

A New Route to 2,4,6-Trisubstituted-6*H*-1,3-Oxazines

Mazaahir Kidwai,* Ruby Thakur, and Richa Mohan

Department of Chemistry, University of Delhi, Delhi-110007, India

Received July 27, 2004; E-mail: mkidwai@mantraonline.com

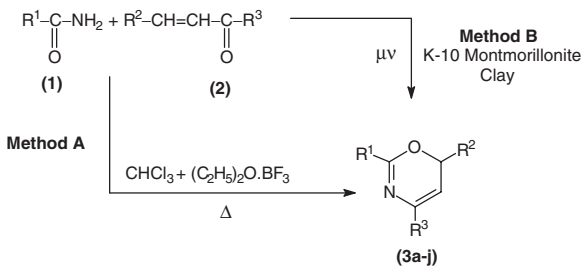
The Lewis acid (borontrifluoride etherate) catalyzed novel synthesis of 2,4,6-trisubstituted-6*H*-1,3-oxazines is described here. Also, a new route towards an environmentally benign synthesis of the title compounds has been developed using montmorillonite K-10 clay as a catalyst under microwave irradiation (MWI). The procedure replaces the Lewis acid, and the products are obtained in a high yield and shorter reaction time.

Industrial chemistry in the new millennium is widely adopting the concept of "green chemistry" to meet fundamental scientific challenges. The use of heterogeneous catalysts in particular montmorillonite K-10 clay (a class of inexpensive and non-corrosive solid acid), coupled with microwaves have made a landmark in different areas of organic synthesis[1–4] due to their environmental compatibility combined with the good yields and selectivities that can be achieved.[5–7]

In past decades, 1,3-oxazines and their derivatives have been extensively investigated by organic chemists due to their close association with medicinal properties such as use as chemotherapeutic agents.[8–11] Substituted-6*H*-1,3-oxazines are the least investigated group of derivatives of 1,3-oxazines.[12] This class of compounds has been synthesized previously by the pyrolysis of β-acylamino-α,β-unsaturated ester in diphenyl ether,[13] by cyclization of ethynylalkyl arylcarbamates,[14] by the oxidation of pyrrole derivatives,[15] and by the pyrolysis of 3-ethoxycarbonylaminoprop-2-enal.[16] However, these methods suffer from several drawbacks, such as longer reaction times, complicated works up, the use of noxious solvents like benzene,[17] P_2O_5,[18] and $POCl_3$, etc. They also require multiple steps in the synthesis at the precursor stage. Moreover, no general method applicable for the synthesis of titled compound using easily available precursors (amides and chalcones) is known.

In view of the above mentioned biological activity of 6*H*-1,3-oxazine, and in continuation of our interest in the development of environmentally benign protocols,[19,20] we herein report a new facile, rapid, and environmentally benign one pot synthesis of 2,4,6-trisubstituted-6*H*-1,3-oxazine in dry media under MWI. Moreover, novel reactions were also performed using borontrifluoride etherate [$(C_2H_5)_2O\cdot BF_3$] under conventional heating, and we developed a new synthetic procedure for the synthesis of 2,4,6-trisubstituted-6*H*-1,3-oxazine.

The condensation of amides (**1**) with α,β-unsaturated ketones (**2**) in the presence of $(C_2H_5)_2O\cdot BF_3$ with chloroform as a solvent was carried out under conventional heating (Scheme 1) (Method A). The products (**3a–j**) were obtained in 4–6 h with moderate yields (Table 1). Here, $(C_2H_5)O\cdot BF_3$



R^1 = phenyl, furyl
R^2 = phenyl, p-methoxyphenyl, furyl, indolyl, benzo[1,3]dioxolyl
R^3 = phenyl, methyl, p-bromophenyl

Scheme 1. Conventional and microwave assisted synthesis of 2,4,6-trisubstituted-6*H*-1,3-oxazines.

