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Reductive Ring Opening of 3,5-Bis(2-arylethenyl)isoxazoles with Molybdenum Hexacarbonyl: A Novel Route to Symmetrical and Unsymmetrical Curcumin Derivatives

VIWAT HAHNVAJANAWONG*, THANAPHAT THAIMA, RUCHANOK TEARAVARICH and PARINYA THERAMONGKOL

Department of Chemistry and Center for Innovation in Chemistry, Faculty of Science, Khon Kaen University, Khon Kaen 40002, Thailand.
*Corresponding author E-mail: viwhah@kku.ac.th

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ABSTRACT

Curcumin derivatives were successfully synthesized from 3,5-dimethylisoxazole by lateral metalation and condensation with various aromatic aldehydes sequentially at C_5- and C_3-methyl groups. After dehydration, further transformation of isoxazole ring to β-diketone moiety was accomplished by reductive ring opening using molybdenum hexacarbonyl [$Mo(CO)_6$] and subsequent simple acidic hydrolysis.

Key words : Curcumin derivatives, Reductive ring opening, Molybdenum hexacarbonyl, Lateral metalation

INTRODUCTION

Curcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione, is a bioactive compound isolated from *Curcuma longa* rhizomes. Curcumin has been reported to possess antioxidant, anti-inflammatory, antitmicrobial and anticarcinogenic activities.[1] Various curcumin derivatives have been synthesized for testing their biological activities. Synthetic symmetrical curcumin derivatives reported in literature[2-5] were obtained from Pabons procedure.[6] Unsymmetrical curcumin derivatives, on the other hand, were synthesized by solid-phase synthetic strategy.[7] Both syntheses proceeded through acetylacetone-boric anhydride complex which methyl terminals of this complex were allowed to undergo aldol condensation.

Isoxazoles can be employed as masked 1,3-dicarbonyl compounds because reductive cleavage of the N-O bond in isoxazoles produce β-aminoenones which are readily transform to their corresponding β-hydroxyenones. We have envisioned for using this N-O bond cleavage in our strategy for the synthesis of symmetrical as well as a wide range of unsymmetrical curcumin derivatives

1, *i.e.,* using isoxazole rings of 3,5-bis(2-arylethenyl) isoxazoles **2** as masked 1,3-dicarbonyl moieties of curcumin derivatives **1** (Scheme 1). The synthetic direction to obtain **2** involves transformation of methyl groups of 3,5-dimethylisoxazole **(5)** into 2-aryl-2-hydroxyethyl groups sequentially at C_5 and C_3 to get 5-(2-aryl-2-hydroxyethyl)-3-methylisoxazoles **4** and 3,5-bis(2-aryl-2-hydroxyethyl)isoxazoles **3** respectively. Subsequent dehydration of3,5-bis(2-aryl-2-hydroxyethyl)isoxazoles **3** provides the route to 3,5-bisstyrylisoxazoles **2**.

Experimental Section

General

Melting points were determined by usinga Sanyo Gallenkamp melting point apparatus and are uncorrected. IR spectra were taken with a Perkin Elmer Spectrum One FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using a VARIAN MERCURY plus (400 MHz FT NMR).

n-BuLi and *s*-BuLi were prepared and their concentration were determined following the standard procedure.[8,9]

Preparation of 3,5-dimethylisoxazole (5)[10]

A solution of hydroxylamine hydrochloride (8.34 g, 0.12 mole) in water (10 ml) was added a solution of 2,4-pentanedione (**6**) (10.2 g, 0.1 mole) in ethanol (10 ml). The mixture was heated under reflux temperature for 3 hours, then allowed to cool to room temperature and poured into cold water (60 ml). The resulting mixture was extracted with ether (3x40 ml). The combined organic layer was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The brown oily residue was purified by distilling under reduce pressure to give 3,5-dimethylisoxazole (**5**) (8.10g, 82%) as a colourless liquid (bp 85- 86 °C at 150 mmHg);IR (thin film) ν_{max}: 3132, 2934, 1611, 1455, 1414, 1258, 1011, 886, 795 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.82 (1H, s, *H*-4), 2.36 (3H, s, C=CC*H*$_3$), 2.23 (3H, s, N=CC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ: 11.3, 12.1, 102.3, 159.9, 169.1.

General procedure for preparation of 5-(2-aryl-2-hydroxyethyl)-3-methylisoxazoles 4a-c

To a stirred solution of 3,5-dimethylisoxazole (**5**) (2.91 g, 30.0 mmol) in dry THF (60 ml) was added *n*-BuLi (1.0 M in hexane; 30 ml, 30.0 mmol) dropwise under N_2 at -78 °C and the mixture was stirred for an additional1 hour. A solution of aromatic aldehyde (30.0 mmol) in THF (6 ml) was then added. The resulting mixture was allowed to warm up to room temperature and treated with water. The phases were separated and the aqueous layer was extracted with ethyl acetate (3x120 ml). The combined organic layer was dried (Na_2SO_4) and concentrated under reduce pressure. Purification of the residue using column chromatography on silica gel with a gradient of 10-50% ethyl acetate in hexane as eluent gave 5-(2-aryl-2-hydroxyethyl)-3-methylisoxazoles **4a-c** (70-84%) as yellow oils or as white crystalline solids.

5-(2-Phenyl-2-hydroxyethyl)-3-methylisoxazole (4a)

Yield: 4.69 g (77%); yellow oil; IR (thin film) ν_{max}: 3370, 3031, 2931, 1604, 1493, 1450, 1415,1051, 742, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33-7.20 (5H, m, Ar*H*), 5.80 (1H, s, =C*H*), 4.96 (1H, dd, *J* = 8.2 and 5.1 Hz, OC*H*), 3.10 (1H, dd, *J* = 15.2 and 8.2 Hz, *H*CH), 3.01 (1H, dd, *J* = 15.2 and 5.0 Hz, HC*H*), 2.12 (3H, s, C*H*$_3$);^{13}C NMR ($CDCl_3$) δ: 11.3, 36.6, 72.1, 103.4, 125.7, 128.0, 128.6, 143.0, 159.8, 169.6.

