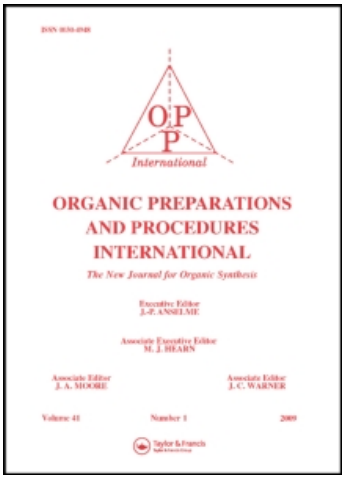


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# CONVENIENT MICROWAVE ASSISTED SYNTHESIS OF NATURALLY OCCURRING METHYL (*E*)-CINNAMATES

Rajesh P. Mahajan[a]; Shamkant L. Patil[a]; Raghao S. Mali[a]
[a] School of Chemical Sciences, North Maharashtra University, Jalgaon, INDIA

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# CONVENIENT MICROWAVE ASSISTED SYNTHESIS OF NATURALLY OCCURRING METHYL (*E*)-CINNAMATES

*Submitted by* (12/15/04) Rajesh P. Mahajan, Shamkant L. Patil* and Raghao S. Mali*

*School of Chemical Sciences, North Maharashtra University*
*Jalgaon - 425 001, INDIA*
*e-mail: rsmali@rediffmail.com; Fax No. + (91) 0257 2258403*



A large number of methyl cinnamates have been isolated from various plant sources. Thus, the parent methyl (*E*)-cinnamate (**3a**) has been isolated[1,2] from *Aragoa lucidula* and *Alpinia galanga,* while the methyl (*E*)-3,4-dimethoxycinnamate (**3b**) from the rhizomes[3] of *Solidago altissima* L. Methyl (*E*)-3,4,5-trimethoxycinnamate (**3c**) is reported from *Hedysarum polybotrys* HAND.-MAZZ.[4] Methyl (*E*)-sinapate (**3d**) has been isolated[5] from the heartwood of *Fagraea gracilipes.* Various methyl cinnamates are reported to possess interesting biological activities and have also been used as valuable building blocks for the synthesis of naturally occurring and biologically active compounds. Thus, methyl cinnamates (**3a-g, 3i, 3k**) have been used for the synthesis of propenamide alkaloids,[6] α- and β-truxillines,[7] quinolizidine alkaloids,[8] lactones,[9] indanes,[10] functionalised naphthalenes,[10] lignans,[10] combretastatin intermediates,[11] (±)-isodeoxypodophyllotoxin[12] and dihydrocinnamate[13] isolated from *Cordia alliodora* Oken.

In view of the considerable importance of methyl cinnamates, various methods have been developed for their synthesis. Methyl cinnamates have been synthesised from aromatic aldehydes mainly by a two-step sequence of reactions involving Knoevenagel condensation followed by esterification.[14] Another approach involves Heck reaction of halobenzenes or arene-diazonium salts.[15] A few of them have also been synthesised from aryl aldehydes using Reformatsky reaction.[16]

Methods involving microwave irradiations[17] have been frequently used in synthetic organic chemistry as these methods are efficient and provide the final products in high yield and in short time. Recently Splnella *et al.* have reported microwave accelerated Wittig reactions under solvent free conditions.[17a] We report here in a convenient, microwave assisted, general and high yield single step method for the synthesis of methyl cinnamates (**3a-k**) from readily available aldehydes **1a-k** (*Scheme 1*). Thus, benzaldehyde (**1a**) on reaction with phosphorane[18] (**2**) under microwave irradiation for 2 min provided the methyl (*E*)-cinnamate (**3a**) in 81% yield. When aldehydes (**1b-k**) were reacted with phosphorane (**2**) under microwave irradiation for 2-3 min the methyl cinnamates (**3b-k**) were obtained in 75-92% yield.


a) $R = R^1 = R^2 = R^3 = R^4 = H$
b) $R = R^3 = R^4 = H$, $R^1 = R^2 = OMe$
c) $R = R^4 = H$, $R^1 = R^2 = R^3 = OMe$
d) $R = R^4 = H$, $R^1 = R^3 = OMe$, $R^2 = OH$
e) $R = R^1 = R^3 = R^4 = H$, $R^2 = OMe$
f) $R = R^3 = R^4 = H$, $R^1 = OH$, $R^2 = OMe$
g) $R = R^3 = R^4 = H$, $R^1$–$R^2$ = O-$CH_2$-O
h) $R = OH$, $R^1 = R^2 = R^3 = R^4 = H$
i) $R = R^2 = OMe$, $R^1 = R^3 = R^4 = H$
j) $R = R^2 = R^4 = OMe$, $R^1 = R^3 = H$
k) $R = R^2 = R^3 = OMe$, $R^1 = R^4 = H$

