Synthesis of 2,6-Bis(1*H*-indole-6-yl)-4*H*-pyran-4-ones *via* Leimgruber–Batcho Indole Synthesis

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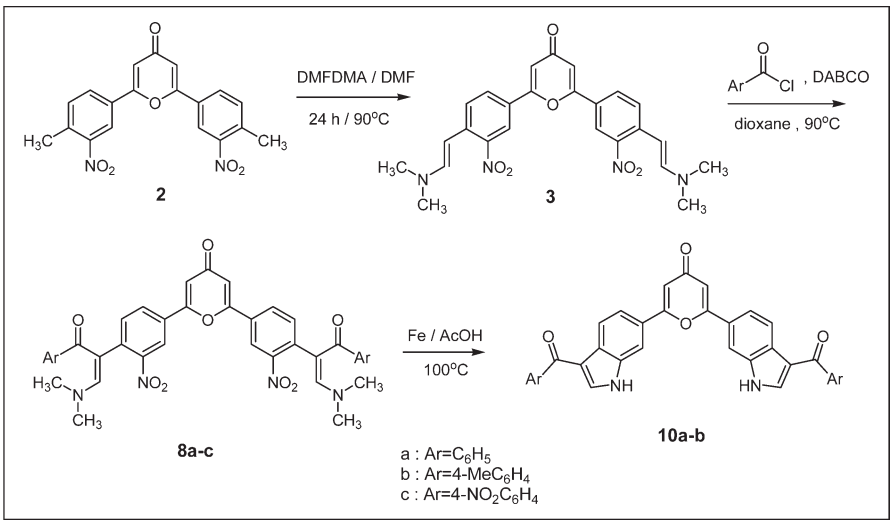
Received August 6, 2008
DOI 10.1002/jhet.80
Published online 13 April 2009 in Wiley InterScience (www.interscience.wiley.com).



2,6-Bis(1*H*-indole-6-yl)-4*H*-pyran-4-one **4** was synthesized *via* Leimgruber–Batcho methodology starting from 2,6-bis(4-methyl-3-nitrophenyl)-4*H*-pyran-4-one **2**. Enamine intermediate in this reaction, **3**, reacts with aroyl chlorides in the presence of 1,4-diazabicyclo[2.2.2]octane in dioxane to give the substituted enamines **8(a-c)**. Enamines **8a,b** undergo reductive cyclization with Fe/AcOH to the corresponding 3-aroylindoles **10a,b**.

J. Heterocyclic Chem., **46**, 273 (2009).

INTRODUCTION

The indole ring system is one of the most ubiquitous heterocycles in nature and an important structural component in many pharmaceutical agents [1]. Therefore synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed [2]. One powerful procedure is the Leimgruber–Batcho indole synthesis [3]. The classical sequence of this reaction that has been used for the preparation of 2,3-unsubstituted indoles, involves the condensation of methyl group positioned adjacent to an aromatic nitro group (as 2, Scheme 1) with *N,N*-dimethyl formamide-dimethyl acetal (DMFDMA) to give the enamine intermediate such as **3**. Subsequent reduction of the nitro group leads to spontaneous cyclization and formation of the corresponding indole derivative (as **4**). Modifications of Leimgruber–Batcho procedure to accelerate products formation [4] or to the production of *N*-substituted indoles [5] have also been described.

Synthesis of 3-substituted indoles has also received continued attention. 3-Acylindoles are precursors to a variety of biologically important alkaloids [6]. 3-Aroylindoles represent significant biological activities, for example, some of these have potential as promising anticancer agents [7]. For the synthesis of 3-aroylindoles, electrophilic substitution at C-3 position of indole ring through reaction of indoles with aroyl chlorides in the presence of Grignard reagents as base and/or metal chlorides as Lewis acid is well known [7]. Another appropriate method for synthesis of 3-substituted indoles, which include functionalization of enamine intermediates in Leimgruber–Batcho procedure, has rarely been reported [8]. This modification, in which reaction of the enamine intermediate with aroyl chlorides carried out in the presence of a tertiary amine, can be considerable for its potential regiochemical control in the synthesis of 3-substituted indoles.

