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Synthesis of polycyclic and 4,5-diacylthiophene-2-carboxylates via intramolecular Friedel–Crafts alkylations and unusual autooxidative fragmentation of the derivatives obtained from the samarium diiodide-promoted coupling reactions of thiophene-2-carboxylate with carbonyl compounds

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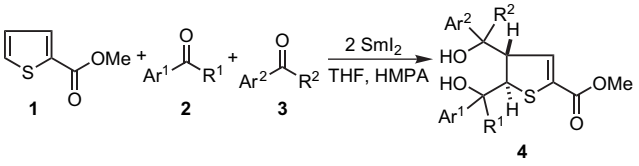
Abstract—Our present study provides an expedient method for the synthesis of novel polycyclic and multi-substituted thiophene derivatives. A series of 4,5-di(hydroxyalkyl)-4,5-dihydrothiophene-2-carboxylates (e.g., **4a–c** and **10**) were prepared by the SmI_2-promoted three-component coupling reactions of thiophene-2-carboxylate with aromatic aldehydes and 4-methoxyacetophenone. Diol **4a** was oxidized by DDQ or pyridinium dichromate to give 5-acyl-4-hydroxyalkyl-4,5-dihydrothiophene-2-carboxylate **6a**, which was subjected to dehydration to give either alkene **7** with terminal C=C double bond or alkene **15a** having conjugation with the ester group, depending on the reaction conditions using different quantities of *p*-toluenesulfonic acid. Alkene **7** underwent an intramolecular Friedel–Crafts alkylation to give a tetralone-fused thiophene-2-carboxylate **9**. By the similar procedure, a carbazole-fused thiophene **14** was also prepared. Alkenes **15a–c** underwent autooxidative fragmentation to give 4,5-diacylthiophene-2-carboxylates **5a–c** that were elaborated to pyridazine-fused thiophenes.

1. Introduction

Thiophenes and their polycyclic derivatives exhibit remarkable electrochemical,[1a,b] optical,[1c] physical,[1d] and biological[1e,f] properties that render their extensive applications in material and pharmaceutical sciences. Though thiophene derivatives have been prepared by various methods,[2] elaboration of the existing thiophene skeleton with multiple substituents at the desired positions is still a challenging task. To our knowledge, there are only a few reports on the derivatization of thiophene-2-carboxylates.[3] For example, methyl thiophene-2-carboxylate reacts with paraformaldehyde in the presence of $ZnCl_2$ to give a mixture of 4-chloromethyl-, 5-chloromethyl-, and 4,5-bis(chloromethyl)thiophene-2-carboxylate.[3a] Metalation of thiophene-2-carboxylate and the subsequent electrophilic substitution usually occur at either C-3 or C-5 position;[3b] however, introduction of substituents at the C-4 position is still difficult.



(1)

In an approach to elaborate thiophene derivatives at C-4 and C-5 positions, we have utilized SmI_2 as the promoter to carry out the tandem double electrophilic reactions of thiophene-2-carboxylate **1** with carbonyl compounds (e.g., **2** and **3**) to obtain the three-component coupling products of 4,5-di(hydroxyalkyl)-4,5-dihydrothiophenes **4** in one-pot operation (Eq. 1).[4] The three-component coupling products prepared as such have been elaborated to the photochromic compounds of 4,5-dialkenylthiophenes[4c] and the sulfur-containing polyaromatic compounds[4d] that are applicable to material and biological researches. In order to understand the scope and limitation of this method, we extended this study to synthesize the previously elusive compounds of 4,5-diacylthiophene-2-carboxylates (Fig. 1), and serendipitously observed an unusual acid-catalyzed autooxidative fragmentation reaction during this course of study.

Keywords: Samarium diiodide; Coupling reaction; Autooxidation; Fragmentation; Thiophene; Thieno[2,3-*d*]pyridazine.
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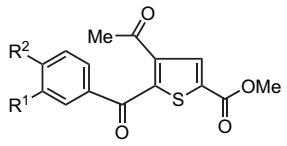


5a $R^1 = R^2 = MeO$
5b $R^1 = H$, $R^2 = MeO$
5c $R^1 = H$, $R^2 = Me$

Figure 1. Example of 4,5-diacylthiophene-2-carboxylates that are not reported previously.