[2-(4-Methoxyphenyl)-2-hydroxyethyl]-3-methylisoxazole (4b)

Yield: 4.90 g (70%); yellow oil; IR (thin film) ν_{max}: 3376, 2934, 2838, 1608, 1513, 1416, 1246, 1177, 1032, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.21 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.82 (2H, d, *J* = 8.6 Hz, Ar*H*), 5.80 (1H, s, =C*H*), 4.92 (1H, dd, *J* = 8.0 and 5.4 Hz, OC*H*), 3.74 (3H, s, OC*H*$_3$), 3.10 (1H, dd, *J* = 15.2 and 8.1 Hz, *H*CH), 2.99 (1H, dd, *J* = 15.2 and 5.3 Hz, HC*H*), 2.15 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ: 11.2, 36.5, 55.2, 71.4, 103.2, 113.8, 127.0, 135.4, 159.1, 159.7, 169.9.

[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-methylisoxazole (4c)

Yield: 6.63 g (84%); white crystals; mp 63-64 °C; IR (thin film) ν_{max}: 3382, 2936, 1603, 1513, 1416, 1260, 1233, 1137, 1023, 809, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.90-6.78 (3H, m, Ar*H*), 5.83 (1H, s, =C*H*), 4.98 (1H, m, OC*H*), 3.83 (6H, s, 2xOC*H*$_3$), 3.14 (1H, dd, *J* = 15.1 and 8.2 Hz, *H*CH), 3.04 (1H, dd, *J* = 15.1 and 5.1 Hz, HC*H*), 2.20 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ: 11.3, 36.7, 55.9, 71.7, 103.5, 109.1, 111.2, 118.1, 136.1, 148.6 149.1, 160.0, 170.0.

General procedure for preparation of 3,5-bis(2-aryl-2-hydroxyethyl)isoxazoles 3a-f

To a solution of 5-(2-aryl-2-hydroxyethyl)-3-methylisoxazole(4.0 mmol) in THF (20 ml) was added *s*-BuLi (1.0 M in hexane, 10.0 ml, 10.0 mmol) dropwise under N_2 at -78 °C. After being stirred at -78 °C for 1 hour, a solution of aromatic aldehyde (5.0 mmol) in THF (2 ml) was then added. The reaction mixture was allowed to warm up to room temperature and treated with water. The phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 ml). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue using column chromatography on silica gel with agradient of 30-70% ethyl acetate in hexane as an eluent gave3,5-bis(2-aryl-2-hydroxyethyl)isoxazoles **3a-**f (46-65%) as crystalline solids or as oils.

3,5-bis(2-Phenyl-2-hydroxyethyl)isoxazole (3a)

Yield: 0.59 g (48%); white crystals; mp 97-98°C; IR (thin film) ν_{max}: 3377, 3031, 1601, 1428, 1052, 754, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38-7.16 (10H, m, Ar*H*), 5.89 and 5.88 (1H, 2s, =C*H*), 5.03-4.84 (2H, m, 2"-and2'-OC*H*), 3.09 (1H, dd,*J*= 15.2 and 8.7 Hz, 1"-*H*CH), 3.02 (1H, dd, *J* = 15.2 and 4.6 Hz, 1"-HC*H*), 2.98-2.89 (2H, m, 1'-CH_2); ^{13}C NMR ($CDCl_3$) δ: 36.0, 36.7, 71.9, 72.4, 103.3, 125.7, 125.8, 127.8, 128.0, 128.5, 128.6 , 142.9, 143.2, 161.4, 169.9.

3,5-*Bis*(2-(4-methoxyphenyl)-2-hydroxyethyl) isoxazole (*3b*)

Yield: 0.72 g (49 %); white crystals; mp 97-99 °C; IR (thin film) ν_{max}: 3377, 2957, 1608, 1514, 1253, 1175, 1033, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.27 (4H, d, *J* = 8.4 Hz, Ar*H*), 6.88 (4H, d, *J* = 8.4 Hz, Ar*H*) 5.88 and 5.87 (1H, 2s, =C*H*), 5.03-4.91 (2H, m, 2"- and 2'-OCH), 3.80 (6H, s, 2xOCH_3), 3.16 (1H, dd, *J* = 15.2 and 8.4 Hz, 1"-*H*CH),3.10-2.92 (3H, m, 1"-HC*H* and 1'-CH_2); ^{13}C NMR ($CDCl_3$) δ: 36.1, 36.6, 55.3, 71.7, 72.1, 103.3, 113.9, 114.0, 127.0, 127.1, 135.1, 135.4, 159.2, 159.4, 161.4, 169.9.

3,5-Bis[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl] isoxazole (*3c*)

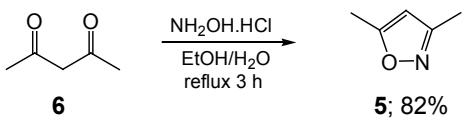
Yield: 1.12 g (65%); yellow crystals; mp 89-91 °C; IR (thin film) ν_{max}: 3384, 2937, 1599, 1513, 1420, 1260, 1138, 1022, 811, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.89 (1H, s, Ar*H*), 6.85 (1H, s, Ar*H*), 6.84-6.74 (4H, m, Ar*H*), 5.90 and 5.87 (1H, 2s, =C*H*), 4.93-4.81 (2H, m, 2"- and 2'-OCH), 3.81 and 3.80 (12H, 2s, 4xOCH_3), 3.08 (1H, d d, *J* = 15.2 and 8.7 Hz, 1"-*H*CH), 3.03-2.86 (3H, m, 1"-HC*H* and 1'-CH_2);^{13}C NMR ($CDCl_3$) δ: 36.0, 36.8, 55.8, 55.9, 71.7, 72.3, 103.3, 108.9, 109.1, 111.0, 117.9, 118.0, 135.8, 136.0, 148.4, 148.5, 148.9, 161.4, 169.9.

