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An Efficient Synthesis and Substitution of 3-Aroyl-2-bromobenzo[*b*]furans

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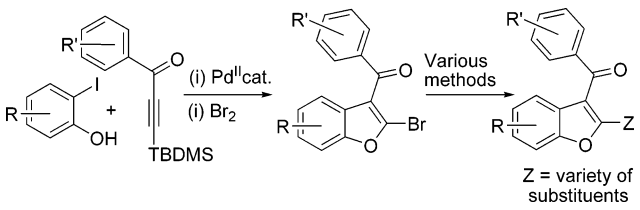


A convenient method for the synthesis of 2-bromo-3-aroylbenzo[*b*]furans from readily accessible precursors has been developed. The 2-bromo group has been employed as a versatile synthetic handle in both palladium-mediated couplings and direct nucleophilic substitutions to give access to a wide range of 2-substituted-3-aroyl-benzo[*b*]furans.

Benzofurans, in particular 3-aroylbenzo[*b*]furans **1** (Figure 1), are core structural components in a range of biologically active compounds.[1] Examples include anti-Alzheimer,[1c] anti-arrhythmic,[1d] tubulin polymerization inhibitory,[1e,f] and anti-estrogenic[1g] compounds among others. Accordingly, the development of concise, flexible syntheses of 3-aroylbenzo[*b*]furans **1** has been the goal of numerous efforts in the development of new synthetic methods.[2,3]

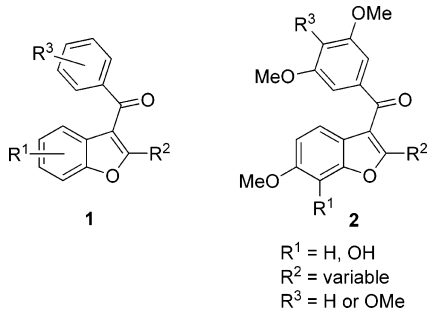
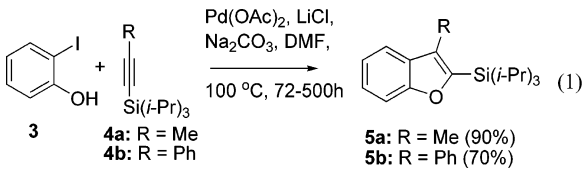


FIGURE 1. 2-Aroylbenzo[*b*]furans.

In our ongoing medicinal chemistry efforts, aimed at the identification of novel tubulin polymerization inhibitors (TPIs) of the formula **2** (Figure 1), we have identified that, so long as the substitution pattern at positions C3−7 are kept within the range shown, considerable variation can be tolerated at C2 while maintaining good activity.[1f,4] We are interested in taking advantage of this factor in the discovery of new TPIs with improved pharmacokinetic properties. Accordingly, we wish to introduce this C2-substituent very late in the synthetic process in a manner that would facilitate the synthesis of a focused library of C2 derivatives of **2** with different physiochemical properties but have been struck by the dearth of existing methods that provide for such a strategy. Most synthetic approaches to 2,3-disubstituted benzofurans introduce the C3-substituent at the end of the synthesis.[2,3] We envisage that a C2-bromo derivative of **2** (R^2 = Br) should serve as a versatile intermediate that would enable us to introduce a significant array of substituents at C2 through subsequent palladium-mediated coupling and nucleophilic substitution reactions. However, no methods for the synthesis of 2-halo-3-aroyl(or acyl)benzo[*b*]furans have been described. In this paper, we describe our efforts toward the synthesis of such 3-aroyl-2-bromobenzo[*b*]furans and their further substitution. This work should have broad applicability for those seeking to utilize the benzo[*b*]furan scaffold in drug discovery.