Table 1. Comparison of Reaction Time/Yield of Compounds (**3a–j**)

Compd No.	R^1	R^2	R^3	Method A	Method B
				Time (h)/Yield (%)	Time (min)/Yield (%)
3a	phenyl	phenyl	phenyl	5.0/68	2.0/96
3b	phenyl	*p*-methoxyphenyl	phenyl	6.2/65	2.5/93
3c	phenyl	2-furyl	methyl	4.5/58	3.5/97
3d	phenyl	3-indolyl	*p*-bromophenyl	4.3/54	4.0/92
3e	phenyl	benzo[1,3]dioxol-5-yl	*p*-bromophenyl	4.9/59	3.9/94
3f	2-furyl	phenyl	phenyl	6.4/69	2.4/93
3g	2-furyl	*p*-methoxyphenyl	phenyl	5.8/62	2.9/92
3h	2-furyl	2-furyl	methyl	4.8/64	3.4/94
3i	2-furyl	3-indolyl	*p*-bromophenyl	5.4/67	3.6/91
3j	2-furyl	benzo[1,3]dioxol-5-yl	*p*-bromophenyl	5.6/63	3.1/93

Published on the web December 10, 2004; DOI 10.1246/bcsj.77.2265

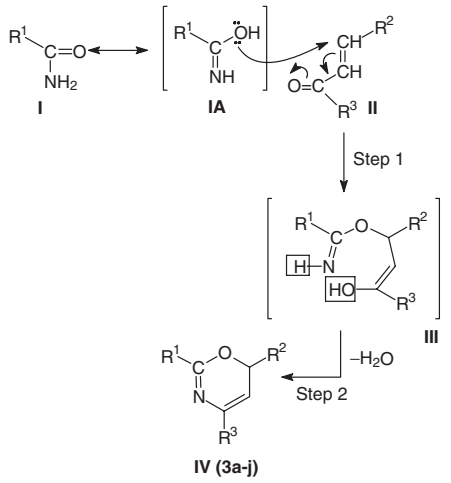


Fig. 1. Probable reaction pathway for the formation of **3a–j**.

acts as a Lewis acid and helps in the cyclization of intermediate (**III**) formed in Fig. 1. However, $(C_2H_5)O \cdot BF_3$ is a corrossive, moisture sensitive Lewis acid.[21] On the other hand, K-10 montmorillonite clay, an acidic solid support when coupled with microwaves,[22] is a well known condensing and cyclizing agent.[14] So, in continuation of our endeavour towards a green synthesis **1** and **2** were condensed under MWI using K-10 montmorillonite clay[23] (Scheme 1) (Method B). The products (**3a–j**) were obtained in excellent yields (Table 1) within several minutes of irradiation (Table 1).

The structural assignment of **3a–j** was based on elemental analyses and spectroscopic data. The molecular formulae were confirmed by elemental analyses and mass spectroscopy (M^+: m/e). In IR spectra, the appearance of a bands at 1532–1604 cm^{-1}, 1243–1373 cm^{-1}, and 1643–1682 cm^{-1} show the presence of (C=N), (C–O), and (C=C) groups, respectively. ^{1}H NMR spectra show the appearance of a doublet at δ (5.11–5.91) and (5.79–6.82) due to the C_6-H and C_5-H protons and further in the ^{13}C NMR spectra the appearance of signals at δ 164.1–164.9 (C_2), 139.2–142.4 (C_4), 117.2–120.0 (C_5), and 69.8–72.1 (C_6) confirmed the formation of products (**3a–j**). A possible reaction route for the formation of **3** is depicted in Fig. 1, in which the lone pair of electrons on the oxygen atom undergoes a Michael 1,4 addition to give intermediate (**III**), which upon dehydration (activated by a Lewis acid or montmorillonite clay) gives the desired product **IV**.