3-[2-Phenyl-2-hydroxyethyl]-5-(2-(4-methoxyphenyl)-2-hydroxyethyl)isoxazole (3d)

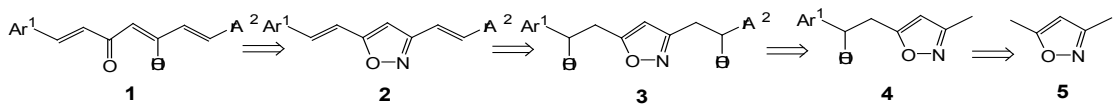
Yield: 0.77 g (57%); brown crystals; mp 63-64°C; IR (thin film) ν_{max}: 3365, 2896, 1606, 1513, 1437, 1246, 1176, 833, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34-7.20 (5H, m, Ar*H*), 7.16 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.80 (2H, d, *J* = 8.7 Hz, Ar*H*), 5.85 and 5.84 (1H, 2s, =C*H*), 4.91-4.80 (2H, m, 2"-and 2'-OC*H*), 3.72 (3H, s, OCH_3), 3.03 (1H, dd,*J* = 15.2 and 8.6 Hz, 1"-*H*CH), 2.99-2.83 (3H, m, 1"-HC*H* and 1'-CH_2); ^{13}C NMR ($CDCl_3$) δ: 36.2, 36.6, 55.3, 71.8, 72.5, 103.3, 114.0, 125.8, 127.0, 127.8, 128.5, 135.0, 143.2, 159.4, 161.3, 169.9.

3-[2-Phenyl-2-hydroxyethyl]-5-(2-(3,4-dimethoxyphenyl)-2-hydroxyethyl) isoxazole (3 e)

Yield: 0.75 g (51%); yellow oil; IR (thin film) ν_{max}: 3381, 2938, 1600, 1514, 1421, 1260, 1138, 1022, 810, 760, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33-7.19 (5H, m, Ar*H*), 6.84 (1H, s, Ar*H*), 6.80 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.76 (1H, d, *J* = 8.2 Hz, Ar*H*), 5.87 and 5.85 (1H, 2s, =C*H*), 4.92-4.84 (2H, m, 2"- and 2'-OC*H*), 3.80 and 3.79 (6H, 2s, 2xOCH_3) 3.07 (1H, dd, *J* = 15.1, 8.7 Hz, 1"-*H*CH), 3.02-2.86 (3H, m, 1'-HC*H* and 1'-CH2);^{13}C NMR ($CDCl_3$) δ: 35.9, 36.7, 55.8, 71.6, 72.4, 103.2, 108.9, 111.0,



6 **5**; 82%



1 **2** **3** **4** **5**

Scheme 1:

117.9, 125.7, 127.7, 128.4, 135.7, 143.2, 148.5, 148.9, 161.3, 169.9.

3-[2-(4-Methoxyphenyl)-2-hydroxyethyl]-5-(2-(3,4-dimethoxyphenyl)-2-hydroxyethyl) isoxazole (3f)

Yield: 0.74 g (46%); green crystals; mp 76-77°C; IR (thin film) ν_{max}: 3383, 2935, 1604, 1513, 1421, 1238, 1139, 1024, 811, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.21 (2H, d, *J* = 8.2 Hz, Ar*H*), 6.85 (1H, s, Ar*H*), 6.84-6.79 (3H, m,Ar*H*), 6.77 (1H, d, *J* = 8.2 Hz, Ar*H*), 5.89 and 5.86 (1H, 2s, =C*H*), 4.93-4.80 (2H, m, 2"- and 2'-OC*H*), 3.82 and 3.81 (6H, 2s, 2xOCH_3), 3.75 (3H, s, OCH_3), 3.08 (1H, dd, *J* = 15.2 and 8.7 Hz, 1"-*H*CH), 3.03- 2.85 (3 H, m, 1"-HC*H* and 1'-CH_2);^{13}C NMR ($CDCl_3$) δ: 35.9, 36.7, 55.2, 55.8, 55.9, 71.7, 72.1, 103.2, 108.9, 111.0, 113.8, 117.9, 127.0, 135.4, 135.8, 148.5, 149.0, 159.1, 161.4, 169.9.

General procedure for dehydration of 3,5-*Bis*(2-aryl-2-hydroxyethyl) isoxazoles 3a-f

A mixture of 3,5-bis(2-aryl-2-hydroxyethyl) isoxazole (1.0 mmol), P_2O_5 (0.4 mmol) in benzene (5 ml) was heated under reflux temperature for 2 hours. The benzene layer was decanted and the residue was washed once with hot benzene. The combined benzene layer was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified using column chromatography on silica gel with CH_2Cl_2 as eluent to give 5-(2-arylethenyl)-3-methylisoxazoles **2a-f** (52-66%) as crystalline solids.

3,5-*Bis*(2-*Phenylethenyl*) isoxazole (2a)

Yield: 0.18 g (66%); white crystals; mp 186-187°C; IR (thin film) ν_{max}:3033, 1644, 1579, 1559, 1429, 1292, 960, 751, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) d: 7.56-7.48 (4H, m, Ar*H*), 7.42-7.29 (7H, m, Ar*H* and Ar^{1}C*H*=CH-), 7.19 (1H, d, *J* = 16.6 Hz, Ar^{2}C*H*=CH-), 7.13 (1H, d, *J* = 16.5 Hz, Ar^{2}CH=C*H*-), 6.96 (1H, d, *J* = 16.4 Hz, Ar^{1}CH=C*H*-), 6.49 (1H, s, =C*H*); ^{13}C NMR ($CDCl_3$) δ: 98.5, 113.0, 116.1, 127.0, 127.1, 128.9, 129.2, 134.9, 135.5, 135.8, 162.0, 168.3.