Larock and co-workers have previously demonstrated that 2-silylbenzo[*b*]furans **5** can be prepared by palladium-catalyzed annulation of *o*-iodophenol **3** with silylalkynes **4** (eq 1).[5,6] We sought to further develop this process by extending it to the synthesis of 3-aroyl-2-silylbenzo[*b*]furans that could then be converted to 3-aroyl-2-bromobenzo[*b*]furans by bromo substitution of the silyl group. This work was undertaken with the specific objective of producing compounds of the formula **2** (R^2 = Br) to aid our medicinal chemistry studies on TPIs (Scheme 1). Iodophenol **8a** was prepared as previously described.[7] Iodophenol **8b** was prepared from *o*-vanillin through a sequence of isopropyl ether protection, Baeyer−Villiger



(1)

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(2) For reveiws, see: (a) Cacchi, S.; Fabrizi.; G.; Goggiamani, A. *Curr. Org. Chem.* **2006**, *10*, 1423. (b) Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2005**, *17*, 142. (c) McCallion, G. D. *Curr. Org. Chem.* **1999**, *3*, 67−76. (d) Kadieva, M. G.; Oganesyan, E. T. *Chem. Heterocycl. Comp.* **1997**, *33*, 1245. (e) Donelly, D. M. X.; Meegan, M. J. Furans and their Benzo Derivatives: Synthesis and Application. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: New York, 1984; Vol. 4, pp 657−712 (f) Cagniant, P.; Cagniant, D. *Adv. Heterocycl. Chem.* **1975**, *18*, 337−482.

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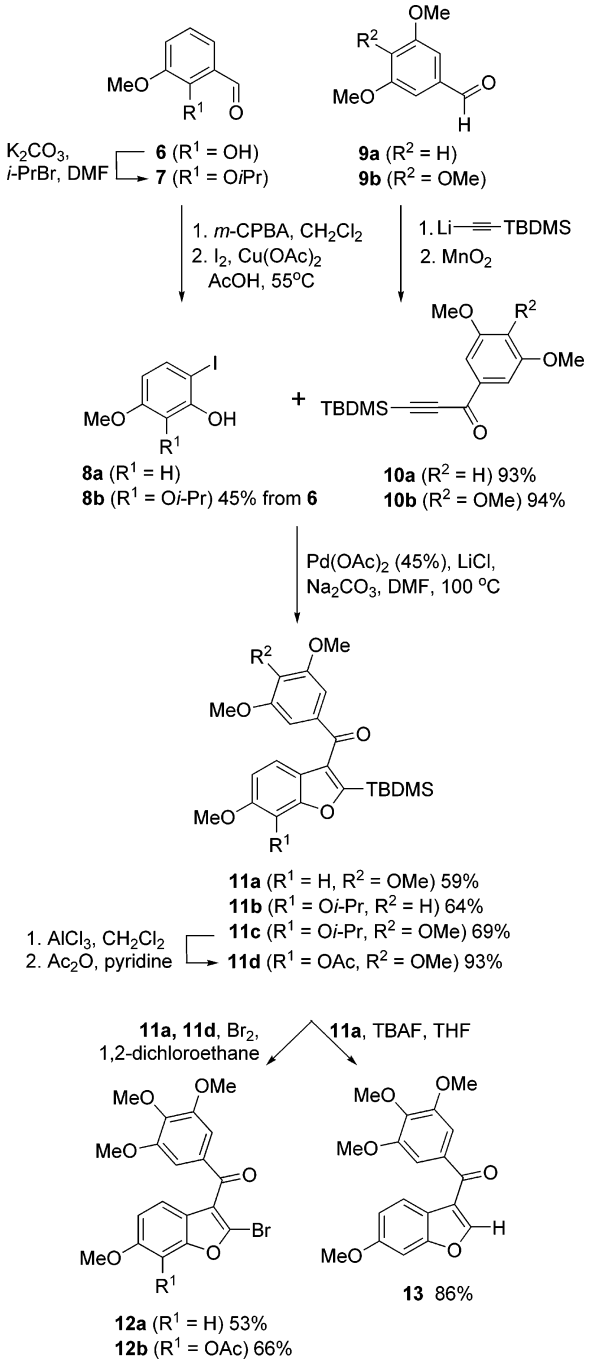
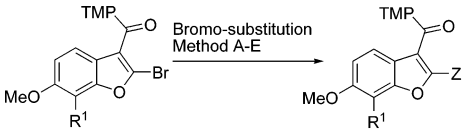
SCHEME 1. Synthesis of 3-Aroyl-2-bromobenzo[*b*]furans



oxidation, and iodination (49% over 3 steps, Scheme 2). The requisite 1-aryl-3-silylpropynones **10a** and **10b** were prepared by addition of lithium *tert*-butyldimethylsilylacetylide to benzaldehydes **9a** and **9b**, respectively, followed by MnO_2 oxidation of the intermediate alcohols.

