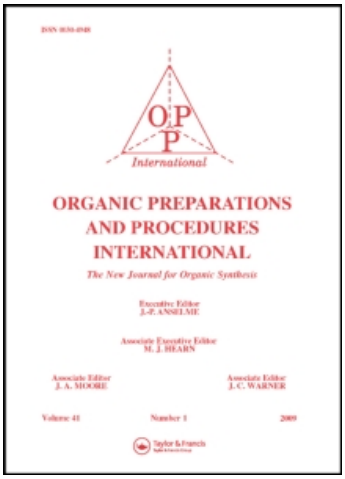
This article was downloaded by:
On: *27 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



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

SIMPLIFIED CONDITION FOR SYNTHESIS OF CURCUMIN I AND OTHER CURCUMINOIDS

K. V. D. Babu[a]; K. N. Rajasekharan[a]
[a] Department of Chemistry, University of Kerala, Trivandrum, Kerala, India

To cite this Article Babu, K. V. D. and Rajasekharan, K. N.(1994) 'SIMPLIFIED CONDITION FOR SYNTHESIS OF CURCUMIN I AND OTHER CURCUMINOIDS', Organic Preparations and Procedures International, 26: 6, 674 — 677
To link to this Article: DOI: 10.1080/00304949409458165
URL: http://dx.doi.org/10.1080/00304949409458165

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.

REFERENCES

1. J. W. Wheeler, S. L. Evans, M. S. Blum, H. H. V. Velthius and J. M. F. de Camargo, *Tetrahedron Lett.*, 4029 (**1976**).

2. a) W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, **43**, 378 (1978); **44**, 2169 (1979); b) K. Mori and S. Senda, *Tetrahedron*, **41**, 541 (1985); c) T. Katsuki and M.Yamaguchi, *Tetrahedron Lett.*, **28**, 651 (1987); d) R. Bernardi and D. Ghiringhelli, *Synthesis*, 938 (**1989**); e) K. Narasaka and Y. Ukagi, *Chemistry Lett.*, 81 (**1986**); f) T. Ibuka, M. Tanaka, S. Nishii and Y. Yamamoto, *J. Am. Chem. Soc.*, **111**, 4864 (1989); g) S. K. Kang, Y. W. Park, D. H. Lee, H. S. Sim and J. H. Jeon, *Tetrahedron: Asymmetry*, **3**, 705 (1992).

3. M. J. Wu, C. C. Wu and P. C. Lee, *Tetrahedron Lett.*, **33**, 2547 (1992).

4. M. J. Wu and J. Y.Yeh, *Tetrahedron*, **50**, 1073 (1994).

5 D. A. Evans, C. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, **110**, 1238 (1988).

6. a) P. A. Bartlett, D. P. Richardson and J. Myerson, *Tetrahedron*, **40**, 2317 (1984); b) H.-S. Moon, N. E. Schore and M. Kurth, *J. Org. Chem*, **57**, 6088 (1992).

7. The amount of $TiCl_4$ (1.3 equiv.) was insufficient to promote these conjugate additions to completion.

8. M. Kawashima, T. Sato and T. Fujisawa, *Tetrahedron*, **45**, 403 (1989).

Downloaded At: 08:57 27 January 2011

****

SIMPLIFIED CONDITION FOR SYNTHESIS OF CURCUMIN I AND OTHER CURCUMINOIDS

Submitted by (03/29/94)

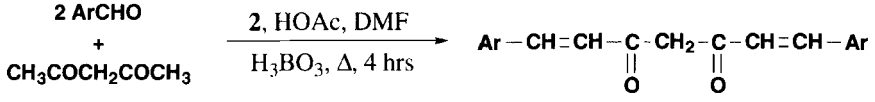
K. V. D. Babu and K. N. Rajasekharan*

Department of Chemistry, University of Kerala
Trivandrum 695581, Kerala, INDIA

Curcumin I (**1a**), the yellow pigment of turmeric exhibits a variety of pharmacological properties including recently reported antitumour[1] and anticancer[2] properties. It has also been evaluated as a photodynamic agent useful in the destruction of bacteria[3] and tumor cells.[4] In connection with some of these studies we required several curcuminoids. A practical route for curcumin synthesis has been devised by Pabon.[5] Kashima[6] *et al.* have also synthesised curcumin using 2,3,5-trimethylisoxazolium salt as the starting material. Synthesis of curcumin has also been described in the patent literature.[7]

Generally these syntheses[5,7] feature the masking of the reactive methylene group of acetylacetone by complexation with boric oxide, followed by reaction with vanillin. Along with boric oxide, alkyl borate esters can also be used. We now report operationally much simpler conditions for the synthesis of curcuminoids.