Reactions between **1** and **2** under conventional heating (Method A) were completed in 4–6 h with moderate yields (Table 1), whereas the same reactions under MW (Method B) gave excellent yields within 2–4 min of irradiation (Table 1). In comparison to Method A, the reactions catalyzed by montmorillonite K-10 clay under microwave activation (Method B) resulted in unique chemical processes with special attribute, such as enhanced reaction rates, higher yields (Table 1), greater selectivity and ease of manipulation. So, the microwave method replaces the corrosive and noxious Lewis acid through clay, and makes it an environmentally benign synthesis.

Hence, we have developed a novel synthetic procedure for the preparation of the titled compounds (**3a–j**) using borontrifluoride etherate $[(C_2H_5)_2 \cdot OBF_3]$. Also, we can conclude that catalytic montmorillonite clay contains both acidic centers and basic sites able to abstract protons from methylene active compounds, avoiding the use of the noxious Lewis acid borontrifluoride etherate $[(C_2H_5)_2 \cdot OBF_3]$. The ecofriendly advantages of these solvent-free protocols can be found in instances where a catalytic amount of reagents or supporting agents are used, since they provide the reduction or elimination of solvent, thus preventing pollution "at source".

Experimental

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT IR-1710 spectrophotometer. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance Spectrospin 300 (300 MHz) instrument using TMS as an internal standard and $CDCl_3$/DMSO as a solvent. Elemental analysis was performed on a Heraeus CHN Rapid Analyser. EI mass spectra were recorded on a JEOL-JHS-DX 303 mass spectrometer. Microwave irradiation was carried out in a Kenstar Microwave Oven, Model No. OM 9925E (2450 MHz, 800 W). The temperature of the reaction was measured through an AZ, Mini Gun Type, Non-Contact IR Thermometer, Model No. 8868. The purity of compounds was verified on silica gel coated Al plates (Merck).

General Procedure for the Synthesis of 3a–j Using Borontrifluoride Etherate $[(C_2H_5)_2O \cdot BF_3]$. Method A: An equimolar amount of **1** and **2** (0.05 mol) were put in a round bottomed flask. To this, $CHCl_3$ (20 mL) was added and the reaction mixture was refluxed for 10 min gently with stirring on a magnetic stirrer equipped with an air condenser. Then, 0.005 mol of $(C_2H_5)_2O \cdot BF_3$ was added and refluxed for 4–6 h. On formation of product, as monitored by TLC examination the product was filtered through a Hirsch Funnel and washed with 10 mL of chilled water. The solid obtained was recrystallized with EtOH.

General Procedure for the Synthesis of 3a–j Using K-10 Montmorillonite Clay. Method B: K-10 montmorillonite clay was added to the mixture of **1** (0.05 mol) and **2** (0.05 mol) in ethanol. The reaction mixture was stirred well and dried in air. It was then placed in an alumina bath[24] inside a microwave oven for 2–4 min. The progress of the reaction was monitored through TLC at intervals of 30 s. On completion of reaction, the product was extracted using EtOH, and the solvent was removed under reduced pressure, which yielded the corresponding title compounds (**3a–j**), which were then recrystallized using EtOH.

2,4,6-Triphenyl-6*H*-1,3-oxazine (3a). m.p. 147–149 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 6.74 (d, 1H, $J = 7.5$ Hz, C_5-H), 5.11 (d, 1H, $J = 7.4$ Hz, C_6-H), 7.5–7.8 (m, 14H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO) δ 164.5 (C_2), 142.3 (C_4), 117.2 (C_5), 70.7 (C_6). IR (KBr) ν_{max}: 1681 (C=C), 1587 (C=N), 1265 (C–O) cm^{-1}. Anal. Calcd for $C_{22}H_{17}NO$ (M^+: m/e 311): C, 84.88; H, 5.46; N, 4.50%. Found: C, 84.96; H, 5.76; N, 4.73%.