Palladium-mediated annulation of 2-iodophenol **8a** with **10b** afforded **11a** (59%), while a similar reaction of **8b** with **10a** and **10b** afforded **11b** (64%) and **11c** (69%), respectively. In all cases, the reactions proceeded with complete regioselectivity to provide only the 3-aroyl-2-silylbenzo[*b*]furan derivatives. The 2-*tert*-butyldimethylsilyl group in **11a** was readily substituted for a bromide to give **12a** (53%) upon reaction with bromine in 1,2-dichloroethane. However, in the case of **11c** it was first necessary to replace the isopropyl group with an acetyl group, giving **11d** (93%), to avoid competitive electrophilic bromination of the C4-position of the benzo[*b*]furan. Treatment of **11d** with bromine in 1,2-dichloroethane gave the 2-bromo derivative **12b** in 66% yield. Alternatively, the 2-TBDMS group could also be removed to provide the corresponding 2-H system as demonstrated by the transformation of **11a** to **13** upon treatment with TBAF in THF (86%).

Having achieved efficient access to **12a** and **12b**, we then turned to studying various means of substitution of the C2-bromo group (eq 2, Table 1). Both **12a** and **12b** reacted readily with various boronic acids/esters under standard Suzuki conditions, in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 at 80−100 °C in aqueous 1,4-dioxane. The reactions were complete within 1−2 h (the crude reaction mixtures of 7-OAc compounds were further treated with K_2CO_3 and methanol to ensure complete deacetylation), providing the corresponding coupled products **15a**−**e** in good yields (entries 1−5). Negishi coupling reactions of **12b** with alkyl- and arylzinc bromides proceeded at room temperature to give the products **15f**−**h** in excellent yields (entries 6−8, in situ deacetylation was observed for entries 6 and 8). Heck coupling of **12b** with methyl acrylate and subsequent deacetylation gave **15i** in low yield even in the presence of excess acrylate (>10-fold) and considerable amounts of catalyst (20%) (entry 9). The 2-bromo substituent of **12b** was also exploited in a range of direct substitution reactions with various nucleophiles. Reaction with sodium cyanide in DMSO proceeded with in situ cleavage of the acetyl group to give the 2-cyano derivative **15j** in good yield (entry 10), while reaction with the sodium salt of 1,2,4-triazole in THF/toluene gave the phenol **15k** in moderate yield (entry 11). Both imidazole and ethanolamine were successfully reacted with **12b** in refluxing pyridine to provide **15l** (92%) and **15m** (67%), respectively (entries 12 and 13).



(2)

12a (R^1 = H)
12b (R^1 = OAc)

15

TMP = 3,4,5-trimethoxyphenyl

Method A (Suzuki): $(HO)_2$B-Z, $Pd(PPh_3)_4$ (5-10%), Na_2CO_3, 1,4-dioxane / H_2O, reflux
Method B (Negishi): (Cl/Br)Zn-Z $Pd(PPh_3)_2Cl_2$ (10%), CuI (cat.), THF, 20 °C.
Method C (Heck): H-Z, $Pd(OAc)_2$ (2 x 10%), CH_3CN/Et_3N 2:1, reflux.
Method D (ArS_N2): Na-Z, DMSO or THF/toluene, 55-100 °C
Method E (ArS_N2): H-Z, pyridine, reflux

In conclusion, a concise and convergent protocol for the synthesis of 2-bromo-3-aroylbenzo[*b*]furan systems has been developed. The 2-bromo substituent provides a versatile synthetic handle in both palladium-mediated cross-coupling and direct nucleophilic substitution reactions to give a wide range

(3) (a) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803−2805. (b) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280−9288. (c) Chaplin, J. H.; Flynn, B. L. *Chem. Commun.* **2001**, 1594−1595. Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365−68.