3,5-Bis(2-(4-methoxyphenyl)ethenyl)isoxazole (2b)

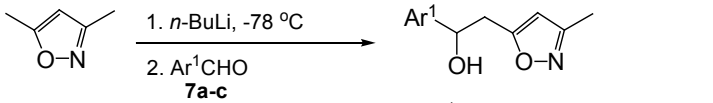
Yield: 0.20 g (61%); yellow crystals; mp 194-196 °C (lit.[11] 180-181 °C); IR (thin film) ν_{max}: 2934, 1644, 1604, 1577, 1512, 1431, 1257, 1175, 1029, 967, 823, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.48 (4H, d, *J* = 8.7 Hz, Ar*H*), 7.31 (1H, d, *J* = 16.4 Hz, Ar^{1}C*H*=CH-), 7.13 (1H, d, *J* = 16.5 Hz, Ar^{2}C*H*=CH-), 7.00 (1H, d, *J* = 16.5 Hz, Ar^{2}CH=C*H*-), 6.92 (4H, d, *J* = 8.5 Hz, Ar*H*), 6.83 (1H, d, *J* = 16.4 Hz, Ar^{1}CH=C*H*-), 6.43 (1H, s, =C*H*), 3.84 (6H, s, 2xOCH_3);^{13}C NMR ($CDCl_3$) δ: 55.4, 97.7, 111.0 114.0, 114.3, 128.3, 128.6, 128.7, 134.4, 135.2, 160.2, 160.5, 162.2, 168.5.

3,5-Bis[2-(3,4-dimethoxyphenyl)ethenyl] isoxazole (2c)

Yield: 0.22 g (56%); white crystals; mp 169-171 °C (lit.[11] 159-160 °C); IR (thin film) ν_{max}: 2937, 1644, 1584, 1561, 1512, 1428, 1264, 1139, 1024, 963, 805, 735 cm^{-1};^1H NMR ($CDCl_3$, 400 MHz) δ: 7.22 (1H, d, *J* = 16.4 Hz, Ar^{1}C*H*=CH-), 7.09-6.93 (6H, m, Ar*H*, Ar^{2}CH=C*H*- and Ar^{2}CH=C*H*-), 6.83 - 6.73 (3H, m, Ar*H* and Ar^{1}CH=C*H*-), 6.36 (1H, s, =C*H*), 3.90 and 3.89 (6H, 2s, 2xOCH_3), 3.86 and 3.85 (6H, 2s, 2xOCH_3); ^{13}C NMR ($CDCl_3$) δ: 55.8, 97.8, 108.8, 109.1, 110.0, 111.1, 113.9, 120.9, 121.0, 128.5, 128.8, 134.5, 135.4, 149.1, 149.8, 150.1, 162.1, 168.4.

5-(2-(4-Methoxyphenyl)ethenyl)-3-[2-phenylethenyl] isoxazole (2d)

Yield: 0.18 g (60%); yellow crystals; mp 155-156°C; IR (thin film) ν_{max}: 3035, 2928, 1643, 1603, 1509, 1430, 1254, 1173, 1032, 963, 822, 754, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (2H, d, *J* = 7.2 Hz, Ar*H*), 7.47 (2H, d, *J* = 8.7 Hz, Ar*H*),



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4a; $Ar^1 = C_6H_5$, 77%
4b; Ar^1 = 4-$OMeC_6H_4$, 70%
4c; Ar^1 = 3,4-di$OMeC_6H_3$, 84%

Scheme 2:

7.42-7.28 (4H, m, Ar*H* and Ar^{1}C*H*=CH-), 7.18 (1H, d, *J* = 16.6 Hz, Ar^{2}C*H*=CH-), 7.13 (1H, d, *J* = 16.5 Hz, Ar^{2}CH=C*H*-), 6.92 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.83 (1H, d, *J* = 16.4 Hz, Ar^{1}CH=C*H*-), 6.44 (1H, s, =C*H*), 3.84 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 55.4, 97.7, 110.9, 114.3, 116.2, 127.0, 128.3, 128.6, 128.8, 135.5, 135.6, 135.9, 160.5, 162.0, 168.7.

5-(2-(3,4-Dimethoxyphenyl)ethenyl)-3-[2-phenylethenyl]isoxazole (2e)

Yield: 0.19 g (58%); white crystals; mp 153-154 °C; IR (thin film) ν_{max}: 2936, 1644, 1583, 1561, 1513, 1433, 1269, 1140, 1025, 964, 754, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ:7.47 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.39-7.28 (3H, m, Ar*H*), 7.25 (1H, d, *J* = 16.4 Hz, Ar^{1}C*H*=CH-), 7.13 (1H, d, *J* = 16.6 Hz, Ar^{2}C*H*=CH-), 7.08 (1H, d, *J* = 16.6 Hz, Ar^{2}CH=C*H*-), 7.05-6.98 (2H, m, Ar*H*), 6.78 (2H, m, Ar*H* and Ar^{1}CH=C*H*-), 6.39 (1H, s, =C*H*), 3.90 (3H, s, OCH_3), 3.85 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 55.8, 55.9, 97.9, 109.1, 111.0, 111.2, 116.1, 121.1, 126.9, 128.5, 128.8, 134.7, 135.6, 135.8, 149.2, 150.1, 161.9, 168.5.