**Scheme 1**

The stereochemistry of the methyl cinnamates was determined on the basis of $^1$H NMR spectroscopy. Thus, the olefinic α- and β-hydrogens in all the methyl cinnamates (**3a-g**) are observed as doublets ($J$ ~ 16 Hz) at δ ~ 6.30 and ~ 7.6 respectively. In case of methyl cinnamates (**3h-k**) having hydroxyl or methoxy group at C-2 position, the α- and β-hydrogens appeared as doublets ($J$ ~ 16Hz) at δ ~ 6.6 and ~ 8.0 respectively.

In conclusion, a stereoselective general method has been developed for the synthesis of methyl (*E*)-cinnamate by the Wittig reaction under microwave irradiation. The products are obtained under milder conditions and in very short time. The present method is very efficient and provides the title compounds in high yields.

**Table**. Methyl (*E*)-Cinnamates **3a-k**[a]

| Cmpd | Yield (%) | mp. (°C) | *lit.* mp. (°C) | Time[b] (min) | $^1$H NMR Data (δ) |
|---|---|---|---|---|---|
| **3a** | 81 | Colorless Thick liquid | 36[19] | 2 | c |
| **3b** | 75 | 68-69 | 68-69[20] | 3 | 3.73 (3H, s, OMe), 3.84 (6H, s, 2 x OMe), 6.24 (1H, d, $J$ = 16 Hz, CH=CHCO), 6.79 (1H, d, $J$ = 8 Hz, $C_5H$), 6.98 (1H,d, $J$ = 1. 5 Hz, $C_2H$), 7.06 (1H, dd, $J$ = 8 and 1.5 Hz, $C_6H$), 7.6 (1H, d, $J$ = 16 Hz, CH=CHCO) |
| **3c** | 79 | 90 | 91-91.5[4] | 3 | 3.81 (3H, s, OMe), 3.89 (9H, s, 3 x OMe), 6.36 (1H, d, $J$ = 16 Hz, CH=CHCO), 6.76 (2H, s, $C_2H$ and $C_6H$), 7.62 (1H, d, $J$ = 16 Hz, CH=CHCO) |
| **3d** | 80 | 87 | 88[21] | 3 | 3.80 (3H, s, OMe), 3.92 (6H, s, 2 x OMe), 5.81 (1H, s, exchangeable with $D_2O$, OH), 6.31 (1H, d, $J$ = 16 Hz, CH=CHCO), 6.77 (2H, s, $C_2H$ and $C_6H$), 7.61 (1H, d, $J$ = 16 Hz, CH=CHCO) |
| **3e** | 92 | 88-89 | 87-89[22] | 2 | 3.79 (3H, s, OMe), 3.83 (3H, s, OMe), 6.31 (1H, d, $J$ = 16 Hz, CH=CHCO), 6.90 (2H, d, $J$ = 8.8 Hz, $C_3H$ and $C_5H$), 7.47 (2H, d, $J$ = 8.8Hz, $C_2H$ and $C_6H$), 7.65 (1H, d, $J$ = 16Hz, CH=CHCO) |