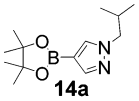
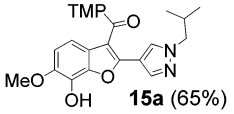
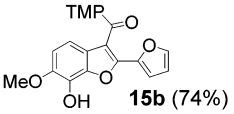
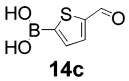
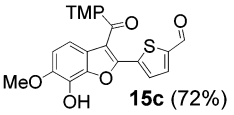
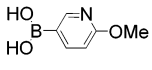
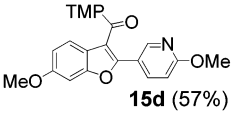
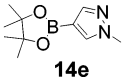
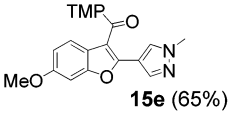
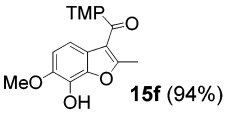
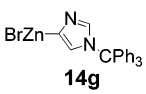
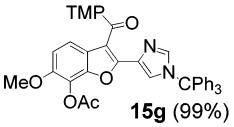
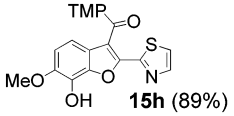
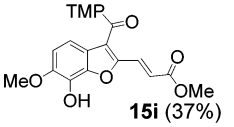
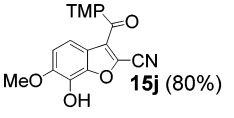
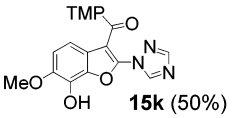
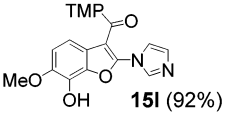
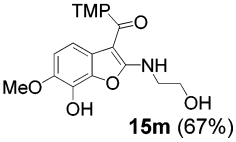
(4) Chaplin, J. H.; Gill, G. S.; Grobelny D. W.; Flynn, B. L. Int. Pat. Appl. No. WO2006084338.

(5) (a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111−124. (b) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. C. *J. Org. Chem.* **1995**, *60*, 3270−3271.

(6) Bishop, B. C.; Cottrell, I. F.; Hands, D. *Synthesis* **1997**, 1315−1320.

(7) Tsukayama, M.; Utsumi, H.; Kunugi, A.; Nozaki, H. *Heterocycles* **1997**, *45*, 1131−1142.

TABLE 1. Substitution of 12a and 12b (See Also eq 2)

Entry	12	14	Method	Product **15** (Yield)
1	**12b**	 **14a**	A	 **15a** (65%)
2	**12b**	 **14b**	A	 **15b** (74%)
3	**12b**	 **14c**	A	 **15c** (72%)
4	**12a**	 **14d**	A	 **15d** (57%)
5	**12a**	 **14e**	A	 **15e** (65%)
6	**12b**	BrZn–Me **14f**	B	 **15f** (94%)
7	**12b**	 **14g**	B	 **15g** (99%)
8	**12b**	 **14h**	B	 **15h** (89%)
9	**12b**	 **14i**	C	 **15i** (37%)
10	**12b**	NaCN **14j**	D	 **15j** (80%)
11	**12b**	 **14k**	D	 **15k** (50%)
12	**12b**	 **14l**	E	 **15l** (92%)
13	**12b**	 **14m**	E	 **15m** (67%)

of C2-substituted 3-aroylbenzo[*b*]furans. The process as a whole is quite functional group tolerant and efficient.