5-(2-(3,4-Dimethoxyphenyl)ethenyl)-3-[2-(4-methoxyphenyl)ethenyl] isoxazole (2f)

Yield: 0.19 g (52%); white crystals; mp 169-171 °C; IR (thin film) ν_{max}: 2962, 1643, 1603, 1581, 1512, 1430, 1264, 1174, 1140, 1026, 965, 821, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45 (2H, d, *J* = 8.6 Hz, Ar*H*), 7.27 (1H, d, *J* = 16.4 Hz, Ar^{1}C*H*=CH-), 7.10 (1H, d, *J* = 16.6 Hz, Ar^{2}C*H*=CH-), 7.05 (2H, d, *J* = 7.7 Hz, Ar*H*), 6.98 (1H, d, *J* = 16.4 Hz, Ar^{2}CH=C*H*-), 6.93-6.84 (3H, m, Ar*H*), 6.81 (1H, d, *J* = 16.4 Hz, Ar^{1}CH=C*H*-), 6.40 (1H, s, =C*H*), 3.93(3H, s, OCH_3), 3. 90 (3H, s, OCH_3), 3.82 (3H, s, OCH_3);^{13}C NMR ($CDCl_3$) δ: 55.3, 55.9, 97.8, 109.1, 111.1, 111.2, 113.9, 114.3, 121.1, 128.3, 128.6, 134.6, 135.2, 149.2, 150.2, 160.2, 162.2, 168.4.

General procedure for reductive ring opening of 3,5-bis(2-arylethenyl) isoxazoles 2a-f

A solution of a 3,5-bis(2-arylethenyl) isoxazole (0.4 mmol), water (0.4 mmol) and [$Mo(CO)_6$] (0.2 mmol) in acetonitrile (8 ml) was heated under reflux temperature for 24 hours and cooled to room temperature. The reaction mixture was filtered through Celite and evaporated to dryness under reduced pressure. Purification of the residue using column chromatography on silica gel with 30% ethyl acetate/ hexane as an eluent gave1,7-diaryl-5-amino-1,4,6-heptatrien-3-ones **8a-f** (43-56%) as yellow crystalline solids or as yellow oils.

5-*Amino*-1,7-diphenylhepta-1,4,6-trien-3-one (8a)

Yield: 61.5 mg (56%); yellow crystals; mp 145-147°C; IR (thin film) ν_{max}: 3388, 3196, 1634, 1570, 1519, 1149, 966, 754, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.60-7.54 (3H, m, Ar*H* and Ar^{1}C*H*=CH-), 7.49 (2H, d, *J* = 7.1 Hz, Ar*H*) 7.41-7.30 (6H, m, Ar*H*), 7.11 (1H, d, *J* = 16.4 Hz, Ar^{2}C*H*=CH-), 6.79 (1H, d, *J* = 15.9 Hz, Ar^{2}CH=C*H*-), 6.53 (1H, d, *J* = 16.4 Hz, Ar^{1}CH=C*H*-), 5.53 (1H, s, =C*H*CO); ^{13}C NMR ($CDCl_3$) δ: 98.7, 124.8, 127.4, 127.9, 128.6, 128.8, 129.0, 129.4, 129.5, 134.5,135.2, 135.7, 138.7, 157.7, 188.4.

5-*Amino*-1,7-bis(4-methoxyphenyl)-1,4,6-heptatrien-3-one (8b)

Yield: 66.8 mg (50%); yellow crystals; mp 158-160°C; IR (thin film) ν_{max}: 3393, 3006, 1630, 1601, 1565, 1515, 1256, 1174, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.56-7.47 (3H, m, Ar*H* and Ar^{1}C*H*=CH-), 7.43 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.05 (1H, d, *J* = 16.3 Hz, Ar^{2}C*H*=CH-), 6.93-6.86 (4H, m, Ar*H*), 6.66 (1H, d, *J* = 15.8 Hz, Ar^{2}CH=C*H*-), 6.39 (1H, d, *J* = 16.3 Hz, Ar^{1}CH=C*H*-), 5.47 (1H, s, =C*H*CO), 3.83 (6H, s, 2xOCH_3);^{13}C NMR ($CDCl_3$) δ: 55.3, 55.4, 98.4, 114.2, 114.4, 122.4, 126.6, 128.0, 128.5, 128.8, 129.4, 134.0, 138.2, 158.1, 160.7, 188.3.

5-*Amino*-1,7-bis(3,4-dimethoxyphenyl)-1,4,6-heptatrien-3-one (8c)

Yield: 76.2 mg (48%); yellow oil; IR (thin film) ν_{max}: 3417, 2937, 1629, 1587, 1513, 1461, 1263, 1139, 1024, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.51 (1H, d, *J* = 15.7 Hz, Ar^{1}C*H*=CH-), 7.14-7.01 (5H, m, Ar*H* and Ar^{2}C*H*=CH-), 6.85 (2H, d, *J* = 8.3 Hz, Ar*H*), 6.67 (1H, d, *J* = 15.8 Hz, Ar^{2}CH=C*H*-), 6.39 (1H, d, *J* = 16.3 Hz, Ar^{1}CH=C*H*-), 5.52 (1H, s, =C*H*CO),3.92 and 3.90 (12H, 2s, 4xOCH_3);^{13}C NMR ($CDCl_3$) δ: 55.9, 56.0, 98.3, 109.3, 109.7, 111.1, 111.2, 121.5, 122.2, 122.6, 126.7, 128.3, 128.8, 134.4, 138.5, 149.1, 149.3, 150.4, 158.1, 188.2.

5-*Amino*-1-(4-methoxyphenyl)-7-phenyl-1,4,6-heptatrien-3-one (8d)

Yield: 66.0 mg (54%); yellow crystals; mp 161-162 °C; IR (thin film) ν_{max}: 3364, 3008, 1631,

1602, 1564, 1515, 1256, 1145, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.56-7.45 (5H, m, Ar*H* and Ar^1CH=CH-), 7.42-7.29 (3H, m, Ar*H*), 7.09 (1H, d, *J* = 16.4 Hz, Ar^2CH=CH-), 6.88 (2H, d, *J* = 8.4 Hz, Ar*H*), 6.67 (1H, d, *J* = 15.8 Hz, Ar^2CH=C*H*-), 6.51 (1H, d,*J* = 16.4 Hz, Ar^1CH=C*H*-), 5.49 (1H, s, =C*H*CO), 3.81 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 55.3, 98.8, 114.2, 124.9, 126.5, 127.3, 128.4, 128.9, 129.3, 129.5, 134.3, 135.3, 138.5, 157.5, 160.8, 188.6.

