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Studies in sigmatropic rearrangement: synthesis of 4-aryloxy-methylene-1,7-dimethyl-1,2,3-trihydropyridino-[3,2-*c*]pyran-5-ones

K. C. Majumdar* and S. Ghosh

Department of Chemistry, University of Kalyani, Kalyani 741235, W.B., India

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Abstract—A number of 4-[*N*-4′-aryloxy but-2-ynyl *N*-methyl amino-6-methyl pyran-2-ones **(4a–g)** have been prepared in excellent yields from *N*-(1-aryloxy-but-2-ynyl)-*N*-methyl amine (**3**) and 4-tosyloxy-6-methyl-pyran-2-one (**2**). Thermal rearrangement of compounds **4(a–g)** gave 4-aryloxy-methyl-1,7-dimethyl-1,2-dihydropyridino-[3,2-*c*] pyran-5-ones (**6**) and/or 4-aryloxymethylene-1,7-dimethyl-1,2,3-trihydro-pyridino-[3,2-*c*] pyran-5-ones (**5**). © 2001 Published by Elsevier Science Ltd.

4-Hydroxy-6-methyl-2-pyrone (triacetic acid lactone) **1** is a natural product of polyketide origin.[1] This may also be obtained by deacetylation of dehydroacetic acid.[2] Many natural products containing the basic structures of 4-hydroxy or (methoxy)-6-methyl-2-pyrone have been isolated, some of them carrying biogenetically plausible groups at C3 or C5 or both. Elasnin, isolated from *Streptomices* sp., for example, is a specific inhibitor of human leucocyte elastase, an enzyme involved in inflammatory processes such as pulmonary emphysema.[3] As a logical extension, many more simple pyrones structurally related to elasnin have been synthesized and evaluated as inhibitors of several elastases.[4] Some 4-hydroxy-2-pyrones have also been tested as anticoagulant agents.[5] In a continuation of our work on the synthesis of bioactive heterocycles by the application of [3,3] sigmatropic rearrangements[6–10] we became interested in incorporating the 4-hydroxy-6-methyl-2-pyrone system in the substrates in order to achieve the synthesis of new heterocycles.

The starting materials, 4-(*N*-4′-aryloxybut-2-ynyl)-4-*N*-methylamino-6-methyl-pyran-2-ones **4(a–g)** were synthesized from 4-hydroxy-6-methyl-pyran-2-one (**1**). Compound **1** was converted to its tosyl derivative[11] (**2**) which was then allowed to react with 4-aryloxybut-2-ynylmethyl-amine in alcohol at room temperature for 12–16 h to give starting materials **4(a–g)** in 80–90% yields (Scheme 1).

1. Results and discussion

Substrates **4(a–g)** contain a vinyl propargylamine moiety as well as aryl propargyl ether moiety and it is reasonable to expect that these may undergo a [3,3] sigmatropic rearrangement. With this goal, substrate **4a** was refluxed in chlorobenzene but the starting material was found unchanged even after 5 h. Solvents with higher boiling points were then tried, but **4a** failed to record any change even when it was heated in *o*-dichlorobenzene at 150, 160 and 170°C in an oil bath. Then **4a** was refluxed in *o*-dichlorobenzene at 178–181°C and a change was observed on TLC within 1 h of beginning the reaction. Complete disappearence of starting material required almost 12 h. but the yield of the product **5a** was found to be extremely low with the formation of some untractable mass. Then the reaction time was optimized to 2–2.5 h when the yield of the product **5a** was found to be the maximum. However, a fairly large quantity of starting material **4a** (~40%) was found to remain unchanged. This was recovered and subjected again to rearrangement in order to obtain more of the product **5a**. Product **5a** was characterized from its elemental analysis and spectral data. The ^{1}H NMR spectrum of **5a** showed two triplets for two methylenes each with *J* values of 6 Hz centered at δ 2.85 and δ 3.37 and a one proton singlet at δ 7.99. This NMR pattern with other data indicated this to be the exocyclic product **5a**. This was also corroborated by a proton decoupling experiment. Unusual exocyclic products **5(a–g)** were obtained in all cases. The endocyclic product **6** was only obtained in three cases **(a,b,c)** along with the exocyclic product. When the rearrangements of **4(a,b,c)** were monitored by TLC, only spots corresponding to endocyclic products **6(a,b,c)** were found up to 30 min after the commencement of the reaction. After 30 min the spots of **5(a,b,c)** began to appear. Compounds **6(a,b,c)** afforded a mixture of **5(a,b,c)** and **6(a,b,c)** when refluxed in *o*-dichlorobenzene for 1 h. It could, therefore, be concluded that both the compounds **5**