Polycyclic aryl and heteroaryl substituted 4-pyrones have also been found in a variety of natural and synthetic biologically active compounds [9]. They have been shown to be anticoagulant [10a], anti-HIV [10b], and antitumor [10c] agents. Through our attempts to prepare various azaaryl substituted 4-pyrones, we turned

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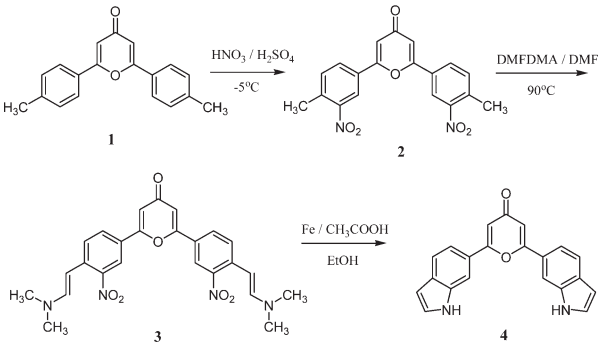
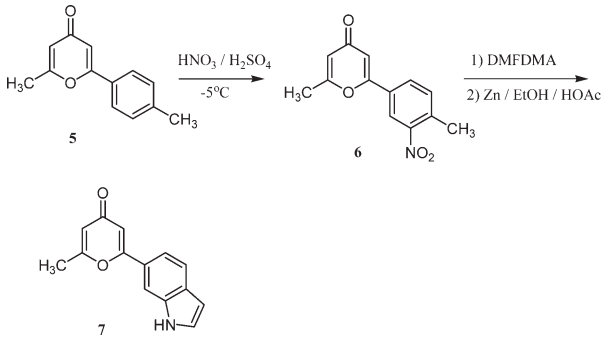
Scheme 1



Scheme 2



our attention to the 4-pyrone derivatives that would allow for the construction of the indole moiety. Herein, we report synthesis of two (1*H*-indole-6-yl)-4-pyrones *via* the Leimgruber–Batcho methodology and then reaction of enamine intermediate **3** with aroylchlorides in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as tertiary amine and the results of reductive cyclization of obtained enaminones for synthesis of 3-aroyl substituted indole derivatives.

RESULTS AND DISCUSSION

Scheme 1 shows the synthetic sequences for preparation of product **4**. The starting compound **1** was synthesized through cyclization of related 1,3,5-triketone derivative under acidic conditions, which is an important method for the synthesis of a variety of 4-pyrone structures [11]. Nitration of **1** with HNO_3/H_2SO_4 at $-5°C$ for 0.5 h afforded the dinitro **2** in quantitative yield. These nitration conditions were different from those reported for nitration of diphenyl-4-pyrones [12]. Treatment of **2** with 8 equiv. of DMFDMA at 90°C for 24 h gave stable dienamine **3** in 86% yield. Reductive cyclization of **3** was carried out using Fe or Zn in EtOH/HOAc at 80°C, that provided the 2,6-bis(1*H*-indole-6-yl)-4*H*-pyran-4-one **4** after 5 and 24 h, respectively. Therefore the conditions using Fe/EtOH/AcOH were optimal resulting in a faster and also a cleaner reaction.

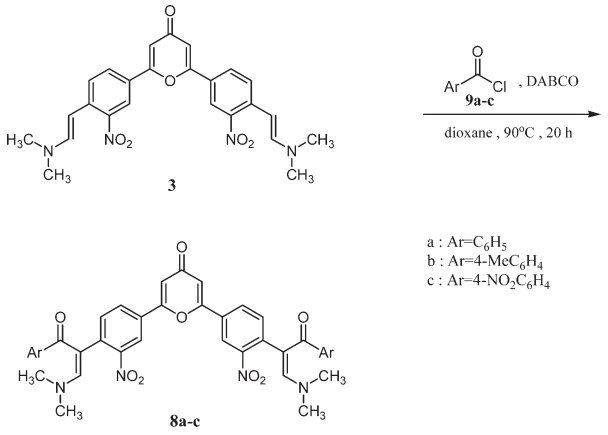
We also used 2-(4-methylphenyl)-6-methyl-4*H*-pyran-4-one **5** in the same synthetic sequence. This compound was synthesized according to reported procedure [13]. Nitration of **5** gave the *ortho*-nitrotolyl derivative **6**. Treatment of **6** with DMFDMA at 80°C and subsequent reduction of nitro group resulted the indole **7** in 33% yield. The enamine intermediate in this reaction that was not isolated was readily converted to indole **7**, by stirring with the Zn/EtOH/AcOH mixture at room temperature for 4 h. This result indicated that oxidation of the methyl ortho- to nitro-group in compound **6** has predominantly been achieved (Scheme 2).