5-*Amino*-1-(3,4-dimethoxyphenyl)-7-phenyl-1,4,6-heptatrien-3-one (8e)

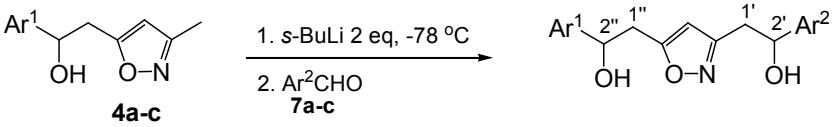
Yield: 62.6mg (47%); yellow oil; IR (thin film) ν_{max}: 3395, 2959, 1631, 1575, 1516, 1264, 1139, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.55-7.47 (3H, m, Ar*H* and Ar^1CH=CH-), 7.41-7.31 (3H, m, Ar*H*), 7.14-7.08 (3H, m, Ar*H* and Ar^2CH=CH-), 6.85 (1H, d, *J* = 8.3 Hz, Ar*H*), 6.68 (1H, d, *J* = 15.8 Hz, Ar^2CH=C*H*-), 6.52 (2H, d, *J* = 16.4 Hz, Ar^1CH=C*H*-), 5.53 (1H, s, =C*H*CO),3.92(3H, s, OCH_3), 3.90 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 55.9, 56.0, 98.6, 109.8, 111.2, 122.2, 124.9, 126.7, 127.3, 128.7, 128.9, 129.4, 134.3, 135.3, 138.7, 149.2, 150.5, 157.5, 188.5.

5-Amino-1-(3,4-dimethoxyphenyl)-7-(4-methoxyphenyl)-1,4,6-heptatrien-3-one (8f)

Yield: 62.7 mg (43%); yellow oil; IR (thin film) ν_{max}: 3394, 2964, 1597, 1514, 1262, 1141, 1027, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.51 (1H, d, *J* = 15.7 Hz, Ar^1CH=CH-), 7.43 (2H, d, *J* = 8.6 Hz, Ar*H*), 7.15-7.02 (3H, m, Ar*H* and Ar^2CH=CH-), 6.92-6.82 (3H, m,Ar*H*), 6.67 (1H, d, *J* = 15.7 Hz, Ar^2CH=C*H*-), 6.39 (1H, d, *J* = 16.3 Hz, Ar^1CH=C*H*-), 5.50 (1H, s, =C*H*CO), 3.92 (3H, s, OCH_3), 3.90 (3 H, s, OCH_3), 3.83 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ:55.3, 55.9, 98.1, 109.7, 111.1, 114.4, 122.2, 122.3, 126.9, 128.0, 128.8, 134.2, 138.4, 149.1, 150.4, 158.3, 160.7, 188.1.

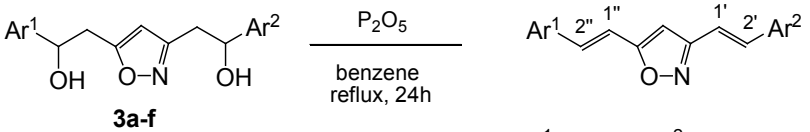
General procedure for hydrolysis of 5-amino-1,7-diaryl-1,4,6-heptatrien-3-ones 8a-f

To a stirred solution of 5-amino-1-aryl-1,4-hexadien-3-one (0.1 mmol) in ethanol (1.5 ml) was added concentrated HCl dropwise to adjust the pH between 4 and 5. The solution was then stirred at 50°C. After 24 hours,the reaction mixture was neutralized with a saturated K_2CO_3 solution.



3a; $Ar^1 = C_6H_5$, $Ar^2 = C_6H_5$, 48%
3b; $Ar^1 = 4\text{-}OMeC_6H_4$, $Ar^2 = 4\text{-}OMeC_6H_4$, 49%
3c; $Ar^1 = 3,4\text{-}diOMeC_6H_3$, $Ar^2 = 3,4\text{-}diOMeC_6H_3$, 65%
3d; $Ar^1 = 4\text{-}OMeC_6H_4$, $Ar^2 = C_6H_5$, 57%
3e; $Ar^1 = 3,4\text{-}diOMeC_6H_3$, $Ar^2 = C_6H_5$, 51%
3f; $Ar^1 = 3,4\text{-}diOMeC_6H_3$, $Ar^2 = 4\text{-}OMeC_6H_4$, 46%

Scheme 3:



2a; $Ar^1 = C_6H_5$, $Ar^2 = C_6H_5$, 66%
2b; $Ar^1 = 4\text{-}OMeC_6H_4$, $Ar^2 = 4\text{-}OMeC_6H_4$, 61%
2c; $Ar^1 = 3,4\text{-}diOMeC_6H_3$, $Ar^2 = 3,4\text{-}diOMeC_6H_3$, 56%
2d; $Ar^1 = 4\text{-}OMeC_6H_4$, $Ar^2 = C_6H_5$, 60%
2e; $Ar^1 = 3,4\text{-}diOMeC_6H_3$, $Ar^2 = C_6H_5$, 58%
2f; $Ar^1 = 3,4\text{-}diOMeC_6H_3$, $Ar^2 = 4\text{-}OMeC_6H_4$, 52%

Scheme 4:

The aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduce pressure. Purification of the residue using column chromatography on silica gel with a gradient of 30-50% ethyl acetate/hexane as eluent gave 1-aryl-5-hydroxy-1,4-hexadien-3-ones **1a-f** (48-63%) as crystalline solids.