6-(4-Methoxyphenyl)-2,4-diphenyl-6*H*-1,3-oxazine (3b). m.p. 152–153 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 6.81 (d, 1H, $J =$ 7.9 Hz, C_5-H), 5.23 (d, 1H, $J = 7.8$ Hz, C_6-H), 7.5–7.9 (m, 15H, Ar-H), 3.71 (s, 3H, –OMe); ^{13}C NMR ($CDCl_3$ + DMSO) δ 167.1 (C_2), 142.1 (C_4), 117.8 (C_5), 69.8 (C_6), 56.0 (–OMe). IR (KBr) ν_{max}: 1650 (C=C), 1567 (C=N), 1295 (C–O) cm^{-1}. Anal. Calcd for $C_{23}H_{19}NO_2$ (M^+: m/e 341): C, 80.93; H, 5.57; N, 4.10%. Found: C, 81.12; H, 5.61; N, 4.35%.

6-(Furan-2-yl)-4-methyl-2-phenyl-6*H*-1,3-oxazine (3c). m.p. 144–145 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 5.79 (d, 1H, $J = 8.1$ Hz, C_5-H), 5.41 (d, 1H, $J = 8.3$ Hz, C_6-H), 1.71 (m, 3H, CH_3);

^{13}C NMR ($CDCl_3$ + DMSO) δ 164.2 (C_2), 139.2 (C_4), 120.0 (C_5), 72.1 (C_6), 23.8 (CH_3). IR (KBr) ν_{max}: 1643 (C=C), 1583 (C=N), 1243 (C–O) cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO_2$ (M^+: *m/e* 239): C, 75.31; H, 5.43; N, 6.85%. Found: C, 78.25; H, 6.00; N, 6.50%.

4-(4-Bromophenyl)-6-(indole-3-yl)-2-phenyl-6*H*-1,3-oxazine (3d). m.p. 149–151 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 6.32 (d, 1H, J = 7.6 Hz, C_5-H), 5.11 (d, 1H, J = 7.9 Hz, C_6-H), 6.8–7.6 (m, 8H, Ar-H), 10.1 (s, brs, 1H, indole NH); ^{13}C NMR ($CDCl_3$ + DMSO) δ 164.3 (C_2), 142.2 (C_4), 117.2 (C_5), 70.4 (C_6), 122.8 (C_2 of indole). IR (KBr) ν_{max}: 1648 (C=C), 1549 (C=N), 1373 (C–O) cm^{-1}. Anal. Calcd for $C_{24}H_{17}BrN_2O$ (M^+: *m/e* 428): C, 67.28; H, 3.97; N, 6.54%. Found: C, 67.34; H, 3.69; N, 6.45%.

4-(4-Bromophenyl)-6-(benzo[1,3]dioxo-3-yl)-2-phenyl-6*H*-1,3-oxazine (3e). m.p. 154–156 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 6.71 (d, 1H, J = 7.8 Hz, C_5-H), 6.12 (d, 1H, J = 7.5 Hz, C_6-H), 5.80 (s, 2H, piperonal CH_2), 6.8–7.6 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO) δ 164.4 (C_2), 142.2 (C_4), 117.9 (C_5), 71.1 (C_6), 91.3 (piperonal CH_2). IR (KBr) ν_{max}: 1675 (C=C), 1576 (C=N), 1352 (C–O) cm^{-1}. Anal. Calcd for $C_{23}H_{16}BrNO_3$ (M^+: *m/e* 433): C, 63.60; H, 3.68; N, 3.22%. Found: C, 64.00; H, 3.59; N, 3.12%.