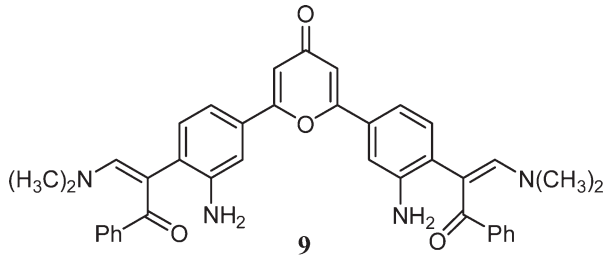
We then examined the incorporation of aroyl substituents onto the enamine intermediate **3**. The reactivity of enamine **3** toward aroyl chlorides such as benzoylchloride, 4-methylbenzoylchloride, and 4-nitrobenzoylchloride was explored initially using triethylamine in dry dioxane at 90°C. Under these conditions no reactivity was observed. Then, we used 2 equiv. of DABCO instead of triethylamine, and the substitution was successfully achieved as shown in Scheme 3. The structures of products **8a-c** were characterized by spectroscopic data and elemental analysis.

In the final step, a few reagents and conditions were evaluated to optimize the reductive cyclization of enaminones **8a-c** to form the 3-aroyl substituted indole derivatives. When the compound **8a** was treated with Zn or Fe in 1:1 mixture of EtOH–AcOH at 90–100°C for 24 h, the major product that was formed and separated, showed a singlet at 3.0 ppm for 12 protons in ^{1}H NMR spectrum (in DMSO-d_6), which indicated the presence of $-N(CH_3)_2$ groups in molecule and established that the cyclization has not been accomplished. Spectroscopic data confirmed the symmetrical structure of **9**, which was obtained in 32% yield under these conditions (Fig. 1).

Treatment of enaminones **8a** and **8b** with Fe/AcOH at 100°C for 24 h, gave the desired bis(indole) derivatives

Scheme 3





9

Figure 1. Structure of compound **9** obtained from reduction of the enaminone **8a** with Zn in EtOH–AcOH (1:1).

10a and **10b** as major products, respectively (Scheme 4). These compounds were separated and characterized by spectroscopic methods. The Fe/AcOH system has been described previously for reduction-cyclization of nitro group for construction of a variety of indole structures [14].

We also found that using Fe in 1*M* aqueous HCl solution/MeOH with heating resulted in a complex mixture with unidentified residues.

In conclusion, we have reported the synthesis of two (1*H*-indole-6-yl)-4-pyrones *via* Leimgruber–Batcho indole synthesis, starting from the corresponding *ortho*-methylnitrophenyl derivatives. Aroyl substituents at C-3 of the bis(indole) derivative were installed *via* reaction of the enamine intermediate with aroylchlorides before the final reductive cyclization. Among the different conditions and reagents that were examined for reductive cyclization of enaminoketones, the Fe/AcOH at 100°C was the appropriate method for this purpose. This modified Leimgruber–Batcho procedure is attractive because of the regioselectivity of substitution, which may be observed less in the direct C-3 aroylation of indole nucleus.

