Chemistry of Natural Compounds, Vol. 41, No. 4, 2005

MICROWAVE-ASSISTED MINUTES SYNTHESIS OF BIOACTIVE PHENYLBUTANOIDS OCCURRING IN *Zingiber cassumunar*

B. P. Joshi, N. P. Singh, A. Sharma, and A. K. Sinha

UDC 547.53

*Microwave-assisted condensation of benzaldehyde (**3a,b**) with acetone in aqueous sodium hydroxide adsorbed on basic alumina provides phenylbutenone (**4a–4b**) in 68–71% yield within 4 min, which upon further reduction with sodium borohydride and basic alumina gives phenylbutenol (**5a,b**) in 91–94% yield within 2 min. Dehydration of **5** with anhydrous copper (II) sulfate gives phenylbutadiene (**1a,b**), a metabolite of* Zingiber cassumunar, *within 3 min in 42–48% yield, respectively. All the steps involve environmental friendly solvents and reagents, mild reaction conditions, and overall formation of product **1a,b** from **3a,b** in 34–38% yield within 9 min under microwave irradiation.*

Key words: microwave, phenylbutanoids, phenylbutadiene, *Zingiber cassumunar*.

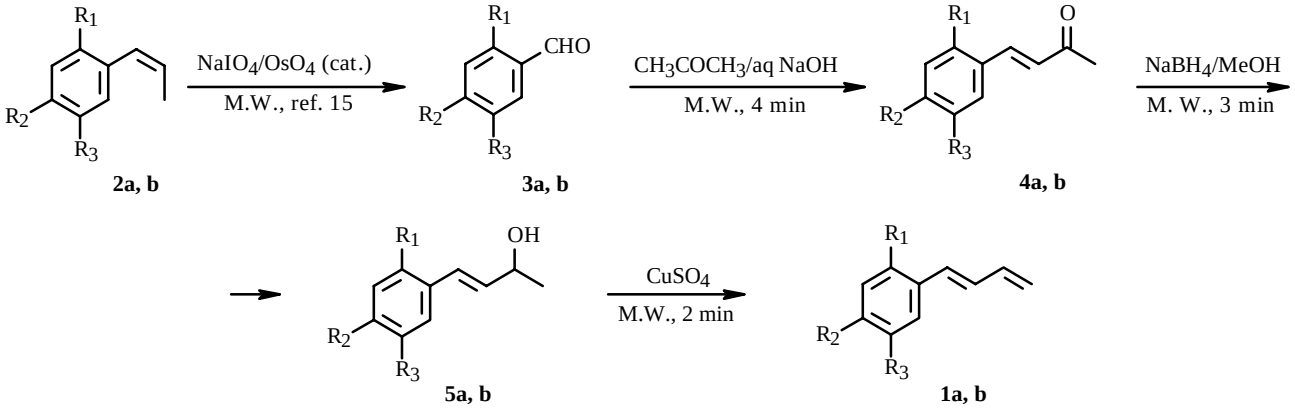
A large number of methoxylated phenylbutanoids have been isolated form plants sources [1] that exhibit promising biological activities [2], including modifiers in flavor and perfumery formulations [3]. Moreover, these phenylbutanoids are also employed as simple starting materials for synthesis of various organic compounds, including natural products [4]. E-4-(2′,4′,5′-trimethoxyphenyl)buta-1,3-diene (**1a**) and (E)-4-(3′,4′-dimethoxyphenyl)but-1-ene (**1b**), metabolites of *Zingiber cassumunar* [5], are two such important phenylbutenes, which are known to possess numerous pharmacological activities such as anti-inflammatory [6], antioxidant [7], insecticidal [8], and, most importantly, hypolipidemic [9] activities. However, both **1a** and **1b** are isolated together in minute amounts and their separation from each other is reported to be difficult even by preparative TLC [5]. There are a few methods reported for the synthesis of these all important **1a** and **1b** which include multistep synthesis employing the Grignard [4] reaction, Friedel-Crafts [10] reaction, Wittig [5] reaction, and aldol condensation [11] etc. However, maintenance of anhydrous conditions, use of expensive and highly acidic catalyst, and prolonged reaction times affects the viability of all these methods. Furthermore, use of a large amount of solvents in conventional methods is neither economically nor environmentally benign. Microwave induced Organic Reaction Enhancement [12] (MORE chemistry) has created a lot of interest in the organic chemistry due to less solvent consumption, higher yields, more selectivity, mild reaction conditions, easier work-up, and rapid synthesis as compared to conventional heating. Furthermore, "dry media" synthesis using inorganic solid supports coupled with microwave irradiation have attracted significant interest worldwide, and many such microwave-assisted synthesis with solid mineral supports [13] such as alumina, silica gel, and clays have been reported with higher selectivity, yield, and purity as compared to the traditional methods. We, in this regard, report a microwave-mediated simple and efficient protocol for the synthesis of natural bioactive phenylbutanoids **1a** and **1b** in three steps as outlined in Scheme 1.

