene was removed under vacuum. The crude residue was washed with water, dried and recrystallized from 95% ethanol to afforded pure product as white solid.

Acknowledgments.- Financial support for this project from the Shanghai Education Committee is gratefully acknowledged.

REFERENCES

1. K. Ishimitsu, H. Imagawa, T. Yamada, M. Matsuda and Y. Kitagawa, *WO* 8800943 (1988); *Chem. Abstr.*, **109**, 54764 (1988).

2. D. H. Boschelli and D. T. Connor, *US* 5143927 (1992); *Chem. Abstr.*, **118**, 22244 (1993).

3. a) S. H. El-Feky and Z. K. Abd El-Samii, *J. Chem. Technol. Biotechnol.*, **51**, 61 (1991); b) S. H. El-Feky, *Pharmazie*, **48**, 894 (1993); c) N. Ergenc and G. Capan, *Farmaco*, **49**, 133 (1994); d) N. Karali and A. Gursoy, *Farmaco*, **49**, 819 (1994).

4. R. Lakhan, P. N. Bhargava and S. Prakash, *J. Nepal Chem. Soc.*, **1**, 51 (1981); *Chem. Abstr.*, **103**, 136976 (1985).

5. J. M. Cox, J. M. Clough, N. J. Barnes, D. P. J. Pearson, I. R. Matthews, S. K. Vohra, S. C. Smith, G. Mitchell and R. A. Barber, *WO* 9533719 (1995); *Chem. Abstr.*, **124**, 261022 (1996).

6. D. Wobig, *Ann.*, **4**, 415 (1992).

7. For recent reviews, see: a) R. S. Varma, *Green Chem.*, **1**, 43 (1999); b) N. Elander, J. R. Jones, S. Y. Lu and S. Stone-Elander, *Chem. Soc. Rev.*, **29**, 239 (2000); c) P. Lidström, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, **57**, 9225 (2001); d) M. Larhed and A. Hallberg, *Drug Discovery Today*, **6**, 406 (2001); e) M. Larhed, C. Moberg and A. Hallberg, *Acc. Chem. Res.*, **35**, 717 (2002); f) R. S. Varma, in "*Microwaves: Theory and Application in Material processesing IV*", ed. D. E. Clark, W. H. Sutton and D. A. Lewis, American Ceramics Society, Westerville, OH, 1997. g) R. S. Varma, "*Advances in Green Chemistry: Chemical Syntheses Using Microwave Irradiation*", Kavitha Printers, Bangalore, India, 2002.

8. a) M. Kidwai and R. Kumar, *Gazz. Chim. Ital.*, **127**, 263 (1997); b) J. Azizian, A. V. Morady, K. Jadidi, M. Mehrdad and Y. Sarrafi, *Synth. Commun.*, **30**, 537 (2000).

9. T. Dong, P. Zhou, G. Jin, G. Wu and Y. Jia, *Fudan Xuebao, Ziran Kexueban*, **32**, 287 (1993); *Chem. Abstr.*, **121**, 108597 (1994).

10. Y. Peng, G. Song and X. Qian, *Synth. Commun.*, **31**, 1927 (2001).

11. a) W. P. Reeves, A. Simmons, J. A. Rudis and T. C. Bothwell, *Synth.Commun.*, **11**, 781 (1981); b) J. S. Upadhyaya and P. K. Srivastava, *J. Indian Chem. Soc.*, **59**, 767 (1982); c) K. A. Gupta, A. K. Saxena and P. C. Jain, *Indian J. Chem., Sect. B*, **21B**, 228 (1982).

****

Downloaded At: 19:25 26 January 2011