EXPERIMENTAL

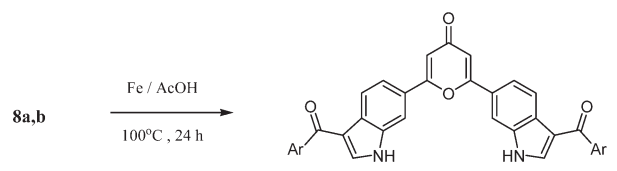
Melting points were determined on a 1202D model Electrothermal MEL-TEMP apparatus and are uncorrected. FTIR spectra were obtained with a Bruker Tensor 27 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Spectrospin Avance 400 spectrometer operating at 400 and 100 MHz, respectively; chemical shifts are given in parts per million (ppm, δ) relative to solvent peaks as internal standards (δ: $CDCl_3$: 7.26 ppm (^{1}H), 76 ppm (^{13}C); DMSO-d_6: 2.50 ppm (^{1}H), 39.5 ppm (^{13}C)). Mass spectra (MS) were measured by a Shimadzo (70 ev) spectrometer and elemental analyses were measured by Vario EL III apparatus (Elementar Co.). Column chromatography was done using silica gel (Merk Kieselgel 60, no. 9385, 230-400 mesh ASTM). Thin-layer chromatography was done with prepared glass-backed plates (20 × 20 cm^2, 500 μ) using silica gel (Merk Kieselgel 60 HF_{254}, no. 7739).

2,6-Bis(4-methyl-3-nitrophenyl)-4*H*-pyran-4-one (2). A stirred solution of 3.66 g (0.013 mol) of 2,6-bis(4-methylphenyl)-4*H*-pyran-4-one (**1**) in 11.5 mL of concentrated sulfuric acid (95–98%) cooled to −5°C using ice-salt bath. To this solution, 7 mL of fuming nitric acid was added dropwise over 15 min. The reaction mixture was stirred at −5°C for a further 0.5 h and then poured to 100 g ice. The produced precipitate was collected by filtration and washed with water and dried *in vacuo* to give **2** (4.7 g, 98% yield) as a white solid, mp 254°C; FTIR (KBr): ν 3065, 2977, 1663 (pyrone C=O), 1614, 1528, 1444, 1355 cm^{-1}; ^{1}H NMR($CDCl_3$): δ 2.703 (s, 6H, CH_3), 6.861 (s, 2H, pyrone H-3), 7.564 (d, 2H, J = 8.1 Hz, phenyl H-5), 7.948 (dd, 2H, J = 8.0, 1.9 Hz, phenyl H-6), 8.438 (d, 2H, J = 1.9 Hz, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): δ 19.5 (CH_3), 111.4, 121.1, 128.6, 129.3, 133.0, 136.1, 148.7, 160.0, 178.0 (pyrone CO) ppm. MS (*m/z*, %): 366 (M^+, 30), 338 (100). *Anal*. Calcd. for $C_{19}H_{14}N_2O_6$: C, 62.32; H, 3.82; N, 7.65. Found: C, 61.94; H, 3.89; N, 7.39.

2,6-Bis{4-[*trans*-2-(*N*,*N*-dimethylamino)ethenyl]-3-nitrophenyl}-4*H*-pyran-4-one (3). A mixture of (**2**) (4.70 g, 0.013 mol) and DMFDMA(12.4 g, 0.104 mol) in 100 mL DMF was heated at 90°C under Ar for 24 h. After cooling, the precipitated product was filtered, washed several times with H_2O, and dried *in vacuo* to provide 5.3 g (86.5 %) of **3** as a deep red solid, mp 250°C; FTIR(KBr): ν 3075, 2900, 2802, 1640 (pyrone C=O), 1591, 1516, 1375, 1209, 1098 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.975 (s, 12H, ─N(CH_3)$_2$), 5.713 (d, 2H, J = 13.2 Hz, PhCH=), 6.961 (s, 2H, pyrone H-3), 7.777 (d, 2H, J = 13.2 Hz, =CH─N(Me)$_2$), 7.859 (d, 2H, J = 8.9 Hz, phenyl H-5), 7.935 (dd, 2H, J = 8.8, 1.9 Hz, phenyl H-6), 8.364 (d, 2H, J = 2.0 Hz, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): δ 39.9 (CH_3-N), 89.5, 109.2, 122.4, 123.0, 123.2, 127.6, 137.8, 143.2, 145.7, 160.4, 178.6 (pyrone CO) ppm; MS (*m/z*, %): 476 (M^+, 65), 459 (40), 386 (50), 42 (100); *Anal*. Calcd. for $C_{25}H_{24}N_4O_6$: C, 63.02; H, 5.04; N, 11.76. Found: C, 62.86; H, 5.27; N, 11.90.