As an endeavor towards synthesis of rare bioactive molecules [14] employing microwave irradiation, we initially decided to synthesize **1a**, taking 2,4,5-trimethoxybenzaldehyde (**3a**) as the starting compound, which itself was obtained from microwave-assisted oxidation of abundantly available toxic β-asarone [15] of *Acorus calamus*. In the first step, **3a** was condensed with acetone in aqueous NaOH solution under microwave irradiation at 900 w for 2–3 min; however, phenylbutenone (**4a**) was obtained in a mere 42% yield only and the rest remained the unreacted **3a**. There was no increase in the yield of the product on further irradiation of the reaction mixture. During the reaction, we realized that there was tremendous evaporation of acetone going on inside the reactor, which might have adversely affected the yield of **4a**. Consequently, the reaction mixture was

Natural Plant Products Division, Institute of Himalayan Bioresource Technology, Palampur (H.P.), 176061, India, fax 91 1894 230433, e-mail: aksinha08@rediffmail.com. Published in Khimiya Prirodnykh Soedinenii, No. 4, pp. 300-302, July-August, 2005. Original article submitted February 10, 2005.

 0009-3130/05/4104-0370

irradiated at varying low power levels (306 W to 540 W) which, though it checked evaporation of acetone to a large extent, was insufficient for the progress of the reaction. All this prompted us to perform the above reactions in the solid phase, which we believed would hold back acetone efficiently and check its evaporation.



2a, b **3a, b** **4a, b** **5a, b** **1a, b**

a: $R_1 = R_2 = R_3 = OMe$; **b:** $R_1 = H$, $R_2 = R_3 = OMe$

Hence, we performed another condensation reaction wherein **3a** is reacted with acetone/aq. NaOH under phase transfer conditions using cetyltrimethylammonium chloride in conjugation with basic alumina as a solid support [13, 16]. Interestingly, the above reaction under microwave irradiation at 630 w for 4 min enhanced the yield of pure ketone **4a** up to 68% yield. However, the same reaction under stirring for 5 h at room temperature provided **4a** in 44% yield only, which emphatically manifests the advantage of microwave irradiation. In the next step, ketone **4a** upon treatment with sodium borohydride adsorbed on basic alumina gave 4-(2′,4′,5′-trimethoxyphenyl)but-3-en-2-ol (**5a**) as a light yellow solid in 91% yield under microwave irradiation for 2 min while the same reaction under conventional conditions required 7 h to provide **5a** in 88% yield. The final step involving acid-catalyzed dehydration of alcohol **5a** remained crucial as a variety of reported dehydrating agents [17] such as phosphoryl chloride/pyridine, *p*-toluenesulfonic acid, thionyl chloride/triethylamine, triphenylphosphine, oxalic acid, and dilute H_2SO_4 are impregnated with drawbacks such as maintenance of anhydrous conditions or poor yield due to polymerization of highly conjugated product (**5a**). Recently, dehydration of alkanol derivatives with anhydrous copper (II) sulfate [18] is reported as a clean and better yielding process, which encouraged us to investigate this dehydrating agent in our case under microwave irradiation. As a result, dehydration of **5a** with anhydrous copper (II) sulfate was performed under microwave irradiation, which provided **1a** in 42% yield within 3 min with some side products, and the yield did not improve either on increasing the reaction time or the amount of the reagent. Inspite of the moderate yield of the dehydrated product (**1a**) in the above case, the method appeared meritorious in that no strong acidic catalyst (i.e., copper (II) sulfate) is required in contrast to the reported [11] methods which required strong acids as harsh as H_2SO_4 and obtained yields in the range of 20%. Moreover, mere filtration was all that was required for work up of the reaction in our case, which is crucial from the industrial point of view. Having achieved success with **1a**, the same methodology was extended for the synthesis of another bioactive phenylbutanoid **1b** utilizing commercially available **3b** as the starting compound, and the product **1b** was obtained in overall 38% yield and the whole process is completed within 9 min. This is a remarkable improvement in the yield and reaction time as there are reports of formation of **1b** from **3b** following the same synthetic route as ours under conventional conditions in a mere 10% yield in hours.