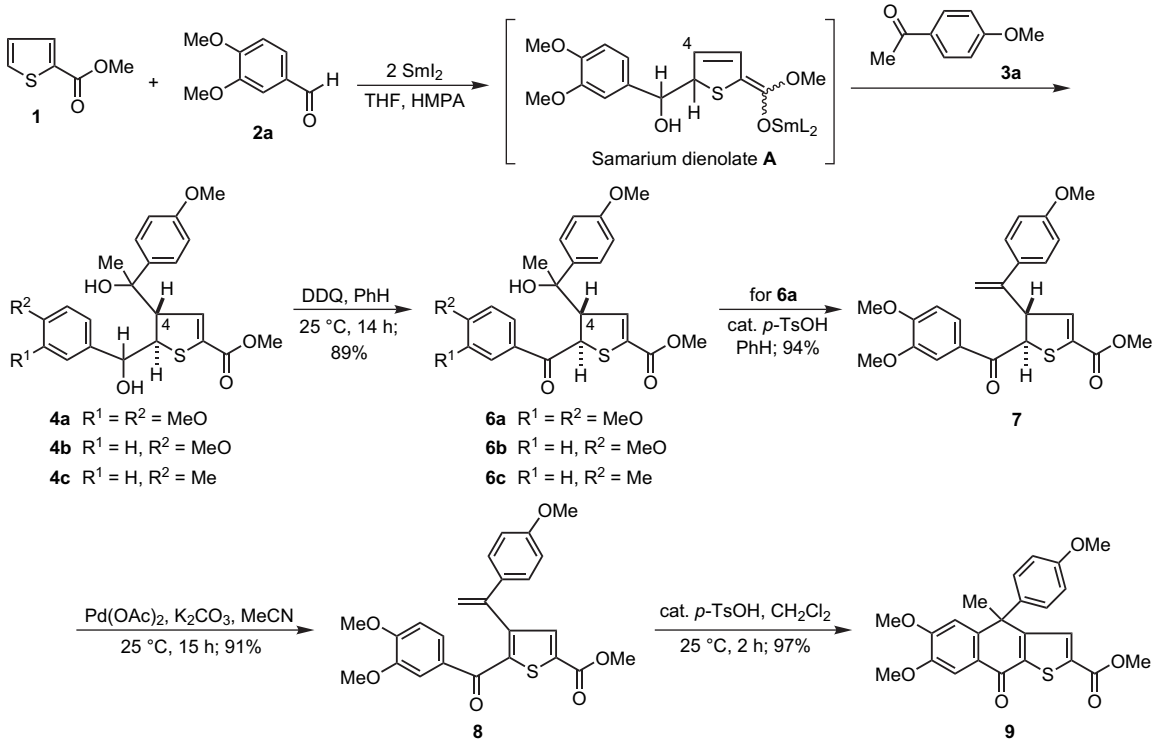
2. Results and discussion

The coupling reaction of thiophene-2-carboxylate with 3,4-dimethoxybenzaldehyde proceeded smoothly by the promotion of SmI_2 (Scheme 1). The intermediate samarium dienolate (**A**) was trapped by 4-methoxyacetophenone to give diol **4a** in one-pot operation. The intermediate diol **4a**, without further purification, was readily converted to ketone **6a** by oxidation with DDQ. Ketone **6a** was then subjected to an acid-catalyzed dehydration, an oxidative aromatization, and an acid-catalyzed cyclization to afford the desired tetralone-fused thiophene **9** via the intermediacy of alkene **7** and thiophene **8**.