Experimental Section

2-*tert*-Butyldimethylsilyl-7-isopropoxy-6-methoxy-3-(3,4,5-trimethoxybenzoyl)benzo[*b*]furan (11a). A suspension of 2-iodo-5-methoxyphenol (**8a**, 250 mg, 1 mmol), 3-(*tert*-butyldimethylsilyl)-1-(3,4,5-trimethoxyphenyl)propynone (**10b**, 468 mg, 1.40 mmol), lithium chloride (42 mg, 1 mmol), and sodium carbonate (424 mg, 4 mmol) in dry dimethylformamide (2.5 mL) was deoxygenated with nitrogen gas. Palladium acetate (100 mg, 0.45 mmol) was added, the reaction mixture was then stirred at 100 °C under nitrogen for 2 h (TLC), and the solvent was removed by distillation under vacuum. The residue was dissolved in ethyl acetate (40 mL), stirred well, and filtered. The solvent was distilled, and the crude was purified by silica gel flash chromatography (eluent = hexane/diethyl ether; 95:5 to 8:2) to give the title compound as a light yellow paste (268 mg, 59%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 2H), 7.05 (s, 1H), 7.04 (d, J = 8.49 Hz, 1H), 6.77 (dd, J = 8.73, 2.19 Hz, 1H), 3.93 (s, 3H), 3.84 (s, 6H), 3.78 (s, 3H), 1.00 (s, 9H), 0.28 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 165.4, 158.6, 158.5, 153.0, 142.6, 133.6, 131.7, 121.5, 120.1, 112.6, 107.4, 95.4, 61.0, 56.3, 55.7, 26.8, 17.7, −5.7; LRMS m/z 457 (M + 1, 100); HRMS ESI (M + H)$^+$ calcd for $C_{25}H_{32}O_6Si$ 457.2046, found 457.2054.

2-Bromo-6-methoxy-3-(3,4,5-trimethoxybenzoyl)benzo[*b*]-furan (12a). To a stirred solution of 2-*tert*-butyldimethylsilyl-6-methoxy-3-(3,4,5-trimethoxybenzoyl)benzo[*b*]furan (**10a**, 200 mg, 0.44 mmol) in 1,2-dichloroethane (2 mL) at room temperature under nitrogen was added bromine (23 μL, 0.44 mmol) dropwise, and the reaction mixture was stirred for 10 min. After this time, the solution was diluted with extracted with ethyl acetate (20 mL), washed with brine (30 mL), the organic layer dried over magnesium sulfate, and the solvent evaporated under reduced pressure. The crude product was directly crystallized from acetonitrile to afford the title compound as a colorless crystalline solid (98 mg, 53%, mp = 136−38 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.73 Hz, 1H), 7.15 (s, 2H), 7.01 (d, J = 2.19 Hz, 1H), 6.90 (dd, J = 8.74, 2.27 Hz, 1H), 3.94 (s, 3H), 3.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.2, 158.3, 155.8, 152.7, 142.6, 132.0, 130.7, 121.0, 120.0, 119.7, 112.9, 107.0, 95.3, 60.7, 55.9, 55.4; LRMS m/z 423/421 (M + H, 100), 421 (M$^+$, 91); HRMS ESI (M)$^+$ calcd for $C_{19}H_{17}O_6Br$ 421.0287, found 421.0284.

2-(1-Iso*b*utyl-1*H*-pyrazol-4-yl)-7-hydroxy-6-methoxy-3-(3,4,5-trimethoxybenzoyl)benzo[*b*]furan (15a). To a stirred solution of 7-acetoxy-2-bromo-6-methoxy-3-(3,4,5-trimethoxybenzoyl)benzo-[*b*]furan (**12b**, 40 mg, 0.084 mmol) and 1-isobutyl-4-(4,4,5,5-tetramethyl-1,2,3-dioxaborolon-2-yl)1*H*-pyrazole (**14a**, 42 mg, 0.168 mmol) in 1,4-dioxane (3 mL) at 90 °C was added $Pd(PPh_3)_4$ (8 mg, 0.008 mmol) followed by the addition of a solution of sodium bicarbonate (40 mg, 0.48 mmol) in distilled water (1 mL). The reaction mixture turned brown after 5 min. After 25 min (TLC), the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). The organic layer was washed with water, the solvent was removed by distillation under vacuum, and the crude residue was treated with potassium carbonate (100 mg, excess) in methanol (10 mL). The material thus obtained was purified by preparative thin layer chromatography to give the title compound as a crystalline yellow solid (26 mg, 65%, mp = 146−48 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.99 (s, 1H), 7.14 (s, 2H), 6.81 (d, J = 8.61 Hz, 1H), 6.75 (d, J = 8.58 Hz, 1H), 5.70 (bs, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.89 (d, J = 7.38 Hz, 2H), 3.77 (s, 6H), 2.23−2.16 (m, 1H), 0.89 (d, J = 6.69 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 154.0, 152.6, 143.4, 141.9, 140.9, 138.7, 133.3, 130.5, 130.2, 123.26, 113.4, 111.8, 111.2, 108.0, 106.7, 106.7, 60.7, 59.58, 56.8, 55.9, 29.2, 19.5; LRMS m/z 481 (M + 1, 100); HRMS ESI (M + H)$^+$ calcd for $C_{26}H_{28}N_2O_7$ 481.1975, found 481.1979.