In conclusion, this microwave-assisted three-step synthesis of **1a,b** starting from **3a,b** is completed within 9 min involving environmental friendly solvents and mild reaction conditions, which makes this method an attractive alternative to the reported classical methods. In addition, using this method, we can greatly increase the yield of products and reduce the reaction cost as generally encountered in reported [4, 5, 10, 11] protocols.

EXPERIMENTAL

Melting points were determined with a Mettler FP80 micromelting point apparatus and are uncorrected. ^1H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded in $CDCl_3$ on a Bruker Avance-300 spectrometer. A Kenstar domestic microwave oven (2450 MHz, 900 Watts) was used for all the reactions.

General Method for Microwave-Assisted Synthesis of Phenylbutenone (4a,b). A mixture of benzaldehyde (**3a** or **3b**) (0.02 mol), acetone (20 mL), and 10% NaOH (30 mL), cetyltrimethylammonium chloride (0.1–0.15 g), and basic alumina (2 gm) was taken in a 100 mL Erlenmeyer flask fitted with a loose funnel at the top. The flask was shaken well, placed inside a microwave oven, and irradiated for 4 min with an interval of 2–3 sec after every 40 sec of irradiation. The reaction mixture was poured into ice cold water, acidified with 5% HCl, and extracted with dichloromethane (3 × 10 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4. The obtained yellow viscous liquid on evaporation was chromatographed on a silica gel column using hexane–ethyl acetate mixture with an increasing proportion of ethyl acetate up to 40% to afford 4-(2′,4′,5′-trimethoxyphenyl)but-3-en-2-one (**4a**) or 4-(3′,4′-dimethoxyphenyl)but-3-en-2-one (**4b**) as a pure compound.

Compound 4a: 68%, mp 106–108°C.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 7.88 (1H, d, J = 15.0, H-4), 7.06 (1H, s, H-6′), 6.52 (1H, s, H-3′), 6.63 (1H, d, J = 15.0, H-3), 3.96 (3H, s, 2′-OCH_3), 3.91 (3H, s, 4′-OCH_3), 3.88 (3H, s, 5′-OCH_3), 2.40 (3H, s, H-1).

^{13}C NMR ($CDCl_3$, δ): 199.5, 154.3, 152.9, 143.8, 138.8, 125.7, 115.7, 110.5, 97.1, 56.8, 56.7, 56.4, 27.3.

Compound 4b: 71%, mp 83–84°C.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 7.14 (1H, d, J = 16.1, H-4), 6.77 (2H, m, H-2′ and H-5′), 6.53 (1H, d, J = 8.1, H-6′), 6.28 (1H, d, J = 16.1, H-3), 3.54 (3H, s, OCH_3), 3.50 (3H, s, OCH_3), 2.01 (3H, s, H-1).

^{13}C NMR ($CDCl_3$, δ): 197.8, 151.1, 149.1, 143.2, 127.1, 124.9, 122.8, 111.0, 109.3, 55.6, 27.0.

General Method for Microwave-Assisted Synthesis of Phenylbutenol (5a,b). Ketone (**4a** or **4b**) (0.004 mol), sodium borohydride (0.005 mol), and basic alumina (1 gm) in methanol (3 mL) were suspended in a 100 ml Erlenmeyer flask and the mixture was irradiated under microwave for 2 min until disappearance of the starting material based upon TLC analysis. The mixture was cooled and washed with dichloromethane (3 × 10 mL) and filtered. The organic layer was washed with water and dried over anhydrous Na_2SO_4. The residue obtained on evaporation of the filtrate was chromatographed on a neutral alumina column using hexane-ethyl acetate mixture with an increasing proportion of ethyl acetate up to 60% to afford 4-(2′,4′,5′-trimethoxyphenyl)but-3-en-2-ol (**5a**) or 4-(3′,4′-dimethoxyphenyl)but-3-en-2-ol (**5b**) as a pure compound.

Compound 5a: 91%, mp 64–65°C.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 6.96 (1H, s, H-6′), 6.84 (1H, d, J = 15.9, H-4), 6.49 (1H, s, H-3′), 6.63 (1H, dd, J = 15.9 and 6.1, H-3), 4.47 (1H, m, H-2), 3.96 (3H, s, 2′-OCH_3), 3.91 (3H, s, 4′-OCH_3), 3.88 (3H, s, 5′-OCH_3), 1.36 (3H, d, J = 6.1, H-1).