* Corresponding author. Tel.: +33-582-8750; fax: +33-582-8282; e-mail: kcm@klyuniv.ernet.in

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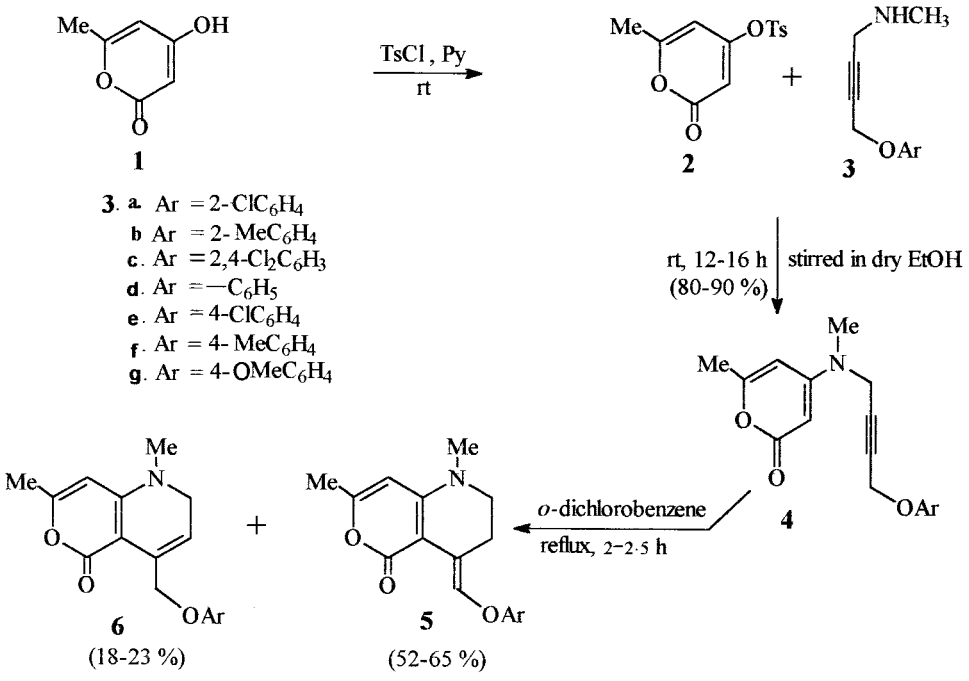


Scheme 1.

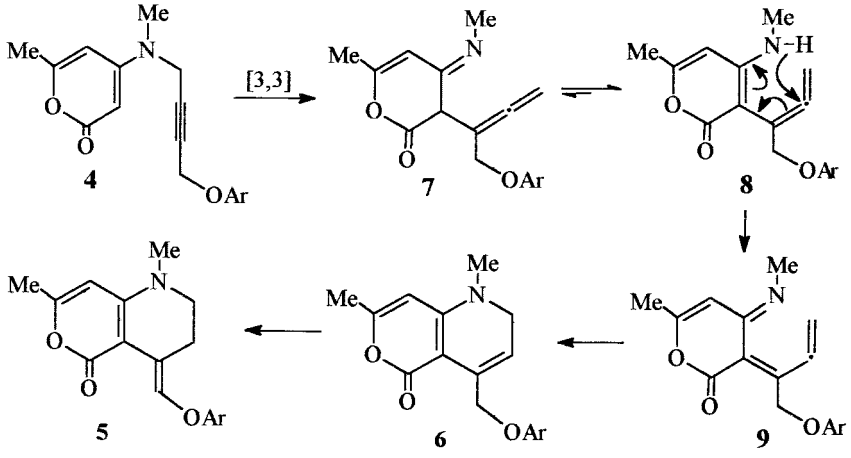
and **6** were formed through the same mechanistic pathway. All the foregoing facts could be explained with the assumption that the endocyclic compound **6** was converted into the exocyclic **5** under the reaction conditions. Formation of **6** from **4** can easily be explained[12] as in Scheme 2.