2,6-Bis(1*H*-indole-6-yl)-4*H*-pyran-4-one (4). A suspension of (**3**) (0.476 g, 1 mmol), AcOH (6 mL), EtOH (6 mL), and Fe (2.24 g, 40 mmol) was heated with stirring at 80°C. After 5 h, the dark color of the reaction mixture disappeared and a brown suspension was obtained, indicating the completion of reaction. The reaction mixture was cooled, concentrated by rotary evaporator to remove EtOH, neutralized by saturated $NaHCO_3$ solution, and then extracted by EtOAc. The extract was dried over anhydrous Na_2SO_4, concentrated and purified by thin-layer chromatography (silica gel, 1:1 acetone:*n*-hexane) to give 0.114 g (35% yield) of **4**, mp 280°C (decomp.); FTIR (KBr): ν 3367 (NH), 3161, 2918, 1637 (pyrone C=O), 1575, 1554, 1456, 1395, 1181 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.557 (t, br., 2H, J = 1.8 Hz, indole H-3), 6.891 (s, 2H, pyrone H-3), 7.568 (t, 2H, J = 2.7 Hz, indole H-2), 7.674 (dd, 2H, J = 8.4, 1.5 Hz, indole H-5), 7.739 (d, 2H, J = 8.4 Hz, indole H-4), 8.091 (s, 2H, indole H-7), 11.506 (s, 2H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 101.6, 109.4,

Scheme 4



10a : Ar=C_6H_5
10b : Ar=4-MeC_6H_4

109.6, 116.6, 120.6, 123.7, 128.6, 130.1, 135.7, 163.9, 178.8 (pyrone CO) ppm; MS (*m/z*, %): 326 (M^+, 80), 298 (100), 269 (20), 141 (45); *Anal*. Calcd. for $C_{21}H_{14}N_2O_2$: C, 77.30; H, 4.29; N, 8.59. Found: C, 77.0; H, 4.55; N, 8.53.

2-(4-Methyl-3-nitrophenyl)-6-methyl-4*H*-pyran-4-one (6). A stirred solution of 0.4 g (2 mmol) of 2-(4-methylphenyl)-6-methyl-4*H*-pyran-4-one (**5**) in 1 mL of concentrated sulfuric acid (95–98 %) cooled to −5°C using ice-salt bath. To this solution, 0.6 mL of fuming nitric acid was added dropwise over 15 min. The reaction mixture was stirred at −5°C for a further 0.5 h and then poured to 100 g ice. The precipitate was collected by filtration, washed with water, and dried *in vacuo* to give **6** (0.45 g, 92% yield) as a white solid, mp 160°C; FTIR (KBr): ν 3066, 2970, 1660 (pyrone C=O), 1612, 1531, 1402, 1350, 1168, 920, 796 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.378 (s, 3H, CH_3), 2.627 (s, 3H, CH_3), 6.172 (d, 1H, J = 1.1 Hz, pyrone H-5), 6.695 (d, 1H, J = 1.9 Hz, pyrone H-3), 7.457 (d, 1H, J = 8.1 Hz, phenyl H-5), 7.828 (dd, 1H, J = 8.4, 1.7 Hz, phenyl H-6), 8.324 (d, 1H, J = 1.6 Hz, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): δ 18.8, 19.3, 110.3, 113.5, 120.7, 128.3, 129.4, 132.6, 135.4, 148.4, 159.7, 164.5, 178.4 (pyrone CO) ppm; MS (*m/z*, %): 245 (M^+, 89), 228 (42), 217 (32), 172 (100), 89 (46); *Anal*. Calcd. for $C_{13}H_{11}NO_4$; C, 63.67; H, 4.49; N, 5.71. Found: C, 63.30; H, 4.52; N, 5.47.