^{13}C NMR ($CDCl_3$, δ): 151.8, 149.9, 143.8, 132.3, 124.7, 118.1, 110.2, 98.4, 69.9, 56.8, 56.5, 56.4, 22.8.

Compound 5b: 94%, liquid.

^{1}H NMR ($CDCl_3$, δ, J/Hz): 6.92 (1H, d, J = 1.8, H-2′), 6.89 (1H, dd, J = 8.6 and J = 1.8, H-6′), 6.79 (1H, d, J = 8.6, H-5′), 6.47 (1H, d, J = 15.9, H-4), 6.12 (1H, dd, J = 15.9 and 6.1, H-3), 4.47 (1H, m, H-2), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 1.35 (3H, d, J = 6.1, H-1).

^{13}C NMR ($CDCl_3$, δ): 148.6, 147.9, 130.4, 128.3, 124.1, 121.3, 110.4, 109.5, 69.7, 55.4, 22.4.

General Method for Microwave-Assisted Synthesis of Phenylbutadiene (1a,b). Alcohol (**5a** or **5b**) (0.002 mol) and copper (II) sulfate (0.002 mol) in dioxane (2 mL) were suspended in a 100 ml Erlenmeyer flask and the mixture was irradiated under microwave for 2 min in parts till disappearance of the starting material based upon TLC analysis. On cooling, the mixture was washed with ethyl acetate (3 × 10 mL) and filtered. The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated and the obtained liquid was chromatographed on a silica gel column using hexane-ethyl acetate mixture with an increasing proportion of ethyl acetate up to 20% to afford a liquid which after recrystallization from methanol-water provided 4-(2′,4′,5′-trimethoxyphenyl)but-1,3-dien (**1a**) or 4-(3′,4′-dimethoxyphenyl) but-1,3-dien (**1b**) as a pure compound.

Compound 1a: 42%, mp 56–58°C.

^{1}H NMR (δ, J/Hz): 7.02 (1H, s, H-6′), 6.87 (1H, d, J = 16.0, H-4), 6.69 (1H, dd, J = 16.0 and 11.0, H-3), 6.53 (1H, dt, J = 16.0 and 11.0, H-2), 6.51 (1H, s, H-3′), 5.29 (1H, brd, J = 16.0, H-1a), 5.09 (1H, brd, J = 11.0, H-1b), 3.91 (3H, s, 2′-OCH_3), 3.89 (3H, s, 4′-OCH_3), 3.85 (3H, s, 5′-OCH_3).

^{13}C NMR ($CDCl_3$, δ): 152.0, 149.9, 143.7, 138.4, 128.4, 127.5, 118.1, 116.5, 109.5, 97.9, 57.1, 56.8, 56.4.

Compound 1b: 48 %, liquid.

^{1}H NMR (δ, J/Hz): 6.98–6.91 (3H, m, H-6′, H-5′ and H-2′), 6.87 (1H, s, H-5′), 6.71 (1H, d, J = 16.1, H-4), 6.51 (1H, dd, J = 16.1 and 12.2, H-3), 6.43 (1H, dt, J = 16.1 and 12.2, H-2), 5.29 (1H, brd, J = 16.1, H-1a), 5.11 (1H, brd, J = 12.2, H-1b), 3.92 (3H, s, OCH_3), 3.88 (3H, s, OCH_3).

^{13}C NMR ($CDCl_3$, δ): 149.2, 148.8, 136.4, 128.5, 127.5, 125.1, 124.8,116.2, 110.9, 110.1, 55.7.

ACKNOWLEDGMENT

Two of us (BPJ and AS) are indebted to CSIR, Delhi for the award of the SRF. The authors gratefully acknowledge the Director of I.H.B.T., Palampur for his kind cooperation and encouragement.