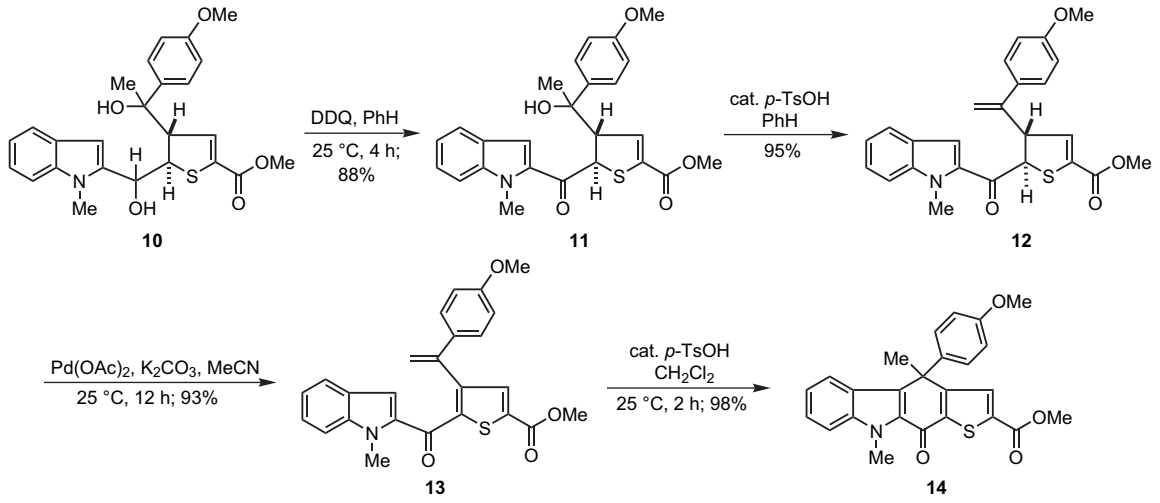
The three-component coupling products **4b** and **4c** were similarly prepared, and then oxidized by DDQ to give the ketone compounds **6b** and **6c**. In a recent communication,[5] we also reported a similar SmI_2-promoted coupling reaction of thiophene-2-carboxylate with 1-methylindole-2-carbaldehyde and 4-methoxyacetophenone to afford diol **10** (Scheme 2).

Diols **5a–c** and **10** likely have the 4,5-trans configuration that can be established by an attack of the second electrophile on the less hindered face of the dienolate intermediate **A** (Scheme 1).[4] The ^1H NMR analysis indicated that diol **10** existed as a mixture of two diastereomers (65:35) differing at the carbinyl centers. Oxidation of diol **10** (as a diastereomeric mixture) with DDQ at room temperature afforded a single product of ketone **11**. This oxidation reaction was also realized by using pyridinium dichromate (PDC) as the oxidizing agent. No dehydrogenation to aromatic thiophene derivatives occurred on treatment with DDQ or PDC under such mild reaction conditions. Under an atmosphere of nitrogen, alcohol **11** was treated with a catalytic amount of *p*-TsOH in refluxing benzene to give the dehydration product **12** having a terminal C=C double bond, instead of giving the conjugated isomer. The oxidative aromatization of dihydrothiophene **12** to alkenylthiophene **13** is realized by using $Pd(OAc)_2$ as the oxidizing agent. The intramolecular Friedel–Crafts alkylation of **13** is then carried out by the catalysis of *p*-TsOH to give the tetracyclic carbazolothiophene **14**. Some carbazole-fused thiophene analogues of **14** exhibiting potent antagonistic activity against the endothelin vasoconstrictor[5,6] were also prepared by the similar procedures.