2-(1*H*-indole-6-yl)-6-methyl-4*H*-pyran-4-one (7). A mixture of (**6**) (0.4 g, 1.63 mmol) and DMFDMA (0.78 g, 6.53 mmol) in 1 mL DMF was heated at 80°C under Ar for 24 h. After cooling, 30 mL H_2O was added to the reaction mixture and the precipitated product was filtered, washed with H_2O, and dried *in vacuo*. The red solid was mixed with Zn (2.12 g, 32.6 mmol), EtOH (4 mL), and AcOH (4 mL). The mixture was stirred at r.t. for 4 h and then concentrated by rotary evaporator. The residue was neutralized by saturated $NaHCO_3$ solution and the precipitate was filtered. This solid was purified by thin-layer chromatography (silica gel, 1:1 acetone:*n*-hexane) to give **7** (0.12 g, 33% yield). mp 228°C; FTIR (KBr): ν 3331(NH), 3002, 2976, 1650 (pyrone C=O), 1590, 1406, 1324, 1159, 916, 676 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.393 (s, 3H, CH_3), 6.185 (d, 1H, J = 1.0 Hz, pyrone H-5), 6.608 (s, 1H, pyrone H-3), 6.768 (d, 1H, J = 2.2 Hz, indole H-3), 7.380 (t, 1H, J = 2.8 Hz, indole H-2), 7.516 (dd, 1H, J = 8.4, 1.5 Hz, indole H-5), 7.710 (d, 1H, J = 8.4 Hz, indole H-4), 7.869 (s, 1H, indole H-7), 8.896 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): δ 18.9 (CH_3), 102.0, 108.1, 108.7, 113.1, 116.4, 120.1, 123.8, 126.2, 129.4, 134.6, 164.1, 164.2, 179.5 (pyrone CO) ppm; MS (*m/z*, %): 225 (M^+, 28); *Anal*. Calcd. for $C_{14}H_{11}NO_2$: C, 74.67; H, 4.89; N, 6.22. Found: C, 74.29; H, 5.00; N, 6.51.

General procedure for the synthesis of enaminoketones (8a-c). A mixture of enamine (**3**) (0.952 g, 2 mmol), DABCO (0.448 g, 4 mmol), and aroylchlorides (**9a-c**) (12 mmol) in 20 mL dioxane (dry) was heated at 90°C for 20 h. The resulting suspension was cooled to r.t. and water (120 mL) was added. The resulting mixture was stirred for 5 min and then extracted with chloroform (4 × 50 mL). The combined chloroform extract was washed with 150 mL of H_2O, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography (silica gel, 6:4 acetone:*n*-hexane) to give the products **9a-c**.

2,6-Bis{4-[(Z)-1-benzoyl-2-(N,N-dimethylamino) ethenyl]-3-nitrophenyl}-4H-pyran-4-one (8a). This compound was obtained as a red solid in 67% yield, mp 160–162°C; FTIR (KBr): ν 3062, 2921, 1702 (benzoyl C=O), 1649 (pyrone C=O), 1579, 1534, 1382, 1312 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.832 (s, 12H, ─$N(CH_3)_2$), 6.887 (s, 2H, pyrone H-3), 7.262 (d, 2H, J = 1.9 Hz, =CH─$N(Me)_2$), 7.470–7.362 (m, 10H, benzoyl-H), 7.519 (d, 2H, J = 6.9 Hz, phenyl H-5), 8.006 (d, 2H, J = 6.5 Hz, phenyl H-6), 8.392 (s, 2H, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): δ 42.8 (CH_3-N), 106.5, 111.4, 120.5, 127.0, 127.4, 127.6, 129.0, 129.5, 134.2, 134.7, 139.6, 149.8, 154.3, 160.1, 178.2 (pyrone CO), 192.3 (benzoyl CO) ppm; *Anal*. Calcd. for $C_{39}H_{32}N_4O_8$: C, 68.35; H, 4.67; N, 8.18. Found: C, 68.63; H, 5.00; N, 8.05.