[3,3] Sigmatropic rearrangement of **4** afforded allene **7**. Compound **7** may undergo tautomerisation to furnish **8** followed by [1,5] H shift to give **9** and 6π electrocyclic ring closure finally gives **6**. Compound **6** may undergo prototropic rearrangement under the reaction conditions to generate **5**. One striking feature is that the presence of *o*-substituents in the phenyl ring permits formation of *endo*-cyclic product **6**. This prompted us to conclude that the *o*-substituent in the phenyl ring probably destabilised the exocyclic derivatives **5(a,b,c)** thereby allowing isolation of **6(a,b,c)**.

The reaction is found to be of general nature. All the seven substrates underwent [3,3] sigmatropic rearrangement at the vinyl amine moiety instead of the propargyl ether part.[13] Exocyclic products were obtained in all cases whereas *endo*-cyclic products were isolated only in cases where the aryloxy group contained *ortho*-substituents.

2. Experimental

Melting points were measured on a sulphuric acid bath and are uncorrected. UV absorption spectra were recorded in EtOH on a Hitachi 200-20 Spectrophotometer. IR spectra were run on KBr disks on a Perkin–Elmer 1330 apparatus. ^{1}H NMR spectra were determined for solutions in $CDCl_3$ with TMS as internal standard on a Bruker 300 (300 MHz) instrument. Elemental analyses and recording of mass spectra were carried out by RSIC (CDRI), Lucknow on a JEOL D-300 (El) instrument. Silica gel (60–120 mesh), Spectrochem, India, was used for chromatographic



Scheme 2.

separation. Petroleum ether refers to the fraction boiling between 60 and 80°C.

2.1. Preparation of 1-(aryloxy)-4-*N*-methylaminobut-2-yne

1-(Aryloxy)-4-chlorobut-2-yne (1 g) was dissolved in 20 ml of EtOH. This solution was added dropwise at room temperature to a well stirred solution of 23 ml of methylamine (40%) for a period of 10 min. Stirring was continued for another 2 h at room temperature. Methylamine, water and EtOH were removed in vacuo and the residual mass was dissolved in $CHCl_3$ (25 ml). This was washed with water (2×10 ml) and dried (Na_2SO_4). Removal of $CHCl_3$ afforded a gummy mass. Attempt to purify this gummy mass through column chromatography failed and so it was directly used for the subsequent reactions.

2.2. General procedures for the synthesis of compounds 4(a–g)

A mixture of 1-(aryloxy)-4-*N*-methylaminobut-2-yne (5 mmol) and 4-tosyloxy-6-methyl-2-pyrone (0.40 g, 3.3 mmol) in dehydrated EtOH was stirred for 12–16 h at room temperature. Alcohol was removed by distillation and the residual mass was dissolved in $CHCl_3$ (50 ml). This was washed with water (2×25 ml) and dried (Na_2SO_4). Evaporation of $CHCl_3$ afforded a gummy mass which was subjected to column chromatography over silica gel. Elution of the column with benzene-ethyl acetate (3:1) gave compounds **4(a–g)**. All the compounds **4(a–g)** were recrystallised from $CHCl_3$-petroleum ether.

2.2.1. 4-[*N*-[4-(2′-Chlorophenoxy)-but-2-ynyl)-*N*-methylamino-6-methyl-2-pyrone (4a). Yield 90%; mp. 136–138°C; λ_{max}: (log ε) 224 (4.09), 297 (3.53) nm; IR (KBr) ν_{max}: 1690, 1525, 1485, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.17 (s, 3H), 2.97 (s, 3H), 4.03 (t, *J*=1.8 Hz, 2H), 4.78 (t, *J*=1.8 Hz, 2H), 5.05 (s, 1H), 5.75 (s, 1H), 6.95–7.38 (m, 4H); MS m/z 317, 319 (M^+); Anal Calcd. for $C_{17}H_{16}ClNO_3$: C, 64.25; H, 5.03; N, 4.40. Found C, 64.40; H, 5.15; N, 4.48%.