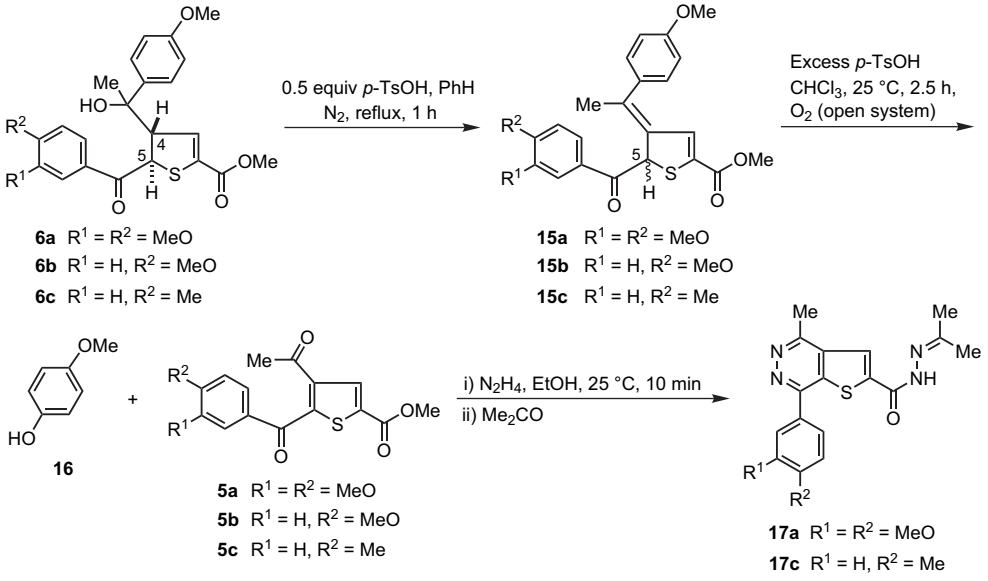
Interestingly, we observed that the treatment of **6a** with an increased amount of *p*-TsOH (~0.5 equiv) in refluxing benzene under an inert atmosphere afforded a 79% yield of the conjugated compound **15a** (Scheme 3), differing from isomer **7** obtained from the acid-catalyzed dehydration (Scheme 1). The (*E*)-configuration in **15a** was determined by the ^1H NMR analysis, which showed a 12.3% nuclear Overhauser enhancement of H-5 (at δ 5.86) upon irradiation of the methyl group at δ 1.90.



Scheme 1. Synthesis of a tetralone-fused thiophene.



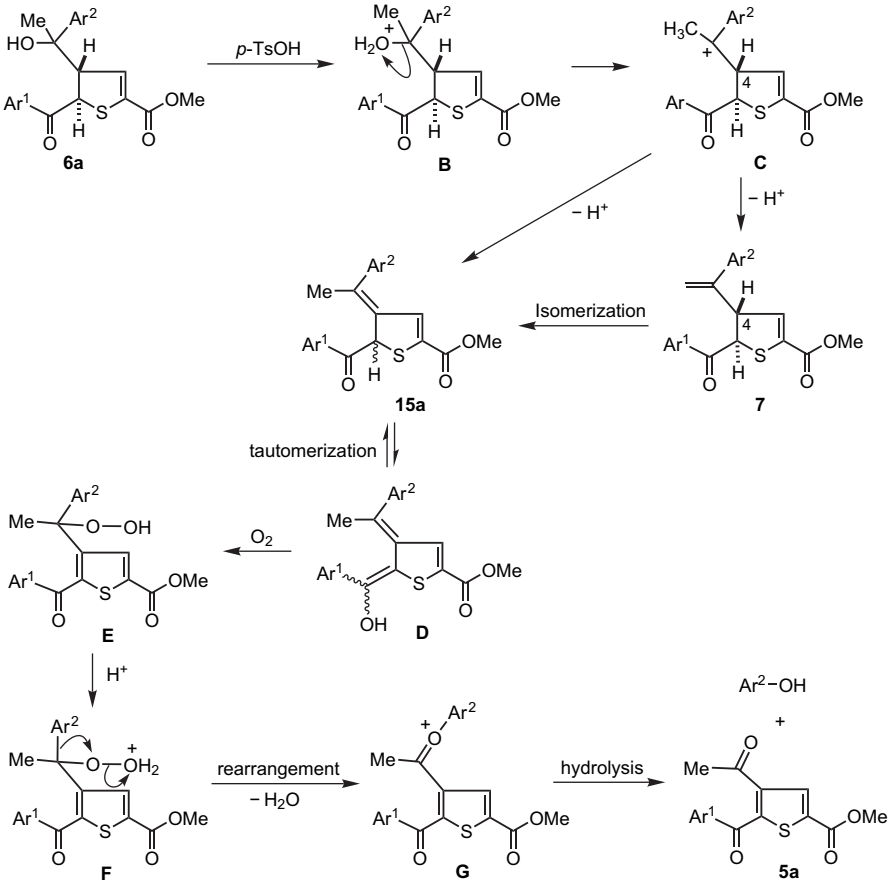
Scheme 2. Synthesis of a carbazole-fused thiophene.



Scheme 3. Formation of 4,5-diacylthiophenes via oxidative fragmentation.