2,6-Bis{4-[(Z)-2-(N,N-dimethylamino)-1-(4-methylbenzoyl) ethenyl]-3-nitrophenyl}-4H-pyran-4-one (8b). This compound was obtained as a red solid in 65% yield, mp 165–168°C; FTIR (KBr): ν 3021, 2918, 1702 (aroyl C=O), 1649 (pyrone C=O), 1579, 1531, 1382, 1308, 1096 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.383 (s, 6H, *p*-CH_3-benzoyl), 2.844 (s, 12H, $N(CH_3)_2$), 6.911 (s, 2H, pyrone H-3), 7.187 (d, 4H, J = 7.8 Hz, aroyl H-3), 7.298 (s, 2H, =CH─$N(Me)_2$), 7.439 (d, 4H, J = 7.9 Hz, aroyl H-2), 7.476 (s, 2H, phenyl H-5), 8.005 (s, br, 2H, phenyl H-6), 8.391 (s, 2H, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): 28.2 (*p*-CH_3-benzoyl), 42.9 (CH_3-N), 106.5, 111.5, 120.6, 127.0, 127.5, 127.6, 129.0, 129.6, 134.2, 134.7, 139.6, 149.8, 154.2, 160.1, 178.1 (pyrone CO), 192.3 (aroyl CO) ppm; *Anal*. Calcd. for $C_{41}H_{36}N_4O_8$: C, 69.03; H, 5.05; N, 7.85. Found: C, 68.98; H, 5.09; N, 7.78.

2,6-Bis{4-[(Z)-2-(N,N-dimethylamino)-1-(4-nitrobenzoyl)-ethenyl]-3–nitrophenyl}-4H-pyran-4-one (8c). This compound was obtained as an orange solid in 54% yield, mp 172–174°C; FTIR (KBr): ν 3070, 2921, 1711 (aroyl C=O), 1648 (pyrone C=O), 1571, 1524, 1389, 1347, 1313, 1097 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.881 (s, 12H, $N(CH_3)_2$), 6.920 (s, 2H, pyrone H-3), 7.184 (s, 2H, =CH─$N(Me)_2$), 7.490 (d, 2H, J = 8.0 Hz, phenyl H-5), 7.666 (d, 4H, J = 8.5 Hz, aroyl H-3), 8.028 (d, 2H, J = 7.8 Hz, phenyl H-6), 8.252 (d, 4H, J = 8.5 Hz, aroyl H-2), 8.429 (d, 2H, J = 1.4 Hz, phenyl H-2) ppm; ^{13}C NMR ($CDCl_3$): δ 45.9 (CH_3-N), 111.7, 120.8, 122.4, 122.5, 127.7, 128.1, 130.1, 133.7, 134.2, 145.6, 147.4, 149.8, 154.3, 178.1 (pyrone CO), 189.9 (aroyl CO) ppm; *Anal*. Calcd. for $C_{39}H_{30}N_6O_{12}$: C, 60.41; H, 3.87; N, 10.84. Found: C, 60.09; H, 4.13, N, 10.71.

2,6-Bis{3-amino-4-[(*Z*)-1-benzoyl-2-(*N*,*N*-dimethylamino)ethenyl]phenyl}-4*H*-pyran-4-one (9). A suspension of **8a** (0.342 g, 0.5 mmol), AcOH (3 mL), EtOH (3 mL), and Zn (1.30 g, 20 mmol) was heated with stirring at 90°C for 24 h. The hot reaction mixture was then filtered and washed with an appropriate amount of warm methanol. The combined filtrate was then concentrated by rotary evaporator to remove the alcohols (EtOH, MeOH), neutralized by saturated $NaHCO_3$ solution and extracted by EtOAc. The extract was dried over anhydrous Na_2SO_4, concentrated, and purified by thin-layer chromatography (silica gel, 1:1 acetone:chloroform) to give 0.099 g (32% yield) of **9** as brown solid, mp 300°C (decomp.), FTIR (KBr): ν 3383, 3217 (NH_2), 3067, 2920, 1737 (benzoyl C=O), 1635 (pyrone C=O), 1562, 1460, 1406 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.024 (s, 12H, ─$N(CH_3)_2$), 6.713 (s, 2H, pyrone H-3), 6.777 (d, 2H, J = 8.5 Hz, phenyl H-5), 7.419 (dd, 2H, J = 8.5, 1.5 Hz, phenyl H-6), 7.493–7.530 (m, 6H: 2H, =CH─$N(Me)_2$, 4H, benzoyl H-3), 7.586 (t, 2H, J = 7.3 Hz, benzoyl H-4), 7.670 (d, 4H, J = 7.6 Hz, benzoyl H-2), 7.957 (d, 2H, J = 1.2 Hz, phenyl H-2), 11.686 (br., NH_2) ppm; ^{13}C

NMR (DMSO-d_6): δ 41.7 (CH_3-N), 97.3, 107.3, 108.0, 117.5, 118.3, 121.6, 128.4, 128.5, 131.2, 131.9, 133.1, 141.9, 155.5, 163.0, 178.9 (pyrone CO), 188.2 (benzoyl CO) ppm; *Anal*. Calcd. for $C_{39}H_{36}N_4O_4$: C, 75.00; H, 5.77; N, 8.97. Found C, 74.88; H, 5.59; N, 9.16.