2.2.2. 4-[*N*-[4-(2′-Methylphenoxy)-but-2-ynyl)-*N*-methylamino-6-methyl-2-pyrone (4b). Yield 89%; mp. 105–106 °C; λ_{max}: (log ε) 224 (3.91), 297 (3.38) nm; IR (KBr) ν_{max}: 1690, 1525, 1485, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.18 (s, 3H), 2.22 (s, 3H), 2.98 (s, 3H), 4.04 (t, *J*=1.8 Hz, 2H), 4.71 (t, *J*=1.8 Hz, 2H), 5.08 (s, 1H), 5.78 (s, 1H), 6.89–7.14 (m, 4H); MS m/z 297 (M^+); Anal Calcd. For $C_{18}H_{19}NO_3$: C, 72.72; H, 6.39; N, 4.71. Found C, 72.82; H, 6.51; N, 4.82%.

2.2.3. 4-[*N*-[4-(2′,4′-Dichlorophenoxy)-but-2-ynyl)-*N*-methylamino-6-methyl-2-pyrone (4c). Yield 85%; mp. 127–129 °C; $\lambda_{max:}$ (log ε) 226 (4.21), 293 (3.75) nm; IR (KBr) ν_{max}: 1690, 1530, 1480, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.18 (s, 3H), 2.97 (s, 3H), 4.03 (t, *J*=1.8 Hz, 2H), 4.76 (t, *J*=1.8 Hz, 2H), 5.06 (s, 1H), 5.74 (s, 1H), 6.81–7.37 (m, 3H); MS m/z 351, 353, 355 (M^+); Anal Calcd. For $C_{17}H_{15}Cl_2NO_3$: C, 57.95; H, 4.26; N, 3.97. Found C, 58.05; H, 4.36; N, 4.11%.

2.2.4. 4-[*N*-[4-Phenoxybut-2-ynyl)-*N*-methylamino-6-methyl-2-pyrone (4d). Yield 86%; mp. 80–82 °C; λ_{max}: (log ε) 224 (4.02), 297 (3.48) nm; IR (KBr) ν_{max}: 1690, 1530,1490, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.17 (s, 3H), 2.97 (s, 3H), 4.04 (t, *J*=1.8 Hz, 2H), 4.69 (t, *J*=1.8 Hz, 2H), 5.07 (s, 1H), 5.76 (s, 1H), 6.91–7.31 (m, 5H); MS m/z 283 (M^+); Anal Calcd. For $C_{17}H_{17}NO_3$: C, 72.08; H, 6.00; N, 4.94. Found C, 72.20; H, 6.15; N, 4.81%.

2.2.5. 4-[*N*-[4-(4′-Chlorophenoxy)-but-2-ynyl)-*N*-methylamino-6-methyl-2-pyrone (4e). Yield 82%; mp. 84–85 °C; λ_{max}: (log ε) 226 (4.47), 295 (3.90) nm; IR (KBr) ν_{max}: 1690, 1530, 1485, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.18 (s, 3H), 2.98 (s, 3H), 4.04 (t, *J*=1.8 Hz, 2H), 4.67 (t, *J*=1.8 Hz, 2H), 5.07 (s, 1H), 5.76 (s, 1H), 6.85–7.25 (m, 4H); MS m/z 317, 319 (M^+); Anal Calcd. For $C_{17}H_{16}ClNO_3$: C, 64.25; H, 5.03; N, 4.40. Found C, 64.42; H, 5.20; N, 4.26%.

2.2.6. 4-[*N*-[4-(4′-Methylphenoxy)-but-2-ynyl)-*N*-methylamino-6-methyl-2-pyrone (4f). Yield 90%; mp. 129–130 °C; λ_{max}: (log ε) 225 (4.31), 296 (3.76) nm; IR (KBr) ν_{max}: 1690, 1530, 1500, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.17 (s, 3H), 2.29 (s, 3H), 2.98, (s, 3H), 4.05 (t, *J*=1.8 Hz, 2H), 4.66 (t, *J*=1.8 Hz, 2H), 5.07 (s, 1H), 5.78 (s, 1H), 6.81–7.10 (m, 4H). MS m/z 297 (M^+); Anal Calcd. For $C_{18}H_{19}NO_3$: C, 72.72; H, 6.39; N,4.71. Found C, 72.90; H, 6.50; N, 4.86%.