2-Methyl-7-hydroxy-6-methoxy-3-(3,4,5-trimethoxybenzoyl)-benzo[*b*]furan (15f). Zinc bromide dihydrate (950 mg, 3.67 mmol) was dried under vacuum at 120−140 °C for 2 h with stirring, cooled to room temperature, and dissolved in 4 mL of dry THF. To this solution was added methyllithium (1.6 M in diethyl ether, 3.3 mL, 5.28 mmol) dropwise at −78 °C under nitrogen. The resulting mixture was allowed to warm to room temperature, stirred for 15 min, and cooled again to −78 °C. To the cooled reaction mixture was added solid 7-acetoxy-2-bromo-6-methoxy-3-(3,4,5-trimethoxybenzoyl)benzo[*b*]furan (**12b**, 480 mg, 1 mmol) followed by $(PPh_3)_2PdCl_2$ (92 mg, 0.131 mmol) and copper(I) iodide (160 mg, 0.084 mmol). The resulting mixture was stirred in vacuo for 3 min at −78 °C, back-filled with dry nitrogen, allowed to warm to room temperature, and stirred for 30 h under nitrogen. After this time, methanol (5 mL) was added, and the resulting mixture was stirred for 30 min at room temperature and evaporated to dryness. The residue was diluted to with ethyl acetate (50 mL) and washed with saturated ammonium chloride (20 mL). The insoluble material was removed by filtration and the organic phase separated, washed with brine, dried over anhydrous magnesium sulfate, and evaporated to dryness. The crude product was purified by flash column chromatography to give pure product as colorless crystals recrystallized from methanol (360 mg, 94%, mp = 156−58 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 2H), 6.93 (d, J = 8.54 Hz, 1H), 6.83 (d, J = 8.56 Hz, 1H), 5.69 (bs, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.83 (s, 6H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 161.2, 152.6, 143.7, 141.8, 141.4, 133.7, 130.5, 122.4, 116.5, 110.9, 108.2, 106.5, 60.6, 56.8, 55.9, 17.4;LRMS *m*/*z* 373 (M + 1, 100); HRMS ESI $(M + H)^+$ calcd for $C_{20}H_{20}O_7$ 373.1287, found 373.1285.

2-(1,2,4-Triazol-1-yl)-7-hydroxy-6-methoxy-3-(3,4,5-trimethoxybenzoyl)benzo[*b*]furan (15k). To a solution of 1,2,4-triazole (**14k**, 22 mg, 0.32 mmol) in dry tetrahydrofuran (2 mL) was added sodium hydride (60%, 24 mg, 0.60 mmol), and resulting suspension was treated with a solution of 7-acetoxy-2-bromo-6-methoxy-3-(3,4,5-trimethoxybenzoyl)benzo[*b*]furan (**12b**, 50 mg, 0.10 mmol) in dry toluene (2 mL). The mixture was stirred at reflux for 6 h (TLC), quenched with saturated ammonium chloride solution, extracted with dichloromethane (10 mL), and dried over magnesium sulfate and the solvent distilled under vacuum. The crude residue was purified over silica gel plate to give the title compound as a yellow solid (22 mg, 50%, mp = 78−80 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.07(s, 1H), 7.11 (d, J = 8.60 Hz, 1H), 7.06 (s, 2H), 6.97 (d, J = 8.65 Hz, 1H), 6.19 (bs, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.77 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 152.9, 145.9, 145.4, 144.8, 143.0, 140.1, 131.7, 131.5, 121.3, 11.9, 110.4, 110.1, 106.68, 60.8, 57.0, 56.0; LRMS *m*/*z* 426 (M + 1, 100); HRMS ESI $(M + H)^+$ calcd for $C_{21}H_{19}N_3O_7$ 426.1301, found 426.1283.

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Supporting Information Available: Synthetic procedures and copies of ^{1}H and ^{13}CNMR spectra and for all synthesized compounds not included in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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