In a serendipitous way, we also found an unusual autooxidation of **15a**, giving two oxidative cleavage products **16** and **5a** in quantitative yields (Scheme 3). The autooxidation occurred when a $CHCl_3$ solution of **15a** was stirred with stoichiometric amount of *p*-TsOH in air (25 °C, 2.5 h). Compound **16** was identified as 4-methoxyphenol, and the structure of **5a** was determined to be methyl 4-acetyl-5-(3,4-dimethoxybenzoyl)thiophene-2-carboxylate by IR, MS, ^{1}H and ^{13}C NMR spectral analyses. By the similar procedures, compounds **6b** and **6c** were, respectively, treated with *p*-TsOH to give the alkene intermediates **15b** and **15c**, which underwent autooxidative cleavages in situ to the corresponding 4,5-diacylthiophene-2-carboxylates **5b** and **5c**, along with the counterpart of 4-methoxyphenol **16**. The diacylthiophenes **5a–c** are equipped with the function of 1,4-diketone, which is useful in the construction of various heterocycles.[7] For example, **5a** and **5c** were, respectively, treated with hydrazine, followed by condensation with acetone, to give thieno[2,3-*d*]pyridazine derivatives **17a** and **17c** in quantitative yields. Thieno[2,3-*d*]pyridazine derivatives have been shown to exhibit anti-inflammatory activity,[7a] and were used as a short-term hypnotic to treat insomnia.[7b] We also attempted to carry out a straightforward synthesis of **5a–c** by the SmI_2-promoted double electrophilic reactions of methyl thiophene-2-carboxylate with aromatic aldehyde Ar^1CHO (or benzoyl chloride) and acetaldehyde (or acetyl chloride). However, all the reactions resulted in complicated mixtures.

Though the real reaction pathways for the dichotomous formation of alkenes **7** and **15a** from the alcohol **6a** were not rigorously determined, we speculated that the dehydration might proceed with E1 mechanism through a stabilized tertiary carbocationic intermediate **C** (Scheme 4). The subsequent removal of a proton from the less hindered methyl group would give alkene **7**, whereas removal of the internal proton at C-4 would furnish the conjugated compound **15a**. Alkene **7** having an isolated C=C double bond was partially



Scheme 4. Putative mechanism for conversion of **6a** to **5a** via dehydration and autooxidative fragmentation.

converted to the conjugated alkene **15a** on treatment with *p*-TsOH in refluxing benzene under an atmosphere of nitrogen. We also proposed a possible mechanism for the conversion of **15a–c** to diacylthiophenes **5a–c** via the fragmentation reaction of a hydroperoxide intermediate. For example, a facilitated enolization of **15a** could be effected by a strong acid, *p*-TsOH (in stoichiometric amount). Upon exposure to air, the dienol intermediate **D** would react with dioxygen to give a hydroperoxide intermediate **E**. The subsequent rearrangement of the hydroperoxide intermediate **E** would afford 4-methoxyphenol (**16**, Ar^2=4-$MeOC_6H_4$) and ketone **5a**, by analogy to the well-known fragmentation reaction of cumyl hydroperoxide to phenol and acetone.[8]

3. Conclusion

We have extended the scope of the previously discovered SmI_2-promoted tandem double electrophilic reactions of thiophene-2-carboxylate with aromatic aldehydes and ketones. The three-component coupling products, e.g., **4a** and **10**, were readily oxidized to the corresponding ketones, e.g., **6a** and **11**, using DDQ or PDC as the oxidizing agents. In one approach, dehydration of **6a** and **11** was carried out by using catalytic amount of *p*-TsOH to give alkenes **7** and **12** with terminal C=C double bonds. The alkenes **7** and **12** were subjected to oxidative aromatization and intramolecular Friedel–Crafts alkylation to afford tetralone- and carbazole-fused thiophene-2-carboxylate **9** and **14**. In another approach using increased amounts of *p*-TsOH (~0.5 equiv), alcohols **6a–c** were converted to the dehydration products **15a–c**, which underwent an unusual autooxidative fragmentation reaction in air to give very high yields of 4,5-diacylthiophene-2-carboxylates. Our present study thus provides an expedient method for the synthesis of novel polycyclic and multi-substituted thiophene compounds. Thiophene derivatives **5a–c** bearing the moiety of 1,4-diketone are ready for further elaboration to numerous heterocyclic compounds, e.g., condensation with hydrazine to form thieno[2,3-*d*]-pyridazine derivatives **17a** and **17c** as demonstrated in this study.