2.2.7. 4-[*N*-[4-(4′-Methoxyphenoxy)-but-2-ynyl)-*N*-methylamino-6-methyl-2-pyrone (4g). Yield 80%; mp. 96–98 °C; λ_{max}: (log ε) 226 (4.46), 294 (4.00) nm; IR (KBr) ν_{max}: 1700, 1535, 1490, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.17 (s, 3H), 2.98 (s, 3H), 3.77 (s, 3H), 4.04 (t, *J*=1.8 Hz, 2H), 4.64 (t, *J*=1.8 Hz, 2H), 5.07 (s, 1H), 5.77 (s, 1H), 6.83–6.85 (m, 4H); MS m/z 313 (M^+); Anal Calcd. For $C_{18}H_{19}NO_4$: C, 69.00; H, 6.07; N, 4.47. Found C, 69.11; H, 6.20; N, 4.38%.

2.3. General procedures for the synthesis of compounds 5(a–g) and 6(a–g)

Compounds **4a–g** (300 mg) were refluxed in *o*-dichlorobenzene (3 ml) for 2–2.5 h. The reaction mixture was then cooled and directly subjected to column chromatography over silica gel. *o*-Dichlorobenzene was eluted out with petroleum ether. All the products **5(a–g)** were obtained when the column was eluted with benzene-ethyl acetate (4:1). Compounds **6(a,b,c)** were eluted with benzene-ethyl acetate (3:1). Unchanged starting materials **4(a–g)** were also carefully eluted out with benzene-ethyl acetate (3:1). Compounds **5(a–g)** and **6(a,b,c)** were recrystallised from $CHCl_3$-petroleum ether. The yields were calculated on the basis of actual conversion of starting material.

2.3.1. Compound (5a). Yield 58%; mp. 116–118 °C; λ_{max}: (log ε) 238 (4.09), 351 (3.86) nm; IR (KBr) ν_{max}: 1670, 1500, 1310, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.21 (s, 3H), 2.85 (t, *J*=6 Hz, 2H), 3.06 (s, 3H), 3.37 (t, *J*=6 Hz,2H), 5.82 (s, 1H), 6.93–7.37 (m, 4H), 7.99 (s, 1H). MS m/z 317, 319 (M^+); Anal Calcd. For $C_{17}H_{16}ClNO_3$: C, 64.25; H, 5.03; N, 4.40. Found C, 64.36; H, 5.18; N, 4.49%.

2.3.2. Compound (5b). Yield 54%; mp. 105–106 °C; λ_{max}: (log ϵ) 238 (4.29), 351 (4.02) nm; IR (KBr) ν_{max}: 1670, 1500, 1315, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.21 (s, 3H), 2.28 (s, 3H), 2.82 (t, *J*=6 Hz, 2H), 3.06 (s, 3H), 3.36 (t, *J*=6 Hz, 2H), 5.82 (s, 1H), 6.90–7.17 (m, 4H), 7.97 (s, 1H). MS m/z 297 (M^+); Anal Calcd. For $C_{18}H_{19}NO_3$: C, 72.72; H, 6.39; N, 4.71. Found C, 72.87; H, 6.48; N, 4.82%.

2.3.3. Compound (5c). Yield 64%; mp. 142–143 °C; λ_{max}: (log ϵ) 237 (4.06), 351 (3.93) nm; IR (KBr) ν_{max}: 1670, 1500, 1310, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.21 (s, 3H), 2.82 (t, *J*=6 Hz, 2H), 3.07 (s, 3H), 3.37 (t, *J*=6 Hz, 2H), 5.82 (s, 1H), 7.11–7.37 (m, 3H), 7.94 (s, 1H). MS m/z 351, 353, 355 (M^+); Anal. Calcd. For $C_{17}H_{15}Cl_2NO_3$: C, 57.95; H, 4.26; N, 3.97. Found C, 58.17; H, 4.40; N, 4.11%.

2.3.4. Compound (5d). Yield 65%; mp. 164–166 °C; λ_{max}: (log ϵ) 238 (4.31), 351 (4.07) nm; IR (KBr) ν_{max}: 1670, 1480, 1310, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.20 (s, 3H), 2.79 (t, *J*=6 Hz, 2H), 3.05 (s, 3H), 3.35 (t, J=6 Hz, 2H), 5.81 (s, 1H), 6.98–7.35 (m, 5H), 7.99 (s, 1H). MS m/z 283 (M^+); Anal Calcd. For $C_{17}H_{17}NO_3$: C, 72.08; H, 6.00; N, 4.94. Found C, 72.19; H, 6.16; N, 5.01%.