5-Hydroxy-1,7-diphenylhepta-1,4,6-trien-3-one (1a)

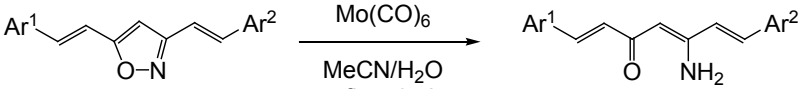
Yield: 14.4 mg (52%); yellow crystals; mp 146-148°C; IR (thin film) ν_{max}: 3057, 1627, 1581, 1445, 1275, 1139, 972, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.67 (2H, d, *J* = 15.9 Hz, Ar^1CH=CH- and Ar^2CH=CH-), 7.56 (4H, dd, *J* = 7.4 and 1.8 Hz, Ar*H*), 7.44-7.34 (6H, m, Ar*H*), 6.64 (2H, d, *J* = 15.9 Hz, Ar^2CH=C*H*- and Ar^1CH=C*H*-), 5.86 (1H, s, =C*H*CO); ^{13}C NMR ($CDCl_3$) δ: 101.8, 124.1, 128.1, 128.9, 130.1, 135.0, 140.6, 183.3.

5-Hydroxy-1,7-Bis(4-methoxyphenyl)-1,4,6-heptatrien-3-one (*1b*)

Yield: 21.2 mg (63%); orange crystals;mp 175-177°C; IR (thin film) ν_{max}: 3037, 2933, 2838, 1628, 1600, 1574, 1512, 1461, 1253, 1173, 1138, 1031, 974, 828 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) d: 7.62 (2H, d, *J* = 15.8 Hz, Ar^1CH=CH- and Ar^2CH=CH-), 7.50 (4H, d, *J* = 8.7 Hz, Ar*H*), 6.91 (4H, d, *J* = 8.7 Hz, Ar*H*), 6.49 (2H, d, *J* = 15.8 Hz, Ar^2CH=C*H*- and Ar^1CH=C*H*-), 5.78 (1H, s, =C*H*CO), 3.84 (6H, s, 2xOCH_3); ^{13}C NMR ($CDCl_3$) δ: 55.4, 101.3, 114.4, 121.8, 127.8, 129.8, 140.1, 161.3, 183.3.

5-Hydroxy-1,7-Bis(3,4-dimethoxyphenyl)-1,4,6-heptatrien-3-one (1c)

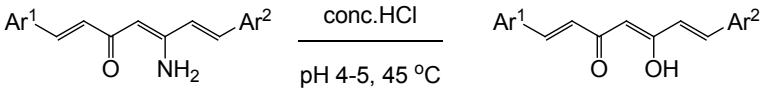
Yield: 19.5 mg (49%); orange crystals; mp115-117°C; IR (thin film) ν_{max}:2935, 2837, 1624, 1583, 1512, 1462, 1262, 1136, 1023, 969, 808 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.61 (2H, d, *J* = 15.8 Hz, Ar^1CH=CH- and Ar^2CH=CH-), 7.14 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.08 (2H, s, Ar*H*), 6.88 (2H, d, *J* = 8.3 Hz, Ar*H*), 6.50 (2H, d, *J* = 15.8 Hz, Ar^2CH=C*H*- and Ar^1CH=C*H*-), 5.82 (1H, s, =C*H*), 3.93 (6 H, s, 2xOCH_3), 3.92 (6H, s, 2xOCH_3); ^{13}C NMR ($CDCl_3$) δ: 55.9, 56.0, 101.3, 109.8, 111.2, 122.1, 122.6, 128.1, 140.4, 149.3, 151.1, 183.3.



2a-f

8a; Ar^1 = C_6H_5, Ar^2 = C_6H_5, 56%
8b; Ar^1 = 4-$OMeC_6H_4$, Ar^2 = 4-$OMeC_6H_4$, 50%
8c; Ar^1 = 3,4-di$OMeC_6H_3$, Ar^2 = 3,4-di$OMeC_6H_3$, 48%
8d; Ar^1 = 4-$OMeC_6H_4$, Ar^2 = C_6H_5, 54%
8e; Ar^1 = 3,4-di$OMeC_6H_3$, Ar^2 = C_6H_5, 47%
8f; Ar^1 = 3,4-di$OMeC_6H_3$, Ar^2 = 4-$OMeC_6H_4$, 43%

Scheme 5:



8a-f

1a; Ar^1 = C_6H_5, Ar^2 = C_6H_5, 52%
1b; Ar^1 = 4-$OMeC_6H_4$, Ar^2 = 4-$OMeC_6H_4$, 63%
1c; Ar^1 = 3,4-di$OMeC_6H_3$, Ar^2 = 3,4-di$OMeC_6H_3$, 49%
1d; Ar^1 = 4-$OMeC_6H_4$, Ar^2 = C_6H_5, 48%
1e; Ar^1 = 3,4-di$OMeC_6H_3$, Ar^2 = C_6H_5, 51%
1f; Ar^1 = 3,4-di$OMeC_6H_3$, Ar^2 = 4-$OMeC_6H_4$, 52%

Scheme 6:

5-Hydroxy-1-(4-methoxyphenyl)-7-phenyl-1,4,6-heptatrien-3-one (1d)

Yield: 14.7 mg (48%); yellow crystals; mp 140-142°C; IR (thin film) ν_{max}: 3050, 2933, 2836, 1623, 1601, 1576, 1512, 1447, 1255, 1175, 1140, 1028, 977, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ:7.64 (1H, d, *J* = 15.9 Hz, Ar^2CH=CH-), 7.63 (1H, d, *J* = 15.8 Hz, Ar^1CH=CH-), 7.55 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.51 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.43-7.35 (3H, m, Ar*H*), 6.91 (2H, d, *J* = 8.2 Hz, Ar*H*), 6.61 (1H, d, *J* = 15.9 Hz, Ar^2CH=CH-), 6.51 (1H, d, *J* = 15.8 Hz, Ar^1CH=CH-), 5.81 (1H, s, =CHCO), 3.83 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 55.4, 101.6, 114.4, 121.8, 124.1, 127.7, 128.1, 128.9, 129.8, 135.1, 140.1, 140.6, 161.4, 182.2, 184.4.