**Table.** Continued...

| Cmpd | Yield (%) | mp. (°C) | *lit.* mp. (°C) | Time[b] (min) | $^1$H NMR Data (δ) |
|---|---|---|---|---|---|
| **3f** | 78 | 78 | 78-79[11] | 3 | 3.79 (3H, s, OMe), 3.92 (3H, s, OMe), 5.69 (1H, s, exchangeable with $D_2O$, OH), 6.29 (1H, d, *J* = 16.1 Hz, CH=CHCO), 6.84 (1H, d, *J* = 8.5 Hz, $C_5H$), 7.03 (1H, dd, *J* = 8.5 and 2.0 Hz, $C_6H$), 7.14 (1H, d, *J* = 2.0 Hz, $C_2H$), 7.60 (1H, d, *J* = 16.1 Hz, CH=CHCO) |
| **3g** | 87 | 137 | 138[6] | 2 | 3.79 (3H, s, OMe), 6.01 (2H, s, $OCH_2O$), 6.26 (1H, d, *J* = 15.8 Hz, CH=CHCO), 6.81 (1H, d, *J* = 7.9 Hz, $C_5H$), 7.03 (2H, m, $C_2H$ and $C_6H$), 7.60 (1H, d, *J* = 15.8 Hz, CH=CHCO) |
| **3h** | 82 | 137 | 136-137[15b] | 1 | 3.84 (3H, s, OMe), 6.65 (1H, d, *J* = 16.1 Hz, CH=CHCO), 6.74 (1H, s, exchangeable with $D_2O$, OH), 6.87 (1H, dd, *J* = 8.0 and 1.5 Hz, $C_3H$), 6.92 (1H, dt, *J* = 7.9 and 1.5 Hz, $C_5H$), 7.25 (1H, dt, *J* = 8.0 and 1.5 Hz, $C_4H$), 7.47 (1H, dd, *J* = 7.9 and 1.5 Hz, $C_6H$), 8.06 (1H, d, *J* = 16.1 Hz, CH=CHCO) |
| **3i** | 77 | 86 | 86.5-7[23] | 3 | 3.78 (3H, s, OMe), 3.83 (3H, s, OMe), 3.86 (3H, s, OMe), 6.43 (1H, d, *J* = 16.1 Hz, CH=CHCO), 6.45 (1H, d, *J* = 2.3 Hz, $C_3H$), 6.50 (1H, dd, *J* = 8.9 and 2.3 Hz, $C_5H$), 7.44 (1H, d, *J* = 8.9 Hz, $C_6H$), 7.91 (1H, d, *J* = 16.1 Hz, CH=CHCO) |
| **3j** | 78 | 139-141 | d | 3 | 3.81 (3H, s, OMe), 3.87 (3H, s, OMe), 3.90 (6H, s, 2 x OMe), 6.14 (2H, s, $C_3H$ and $C_5H$), 6.79 (1H, d, *J* = 16.4 Hz, CH=CHCO), 8.12 (1H, d, *J* = 16.4 Hz, CH=CHCO) |
| **3k** | 80 | 108 | 107-108[13] | 2 | 3.82 (3H, s, OMe), 3.89 (3H, s, OMe), 3.90 (3H, s, OMe), 3.96 (3H, s, OMe), 6.39 (1H, d, *J*16.1Hz, CH=CHCO), 6.53 (1H, s, $C_3H$), 7.04 (1H, s, $C_6H$), 7.99 (1H, d, *J* = 16.1Hz, CH=CHCO). |

a) All products are white solids except for **3a**, which is colourless thick liquid. b) Irradiation time. c) Identical with authentic sample prepared by known method.[19]
d) *Anal.* Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.60; H, 6.34

## EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were obtained as KBr pellets on Shimadzu FTIR-8400S spectrometer. $^1$H NMR spectra were recorded on Varian Mercury spectrometer at 300 MHz, in $CDCl_3$ using TMS as an internal standard. Kenstar-OM 9918C, 2450 MHz (900W) microwave oven was used for microwave irradiation. Silica gel 60-120 mesh supplied by S. D. fine-chem Ltd (India) was activated by microwave irradiation for 10 min before use.

**General Procedure for the Synthesis of Methyl (*E*)-Cinnamates (3a-k).**- Silica gel (6.0 g) was added to a solution of appropriate aldehyde (**1a–k**, 2 mmol) and phosphorane (**2**, 0.86 g, 2.6 mmol) in dichloromethane (10 ml), and the reaction mixture was stirred for 2 min. The solvent was removed, and the residual powder was dried in vacuo. It was then spread in a Petri dish, irra-

diated in a microwave oven for 2-3 min. and chromatographed over silica gel using hexane: ethyl acetate (9:1) as an eluent to afford methyl (*E*)-cinnamate. All these esters were recrystallised from chloroform-hexane except **3c** (from methanol), **3k** (from ethanol); **3a** is liquid.

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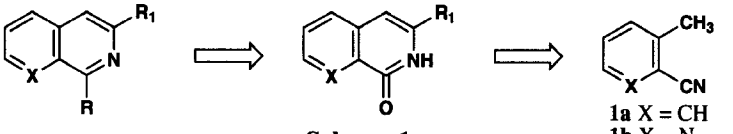
## SYNTHESIS OF FUSED BICYCLO[3.2.2]NONENONES

*Submitted by* (04/04/05) Xinglong Jiang, Kapa Prasad*, and Oljan Repič

*Process Research & Development,*
*Novartis Pharmaceuticals Corporation*
*One Health Plaza, East Hanover, NJ 07936, USA*
*e-mail*: prasad.kapa@novartis.com

Suitably functionalized heterocyclic compounds are of pharmacological interest. In the process of exploring efficient synthetic routes to 1,3-disubstituted isoquinolines and of the corresponding napthyridine systems (*Scheme 1*), we investigated the functionalization of **1** and **2**, and the results led to an efficient preparation of the title compounds described herein.




**1a** X = CH
**1b** X = N

**Scheme 1**