2.3.5. Compound (5e). Yield 56%; mp. 147–149 °C; λ_{max}: (log ϵ) 238 (4.18), 350 (3.92) nm; IR (KBr) ν_{max}: 1670, 1500, 1305, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.21 (s, 3H), 2.77 (t, *J*=6 Hz, 2H), 3.05 (s, 3H), 3.35 (t, *J*=6 Hz, 2H), 5.81 (s, 1H),, 6.99–7.26 (m, 4H), 7.93 (s,1H). MS m/z 317, 319 (M^+); Anal Calcd. For $C_{17}H_{16}ClNO_3$: C, 64.25; H, 5.03; N, 4.40. Found C, 64.48; H, 5.23; N, 4.52%.

2.3.6. Compound (5f). Yield 60%; mp. 122–123 °C; λ_{max}: (log ϵ) 237 (4.26), 351 (3.75) nm; IR (KBr) ν_{max}: 1670, 1500, 1310, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.20 (s, 3H), 2.29 (s, 3H), 2.79 (t, *J*=6 Hz, 2H), 3.05 (s, 3H), 3.35 (t, *J*=6 Hz, 2H), 5.81 (s, 1H), 6.96–7.10 (m, 4H), 7.95 (s, 1H); MS m/z 297 (M^+); Anal Calcd. For $C_{18}H_{19}NO_3$: C, 72.72; H, 6.39; N, 4.71. Found C, 72.91; H, 6.45; N 4.84%.

2.3.7. Compound (5g). Yield 52%; mp. 101–103 °C; λ_{max}: (log ϵ) 238 (4.10), 353 (3.83) nm; IR (KBr) ν_{max}: 1670, 1500, 1310, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.20 (s, 3H), 2.78 (t, *J*=6 Hz, 2H), 3.05 (s, 3H), 3.77 (s, 3H), 3.35 (t, *J*=6 Hz, 2H), 5.81 (s, 1H), 6.82–7.01 (m, 4H), 7.91 (s, 1H); MS m/z 313 (M^+); Anal Calcd. For $C_{18}H_{19}NO_4$: C, 69.00; H, 6.07; N, 4.47. Found C, 69.16; H, 6.21; N 4.61%.

2.3.8. Compound (6a). Yield 23%; mp. 146–147 °C; λ_{max}: (log ϵ) 242 (4.12), 276 (3.79) nm; IR (KBr) ν_{max}: 1670, 1480, 1305, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.19 (s, 3H), 2.89 (s, 3H), 4.21 (d, *J*=6 Hz, 2H), 5.61 (t, *J*=6 Hz,1H), 5.16 (brs, 2H), 5.74 (s, 1H), 6.84–7.35 (m, 4H); MS m/z 317, 319 (M^+); Anal Calcd. For $C_{17}H_{16}ClNO_3$: C, 64.25; H, 5.03; N, 4.40. Found C, 64.41; H, 5.17; N 4.51%.

2.3.9. Compound (6b). Yield 18%; mp. 131–132 °C; λ_{max}: (log ϵ) 242 (4.18), 278 (3.97) nm; IR (KBr) ν_{max}: 1670, 1480, 1310, 1285 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.19 (s, 3H), 2.27 (s, 3H), 2.90 (s, 3H), 4.20 (d, *J*=6 Hz, 2H), 5.50 (t, *J*=6 Hz, 1H), 5.11 (brs, 2H), 5.74 (s, 1H), 6.83–7.13 (m, 4H); MS m/z 297 (M^+); Anal Calcd. For $C_{18}H_{19}NO_3$: C, 72.72; H, 6.39; N, 4.71. Found C, 72.85; H, 6.48; N 4.87%.

2.3.10. Compound (6c). Yield 21%; mp. 156–158 °C; λ_{max}: (log ϵ) 237 (4.22), 279 (3.56) nm; IR (KBr) ν_{max}: 1670, 1470, 1310, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.19 (s, 3H), 2.90 (s, 3H), 4.21 (d, *J*=6 Hz, 2H), 5.55 (t, *J*=6 Hz, 1H), 5.13 (brs, 2H), 5.74 (s, 1H), 6.96–7.34 (m, 3H); MS m/z 351, 353, 355 (M^+); Anal Calcd. For $C_{17}H_{15}Cl_2NO_3$: C, 57.95; H, 4.26; N, 3.97. Found C, 58.10; H, 4.39; N 4.14%.

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