Vanillin, acetylacetone and boric acid in dry N,N-dimethylformamide was treated with a small amount of 1,2,3,4-tetrahydroquinoline (**2**) and glacial acetic acid. Heating and work up as described in the experimental afforded curcumin I as orange yellow powder in 78% yield. The product was found to be fairly pure (tlc, hplc, nmr: impurities less than 2%). Dimethyl sulfoxide could also be used as a solvent but others like acetone, ethanol and acetonitrile did not work. We found that even though boric oxide could be employed, the use of the cheaper boric acid generally resulted in a



(1)

1a, Ar = 4-Hydroxy-3-methoxyphenyl; **1b**, Ar = 2-Hydroxyphenyl
1c, Ar = 4-*N,N*-Dimethylaminophenyl; **1d**, Ar = 4-Hydroxyphenyl
1e, Ar = 3,4-Dimethoxyphenyl; **1f**, Ar = 3,4-Methylenedioxyphenyl
1g, Ar = 4-Methoxyphenyl

Downloaded At: 08:57 27 January 2011

better yield. Several other bases such as morpholine, piperidine, triethylamine, *n*-butylamine, pyridine and *N*-ethylaniline were screened as a reaction promoter. We observed that the use of 1,2,3,4-tetrahydroquinoline resulted in a cleaner product and much higher yields. Morpholine appeared to be the next best choice. In contrast to the slow addition of *n*-butylamine recommended in Pabon's method, here the amine in acetic acid was added in one lot. The omission of acetic acid drastically reduced the yield and purity of the product. The method was found to be suitable for the preparation of a variety of curcuminoids (**1a-1g**). The yields were generally good. In addition, the excellent purity of the crude products and the short reaction time are other noteworthy features of the present method.

EXPERIMENTAL SECTION

Commercial reagents and solvents were from E. Merck (India) and Fluka. ^{1}H NMR and Mass Spectra were run on Varian EM-390 and JEOL JMS D-300 spectrometers. HPLC was done on a Shimadzu LC-6A system using C18 Shimpack ODS analytical column and methanol as solvent. Melting points are uncorrected and element analysis was done at Central Drug Research Institute, India. TLC was done on Eastman chromatogram plastic backed silica gel sheets using ethyl acetate-petroleum ether mixtures.

Typical Procedure.-To a solution of vanillin (1.53 g, 0.01 mol) and acetylacetone (0.51 mL, 0.005 mol) in dry N,N-dimethylformamide (1 mL) was added boric acid (1 g) and the mixture was heated on a water bath for 5 min. Then a mixture of 1,2,3,4-tetrahydroquinoline (0.1 mL) and glacial acetic

acid (0.3 mL) in N,N-dimethylformamide (1 mL) was added and heating was continued for 4 hrs over a water bath. After cooling, acetic acid (20%; 50 mL) was added with vigorous stirring. The orange yellow mixture containing the precipitated curcumin was further stirred for 1 hr; the solid was collected, washed with water and air dried to afford curcumin I [1,7-*bis*-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], (1.45 g, 78%), mp. 172-175°. Further purification was performed by dry column chromatography using silica gel (120-200 mesh) eluted with chloroform (recovery 80%), mp. 182-184° (lit.[8] yield, 78%; mp. 184-186°); ^{1}H NMR ($CDCl_3$): δ 3.91 (6H, s, 2xOMe), 5.96 (1H, s, 4-H), 6.66 (2H, d, *J* = 16 Hz, 2,6-H), 6.86 (2H, d, *J* = 8 Hz, 5-ArH), 7.16 (2H, dd, *J* = 2 Hz and 8 Hz, 6-ArH), 7.3 (2H, d, *J* = 2 Hz, 2-ArH), 7.58 (2H, d, *J* = 16 Hz, 1,7-H); M^+: 368.

Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.46; H, 5.47. Found: C, 68.32; H, 5.37

The following compounds were synthesized as above:

1,7-*bis*-(2-Hydroxyphenyl)-1,6-heptadiene-3,5-dione (**1b**), mp. 163-164°, 73% yield; ^{1}H NMR (DMSO-d_6): δ 6.00, (1H, s, 4-H), 6.70 (2H, d, *J* = 16 Hz, 2,6-H), 6.86 (2H, d, *J* = 3 Hz, 3-ArH), 7.32 (4H, dd, *J* = 3 and 6 Hz, 4,5-ArH), 7.58 (2H, d, *J* = 16 Hz, 1,7-H), 7.80 (2H, d, *J* = 6 Hz, 6-ArH) 10.10 (2H, s, Ar-OH); M^+: 308.

Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H 5.32. Found: C, 74.18; H, 5.23

1,7-*bis*-(4-N,N-Dimethylaminophenyl)-1,6-heptadiene-3,5-dione (**1c**), mp. 210-212°, 82% yield (lit.[5] yield, 36%; mp. 206-207°); ^{1}H NMR ($CDCl_3$): δ 3.00 (12H, s, N-CH_3), 5.70 (1H, s, 4-H), 6.41 (2H, d, *J* = 16 Hz, 2,6-H), 6.71 (4H, d, *J* = 8 Hz, 3,5-ArH), 7.50 (4H, d, *J* = 8 Hz, 2,6-ArH), 7.70 (2H, d, *J* = 16 Hz, 1,7-H); M^+: 362.

Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23. Found: C, 76.05; H, 7.18

Curcumin II [1,7-*bis*-(4-Hydroxyphenyl)-1,6-heptadiene-3,5-dione] (**1d**), mp. 220-224°, 70% yield (lit.[5] mp. 224-226°, 68% yield); ^{1}H NMR (DMSO-d_6): δ 5.90 (1H, s, 4-H), 6.62 (2H, d, *J* = 16 Hz, 2,6-H), 6.90 (4H, d, *J* = 8 Hz, 3,5-ArH), 7.54 (4H, d, *J* = 8 Hz, 2,6-ArH), 7.60 (2H, d, *J* = 16 Hz, 1,7-H), 9.90 (2H, s, Ar-OH); M+: 308.

Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 74.21; H, 5.08

1,7-*bis*-(3,4-Dimethoxyphenyl)-1,6-heptadiene-3,5-dione (**1e**), mp. 135-138° 55% yield (lit.[8] mp. 137-138°, 73% yield); ^{1}H NMR ($CDCl_3$): δ 3.90 (12H, s, 4xOMe), 5.80 (1H, s, 4-H), 6.46 (2H, d, *J* = 16 Hz, 2,6-H), 6.84 (2H, d, *J* = 8 Hz, 5-ArH), 7.06 (2H, d, *J* = 2 Hz, 2-ArH), 7.12 (2H, dd, *J* = 2 and 8 Hz, 6-ArH), 7.58 (2H, d, *J* = 16 Hz, 1,7-H); M^+: 396.

Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.71; H, 5.81

1,7-*bis*-(3,4-Methylenedioxyphenyl)-1,6-heptadiene-3,5-dione (**1f**), mp. 185-190°, 56% yield (lit.[5] mp. 198-199°, 59%); ^{1}H NMR ($CDCl_3$): δ 5.7 (1H, s, 4-H), 5.92 (4H, s, -OCH_2O-), 6.66 (2H, d, *J* = 16 Hz, 2,6-H), 6.86 (2H, d, *J* = 8 Hz, 5-ArH), 7.16 (2H, dd, *J* = 2 and 8 Hz, 6-ArH), 7.31 (2H, d, *J* = 2 Hz, 2-ArH), 7.58 (2H, d, *J* = 16 Hz, 1,7-H); M^+: 364.

Anal. Calcd for $C_{21}H_{16}O_6$: C, 69.22; H, 4.43. Found: C, 69.31; H, 4.29

1,7-*bis*-(4-Methoxyphenyl)-1,6-heptadiene-3,5-dione (**1g**), mp. 166-168° 53% yield (lit.[5] mp. 164-168°, 57% yield); ^{1}H NMR ($CDCl_3$): δ 3.92 (6H, s, OCH_3), 5.80 (1H, s, 4-H), 6.41 (2H, d, *J* = 16 Hz,

Downloaded At: 08:57 27 January 2011

2,6-H), 6.72 (4H, d, J = 8 Hz, 3,5-ArH), 7.3 (4H, d, J = 8 Hz, 2,6-ArH), 7.6 (2H, d, J = 16 Hz, 1,7-H); M^+: 336.

Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.97; H, 5.99. Found: C, 74.87; H, 6.14

Acknowledgement.- K. V. D. B. acknowledges CSIR (Government of India) for a fellowship and is thankful to Dr. George Thomas, RRL (CSIR), Trivandrum for HPLC analysis.

REFERENCES

1. R. Kuttan, P. Bhanumathy, K. Nirmala and M. C. George, *Cancer Lett.*, **29**, 197 (1985).

2. K. K. Soudamini and R. Kuttan, *J. Ethnopharmacol.*, **27**, 227 (1989).

3. T.A. Dahl, W. M. McGowan, M. A. Shand and V. S. Srinivasan, *Arch. Microbiol.*, **151**, 183 (1989).

4. S. Pervaiz, H. Skiles, K. N. Rajasekharan and K. S. Gulliya, *Abstract of 81st Annual Meeting of Amer. Assoc. Cancer Research*, Washington. 1990.

5. H. J. J. Pabon, *Rec. Trav. Chim. Pays-Bas*, **83**, 379 (1964).

6. C. Kashima, N. Mukai, E. F. De Rose, Y. Tsuda and Y. Omote, *Heterocycles*, **7**, 241 (1977).

7. E. Graf, Ger. Patent, 1,280,849 (1968); *Chem. Abstr.*, **70**, 37475e (1969).

8. P. J. Roughley and D. A. Whiting, *J. Chem. Soc. Perkin Trans. 1*, 2379 (**1973**).

Downloaded At: 08:57 27 January 2011

****

A HIGH-YIELD SYNTHESIS OF 3-PENTADECYLPYRIDINE

Submitted by (04/04/94)

Wayne M. Stalick* and Joseph H. Murray

Department of Chemistry, George Mason University
Fairfax, VA 22030

Long chain and fused-ring heteroaromatic compounds which have been identified as major constituents in oil shale and lower rank bituminous and lignite coals[1] are believed to play a major role in their liquefaction properties; however, their influence during thermolyses is unknown.[2] It is estimated that nitrogen-containing compounds constitute 40% of the shale crude and GC/MS analyses shows a preponderance of these to be alkylpyridines.[3] A number of studies have shown that model compounds can give good extrapolations to the natural products under pyrolysis conditions; however,