5-Hydroxy-1-(3,4-dimethoxyphenyl)-7-phenyl-1,4,6-heptatrien-3-one (1e)

Yield: 17.1 mg (51%); orange crystals; mp 138-139°C; IR (thin film) ν_{max}: 2934, 2837, 1624, 1581, 1511, 1446, 1420, 1261, 1136, 1023, 968 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.65 (1H, d, *J* = 15.9 Hz, Ar^2CH=CH-), 7.62 (1H, d, *J* = 15.7 Hz, Ar^1CH=CH-), 7.55 (2H, d, *J* = 7.6, Ar*H*), 7.43-7.34 (3H, m, Ar*H*), 7.15 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.08 (1H, s, Ar*H*), 6.88 (1H, d, *J* = 8.3 Hz, Ar*H*), 6.62 (1H, d, *J* = 15.8 Hz, Ar^2CH=CH-), 6.52 (1H, d, *J* = 15.8 Hz, Ar^1CH=CH-), 5.84 (1H, s, =CHCO), 3.94(3H, s, OCH_3), 3.92 (3 H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 55.9, 56.0, 101.5, 109.9, 111.2, 122.1, 122.8, 124.1, 128.0, 128.1, 128.9, 130.0, 135.1, 140.2, 140.8, 149.3, 151.2, 182.4, 184.2.

5-Hydroxy-1-(3,4-dimethoxyphenyl)-7-(4-methoxyphenyl)-1,4,6-heptatrien-3-one (1f)

Yield: 19.0 mg (52%); orange crystals; mp 155-157°C; IR (thin film) ν_{max}: 3002, 2935, 1625, 1595, 1512, 1461, 1256, 1172, 1136, 1025, 970, 829 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.62 (1H, d, *J* = 15.8 Hz, Ar^2CH=CH-), 7.60 (1H, d, *J* = 15.8 Hz, Ar^1CH=CH-), 7.50 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.13 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.08 (1H, d, *J* = 1.5 Hz, Ar*H*), 6.91 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.87 (1H, d, *J* = 8.3 Hz, Ar*H*), 6.49 (2H, d, *J* = 15.8 Hz, Ar^1CH=CH- and Ar^2CH=CH-), 5.80 (1H, s, =CHCO), 3.93(3H, s, OCH_3), 3.91 (3 H, s, OCH_3), 3.84 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 55.4, 55.9, 56.0, 101.3, 109.8, 111.2, 114.4, 121.8, 122.1, 122.6, 127.8, 128.1, 129.8, 140.2, 140.3, 149.3, 151.1, 161.3, 183.1, 183.4.

RESULTS AND DISCUSSION

3,5-Dimethylisoxazole (**5**) used in our study was readily prepared in 82% yield from condensation between 2,4-pentanedione (**6**) with hydroxylamine hydrochloride in aqueous ethanol at reflux temperature for 3 hours.[10]

Lateral metalation of 3,5-dimethylisoxazole (**5**) occurred regiospecifically at the C_5-methyl group upon treatment with either *n*-BuLi[12] or $NaNH_2$.[13] Metalation at the 3-methyl group could be accomplished when metalating agent was either *s*-BuLi or *t*-BuLi.[14]

As expected, lateral metalation of 3,5-dimethylisoxazole (**5**) with *n*-BuLi in THF at -78°C for 1 hour followed by quenching with aromatic aldehydes **7a-c** gave the corresponding 5-(2-aryl-2-hydroxyethyl)-3-methylisoxazoles **4a-c** in good yields (Scheme 2).

Further treatment of 5-(2-aryl-2-hydroxyethyl)-3-methylisoxazoles **4a-c** with 2 equivalents of *s*-BuLi at -78 °C followed by quenching with aromatic aldehydes **7a-c** led to the formation of four diastereomers of the corresponding 3,5-bis(2-aryl-2-hydroxyethyl)isoxazoles **3a-f** in moderate yields (Scheme 3).

Since P_2O_5 is a very efficient dehydrating agent, it was used as such in dehydration of 3,5-bis(2-aryl-2-hydroxyethyl)isoxazoles **3a-f**. In benzene at reflux temperature[15] (Scheme 4), the reaction between carbinols **3a-f** and P_2O_5 furnished the corresponding 3,5-bis(2-arylethenyl) isoxazoles **2a-f** in moderate yields.

The weak N–O bond of isoxazole ring is easily cleaved into β-aminoenone by either catalytic hydrogenolysis with platinum or palladium and Raney nickel under normal pressure and temperature[16,17] or by treatment with transition metal carbonyls such as molybdenum hexacarbonyl [$Mo(CO)_6$].[18] To avoid catalytic hydrogenation at the two styryl groups, 3,5-bisstyrylisoxazoles **2a-f** were treated with molybdenum hexacarbonyl in moist acetonitrile at reflux temperature. This treatment successfully provided the corresponding 1,7-diaryl-5-amino-1,4,6-

heptatrien-3-ones **8a-f** in moderate yields (Scheme 5).

β-Aminoenones are easily transformed into β-hydroxyenones by simple acidic hydrolysis.[19,20] In our final step, hydrolysis of β-aminoenones **8a-f** was carried out by treatment with hydrochloric acid in ethanol at pH 4-5. The corresponding curcumin derivatives, in their enol forms **1a-f** were obtained in satisfied yields (Scheme 6).

CONCLUSIONS

The present six steps procedure provides a novel alternative route to symmetrical and unsymmetrical curcumin derivatives. Good to moderate yields of expected products were obtained from each step.

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