General procedure for the synthesis of 3-aroylindoles (10a-b). A mixture of the enaminone **8a** or **8b** (0.3 mmol), iron powder (0.5 g), and glacial HOAc (4 mL) was refluxed at 100°C. After 24 h, the dark color of the reaction mixture disappeared and a brown suspension was obtained. The reaction mixture was cooled, neutralized by saturated $NaHCO_3$ solution, and then extracted by EtOAc. The extract was dried over anhydrous Na_2SO_4, concentrated and purified by thin-layer chromatography (silica gel, EtOAc) to give the products **10a** or **10b** in 25 and 22% yield, respectively.

2,6-Bis(3-benzoyl-1H-indole-6-yl)-4H-pyran-4-one (10a). This compound was obtained as a pale-yellow solid in 25% yield, mp 270°C (decomp.); FTIR (KBr): ν 3416 (NH), 3122, 2923, 1736 (benzoyl C=O), 1637 (pyrone C=O), 1576, 1502, 1451 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.011 (s, 2H, pyrone H-3), 7.550–7.586 (m, 4H, benzoyl H-3), 7.639 (t, 2H, $J = 7.0$ Hz, benzoyl H-4), 7.828 (d, 4H, $J = 7.1$ Hz, benzoyl H-2), 7.954 (d, 2H, $J = 8.0$ Hz, indole H-4), 8.140 (s, 2H, indole H-7), 8.234 (s, 2H, indole H-2), 8.404 (d, 2H, $J = 8.5$ Hz, indole H-5), 8.879 (s, 2H, NH, deuterium oxide-exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 110.3, 110.6, 115.2, 119.8, 122.1, 125.9, 128.5, 128.6, 128.7, 131.5, 136.8, 138.2, 140.1, 163.4, 179.1 (pyrone CO), 190.0 (benzoyl CO) ppm; *Anal*. Calcd. for $C_{35}H_{22}N_2O_4$: C, 78.65; H, 4.12; N, 5.24. Found: C, 78.60; H, 4.23; N, 5.01.

2,6-Bis[1H-indole-3-(4-methylbenzoyl)-6-yl]-4H-pyran-4-one (10b). This compound was obtained as a pale-yellow solid, mp 240°C (decomp.); FTIR (KBr): ν 3398 (NH), 3100, 2925, 1737 (aroyl C=O), 1641 (pyrone C=O), 1600, 1517, 1452, 1423, 1383 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.422 (s, 6H, CH_3), 7.011 (s, 2H, pyrone H-3), 7.376 (d, 4H, $J = 7.9$ Hz, aroyl H-3), 7.751 (d, 4H, $J = 7.9$ Hz, aroyl H-2), 7.946 (d, 2H, $J = 8.6$ Hz, indole H-4), 8.147 (s, 2H, indole H-7), 8.225 (s, 2H, indole H-2), 8.302 (s, 2H, NH, deuterium oxide-exchangeable) 8.389 (d, 2H, $J = 8.5$ Hz, indole H-5) ppm; ^{13}C NMR (DMSO-d_6): δ 28.4, 109.6, 110.8, 115.3, 119.3, 121.9, 125.3, 128.7, 128.9, 129.1, 131.2, 137.6, 138.2, 141.4, 162.9, 179.0 (pyrone CO), 189.6 (aroyl CO) ppm; *Anal*. Calcd. for $C_{37}H_{26}N_2O_4$: C, 79.00; H, 4.62; N, 4.98. Found: C, 78.77; H, 4.45; N, 4.77.

Acknowledgment. The authors thank research affairs of University of Tabriz for financial support.

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