2-(Furan-2-yl)-4,6-diphenyl-6*H*-1,3-oxazine (3f). m.p. 156–157 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 6.82 (d, 1H, J = 7.5 Hz, C_5-H), 5.41 (d, 1H, J = 7.6 Hz, C_6-H), 7.6–7.8 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO) δ 164.8 (C_2), 142.3 (C_4), 117.2 (C_5), 68.3 (C_6), 143.1 (C_2 and C_5 furyl), 110.0 (C_3 and C_4 furyl). IR (KBr) ν_{max}: 1656 (C=C), 1600 (C=N), 1246 (C–O) cm^{-1}. Anal. Calcd for $C_{20}H_{15}NO_2$ (M^+: *m/e* 301): C, 79.73; H, 4.98; N, 4.65%. Found: C, 79.60; H, 5.01; N, 4.36%.

2-(Furan-2-yl)-6-(4-methoxyphenyl)-4-phenyl-6*H*-1,3-oxazine (3g). m.p. 142–143 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 6.66 (d, 1H, J = 7.9 Hz, C_5-H), 5.60 (d, 1H, J = 7.8 Hz, C_6-H), 7.5–7.7 (m, 9H, Ar-H), 3.81 (s, 3H, –OMe); ^{13}C NMR ($CDCl_3$ + DMSO) δ 164.9 (C_2), 142.1 (C_4), 117.8 (C_5), 69.8 (C_6), 56.1 (OMe). IR (KBr) ν_{max}: 1662 (C=C), 1603 (C=N), 1338 (C–O) cm^{-1}. Anal. Calcd for $C_{21}H_{17}NO_3$ (M^+: *m/e* 331): C, 76.13; H, 5.13; N, 4.22%. Found: C, 76.54; H, 5.08; N, 4.52%.

2,5-(Difuran-2-yl)-4-methyl-6*H*-1,3-oxazine (3h). m.p. 124–125 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 6.95 (d, 1H, J = 8.2 Hz, C_5-H), 5.8 (d, 1H, J = 8.4 Hz, C_6-H), 1.72 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$ + DMSO) δ 164.8 (C_2), 139.2 (C_4), 120.0 (C_5), 72.1 (C_6), 23.8 (CH_3). IR (KBr) ν_{max}: 1692 (C=C), 1604 (C=N), 1336 (C–O) cm^{-1}. Anal. Calcd for $C_{13}H_{11}NO_3$ (M^+: *m/e* 229): C, 68.12; H, 4.80; N, 6.11%. Found: C, 68.06; H, 4.97; N, 6.15%.

2-(Furan-2-yl)-6-(indole-3-yl)-4-(4-bromophenyl)-6*H*-1,3-oxazine (3i). m.p. 132–134 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 6.41 (d, 1H, J = 7.7 Hz, C_5-H), 5.91 (d, 1H, J = 7.8 Hz, C_6-H), 7.4–7.5 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO) δ 164.9 (C_2), 142.2 (C_4), 117.3 (C_5), 70.5 (C_6), 122.8 (C_2-indole). IR (KBr) ν_{max}: 1682 (C=C), 1599 (C=N), 1247 (C–O) cm^{-1}. Anal. Calcd for $C_{22}H_{15}BrN_2O_2$ (M^+: *m/e* 331): C, 63.17; H, 3.35; N, 6.70%. Found: C, 63.30; H, 3.29; N, 7.03%.

2-(Furan-2-yl)-6-(benzo[1,3]dioxo-3-yl)-4-(4-bromophenyl)-6*H*-1,3-oxazine (3j). m.p. 136–137 °C; ^{1}H NMR ($CDCl_3$ + DMSO) δ 6.12 (d, 1H, J = 7.8 Hz, C_5-H), 5.61 (d, 1H, J = 7.6 Hz, C_6-H), 5.90 (s, 2H, CH_2-piperonal), 7.2–7.4 (m, 7H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO) δ 164.8 (C_2), 142.2 (C_4), 117.9 (C_5), 71.2 (C_6), 91.3 (CH_2-piperonal). IR (KBr) ν_{max}: 1656 (C=C), 1532 (C=N), 1323 (C–O) cm^{-1}. Anal. Calcd for $C_{21}H_{14}BrNO_4$ (M^+: *m/e* 423): C, 59.44; H, 3.30; N, 3.30%. Found: C, 59.16; H, 3.22; N, 3.60%.