REFERENCES

1. J. B. Harborne and H. Baxter, *Phytochemical Dictionary: A Handbook of Bioactive Compounds from Plants*, Taylor & Francis Ltd., Washington DC (1993); T. Masuda and A. Jitoe, *Phytochemistry*, **39**, 459 (1995); M. Toshiya, A. Tadao, Y. Sigetomo, and T. Yoshio, *Phytochemistry*, **50**, 163 (1999).
2. M. Habsah, M. Amran, M. M. Mackeen, N. H. Lajis, H. Kikuzaki, N. Nakatani, A. A Rahman, and G. A. M. Ali, *J. Ethnopharma.*, **72**, 403 (2000).
3. A. Steffen, *Perfume and Flavor Chemicals (Aroma Chemicals)*, **1** and **2**, Allured Publishing Corporation, IL, USA (1994).
4. J. S. Meek, B. T. Poon, R. T. Merrow, and S. J. Cristol, *J. Am. Chem. Soc.*, **74**, 2669 (1952); I. Mori and Y. Nakachi, *Tetrahedron Lett.*, **26**, 2297 (1978); T. N. G. Row, H. R. Swamy, K. R. Acharya, V. Ramamurthy, K. Venkatesan, and C. N. R. Rao, *Tetrahedron Lett.*, **24**, 3263 (1983).
5. P. Tuntiwachwuttikul, O. Pancharoen, T. Jaipetch, and V. Reutrakul, *Phytochemistry*, **20**, 1164 (1981).
6. D. Kananapothi, P. Soparat, A. Panthong, P. Tuntiwachwuttikul, and V. Reutrakul, *Planta Med.*, **53**, 329 (1987).
7. A. Jitoe, T. Masuda, I. G. P. Tengah, D. N. Suprata, I. W. Gara, and N. Nakatani, *J. Agric. Food Chem.*, **40**, 1337 (1992).
8. B. W. Nugroho, B. Schwarz, V. Wray, and P. Proksh, *Phytochemistry*, **41**, 29 (1996).
9. A. Cruz, L. Garduno, M. Salazar, E. Martinez, F. Diaz, G. Chamorro, and J. Tamariz, *Med. Chem. Res.*, **10**, 587 (2001).
10. A. Cruz, L. Garduno, M. Salazar, E. Martinez, H. A. Jimenez-Vazquez, F. Diaz, G. Chamorro, and J. Tamariz, *Arzneim.-Forsch./Drug Res.*, **51**, 535 (2001).
11. J. Akiko, M. Toshiya, and N. Nobuji, *Phytochemistry*, **32**, 357 (1993).
12. L. Pelle, T. Jason, W. Bernard, and W. Jacob, *Tetrahedron*, **57**, 9225 (2001); M. Larhed, A. Hallberg, *Drug Discovery Today*, **6**, 406 (2001); G. Gopalakrishnan, N. D. P. Singh, V. Kasinath, M. S. R. Krishnan, R. Malathi, and S. S. Rajan, *Tetrahedron Lett.*, **42**, 6577 (2001); A. Sharma, B. P. Joshi, and A. K. Sinha, *Bull. Chem. Soc. Jpn.*, **77**, 2231 (2004); V. Pathania, A. Sharma, and A. K. Sinha, *Helv. Chim. Acta*, **88**, 811 (2005).
13. A. Y. Usyatinsky and Y. L. Khmelnitsky, *Tetrahedron Lett.*, **41**, 1863 (2000); B. P. Joshi, A. Sharma, and A. K. Sinha, *Tetrahedron*, **61**, 3075 (2005).
14. A. K. Sinha, B. P. Joshi, A. Sharma, J. K. Kumar, and V. K. Kaul, *Nat. Prod. Lett.*, **17**, 419 (2003); A. Sharma, B. P. Joshi, and A. K. Sinha, *Chem. Lett.*, **32**, 1186 (2003); A. K. Sinha, B. P. Joshi, and R. Dogra, U. S. Patent, **6**, 544, 390 (2003).
15. A. K. Sinha, B. P. Joshi, and R. Acharya, *Chem. Lett.*, **32**, 780 (2003).
16. J. Wang, Z. Liu, Y. Hu, B. Wei, and L. Bai, *Synth. Commun.*, **32**, 1607 (2002).
17. E. J. Synder, *J. Org. Chem.*, **37**, 1466 (1972); J. G. Cannon, C. D. True, J. P. Long, R. K. Bhatnagar, and P. Leonard, *J. Med. Chem.*, **32**, 2210 (1989); D. Francisco, C. Leticia, F. Rosa, T. Joaquin, L. Fernando, C. German, and M. Heber, *Org. Prep. Proced. Int.*, **23**, 133 (1991).
18. P. Janusz, L. Bozena, T. D. Alina, L. Barbara, W. Stanislaw, S. Danuta, P. Jacek, K. Roman, C. Jacek, S. Malgorzata, and C. Zdzislaw, *J. Med. Chem.*, **43**, 3671 (2000).