The authors are thankful to the University Grant Commission, New Delhi, for financial support.

References

1 T. S. Li and A. X. Li, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1913.

2 R. K. Ramchandani, B. S. Uphade, M. P. Vinod, R. D. Wakharkar, V. R. Choudhary, and A. Sudalai, *Chem. Commun.*, **1997**, 2071.

3 M. Kidwai, R. Venkataramanan, and B. Dave, *Synth. Commun.*, **32**, 2161 (2002).

4 a) R. S. Varma, *Green Chem.*, **1**, 43 (1999). b) P. Hermkens, H. Ottenheijm, and D. Rees, *Tetrahedron*, **53**, 5643 (1997). c) J. Rebek, D. Brown, and S. J. Zimmerman, *J. Am. Chem. Soc.*, **97**, 454 (1975).

5 a) R. S. Varma and R. K. Saini, *Tetrahedron Lett.*, **38**, 2623 (1997). b) M. Kidwai, *Pure Appl. Chem.*, **73**, 147 (2001).

6 M. Kidwai, P. Sapra, K. R. Bhushan, and P. Misra, *Synthesis*, **2001**, 1509.

7 M. Kidwai, R. Venkataramanan, and B. Dave, *Green Chem.*, **3**, 278 (2001).

8 T. Urbanski, *Nature*, **168**, 562 (1951).

9 T. Urbanski, Cz. Radzikowski, Z. Ledochowski, and W. Czarnocki, *Nature*, **178**, 1351 (1956).

10 T. Urbanski, D. Gürne, S. Slopek, H. Mordarska, and M. Mordarski, *Nature*, **187**, 426 (1960).

11 P. Karrer and R. Widmer, *Helv. Chim. Acta*, **8**, 203 (1925).

12 Z. Eckstein and T. Urabanski, *Adv. Heterocycl. Chem.*, **2**, 331 (1963).

13 a) F. Eiden and B. S. Nagar, *Naturwissenschaften*, **50**, 403 (1963). b) E. Buschmann and W. Steglich, *Angew. Chem.*, **86**, 414 (1974). c) W. Steglich, E. Buschmann, and O. Hollitzer, *Angew. Chem.*, **86**, 594 (1974).

14 S. L. Shaprio, V. Bandurco, and L. Freedman, *J. Org. Chem.*, **26**, 3710 (1961).

15 a) V. Sprio, *Gazz. Chim. Ital.*, **85**, 569 (1956). b) T. T. Yee, W. E. McEwen, and A. P. Wolf, *Tetrahedron Lett.*, **6**, 3115 (1965).

16 A. Krantz and B. Hoppe, *J. Am. Chem. Soc.*, **97**, 6590 (1975).

17 T. Sasaki, K. Kanematsu, and A. Kakchi, *J. Org. Chem.*, **36**, 2451 (1971).

18 B. Horst and J. Gert, *Ger. Offen.*, **1998**, 25.

19 M. Kidwai, S. Rastogi, and R. Venkataramanan, *Bull. Chem. Soc. Jpn.*, **76**, 203 (2003).

20 a) M. Kidwai, R. Venkataramanan, R. K. Garg, and K. R. Bhushan, *J. Chem. Res., Synop.*, **2000**, 586. b) M. Kidwai and P. Sapra, *Synth. Commun.*, **32**, 1639 (2002).

21 Boron trifluoride etherate: 216607 Aldrich.

22 Microwave irradiations were carried out in Kenstar Microwave Oven, Model No. OM9925E (2450 MHz, 800 W).

23 Montmorillonite K-10: K-catalyst, 69866 Fluka, Surface; 200 ± 20 m^2/g.

24 G. Bram, A. Loopy, and M. Majdoub, *Tetrahedron*, **46**, 5167 (1990).