4. Experimental

4.1. General

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of nitrogen. Syringes and needles for the transfer of reagents were dried at 100 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl; chlorinated hydrocarbons from CaH_2. Reactions were monitored by thin-layer chromatography using pre-coated aluminum plates with a 0.25 mm layer of silica gel containing a fluorescent indicator (Merck Art. 5544). Column chromatography was carried out on Kieselgel 60 (40–63 μm).

Melting points were recorded using a Yanagimoto micro-melting point apparatus and were uncorrected. Chemical

shifts of ^1H and ^{13}C NMR spectra are reported relative to $CHCl_3$ [δ_H 7.24, δ_C (central line of t) 77.0]. Coupling constants (J) are given in hertz. Distortionless enhancement polarization transfer (DEPT) spectra were taken to determine the types of carbon signals.

4.1.1. Methyl 5-(3,4-dimethoxybenzoyl)-4-[1-hydroxy-1-(4-methoxyphenyl)ethyl]-4,5-dihydrothiophene-2-carboxylate (6a). Under an atmosphere of argon, a deep blue SmI_2 solution (0.1 M) was prepared by the treatment of Sm (661 mg, 4.4 mmol) with 1,2-diiodoethane (1.01 g, 3.6 mmol) in HMPA (2.8 mL, 16 mmol) and anhydrous THF (20 mL) for 1.5 h at room temperature. To the SmI_2 solution (cooled in an ice bath) was added a THF solution (3 mL) of methyl thiophene-2-carboxylate (142 mg, 1 mmol) and 3,4-dimethoxybenzaldehyde (167 mg, 1.0 mmol). The reaction mixture was stirred at 0 °C for 45 min, and then at room temperature (25 °C) for another 45 min. A solution of 4-methoxyacetophenone (180 mg, 1.2 mmol) in THF (2 mL) was added at 0 °C, and the mixture was stirred at 0–25 °C for additional 10 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (0.1 mL). The mixture was passed through a short silica gel column by eluting with EtOAc/hexane (1:1). The filtrate was concentrated, and chromatographed on a silica gel column by eluting with EtOAc/hexane (3:7) to give the desired coupling product **4a** (354 mg) containing two isomers (45:55) as shown by the ^1H NMR analysis.

Without further purification, **4a** (354 mg, 0.78 mmol) in benzene (10 mL) was stirred with DDQ (216 mg, 0.94 mmol) at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, and chromatographed on a silica gel column by elution with EtOAc/hexane (1:2) to afford the corresponding ketone **6a** (317 mg) in 69% overall yield.

Compound **6a**: oil; TLC (EtOAc/hexane, 1:1) R_f=0.30; IR (neat) 3502, 1709, 1665, 1265, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.49 (1H, d, J=l.9 Hz), 7.45 (1H, dd, J=8.4, 1.9 Hz), 7.37 (2H, d, J=8.6 Hz), 6.85 (2H, d, J=8.6 Hz), 6.84 (1H, d, J=8.4 Hz), 6.27 (1H, d, J=3.0 Hz), 5.36 (1H, d, J=7.2 Hz), 4.67 (1H, dd, J=7.2, 3.0 Hz), 3.91 (3H, s), 3.90 (3H, s), 3.77 (3H, s), 3.65 (3H, s), 2.18 (1H, br s, OH), 1.46 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.5, 161.8, 158.4, 153.6, 149.0, 137.6, 134.6, 133.1, 127.9, 126.0 (2×), 123.1, 113.5 (2×), 110.6, 109.9, 75.6, 61.1, 55.9, 55.7, 54.9, 52.1, 50.l, 27.8; MS m/z (rel intensity) 440 (11, M^+-H_2O), 165 (100); HRMS calcd for $C_{24}H_{26}O_7S$: 458.1399, found: m/z 458.1400 (M^+).

4.1.2. Methyl 4-[1-hydroxy-1-(4-methoxyphenyl)ethyl]-5-(4-methoxybenzoyl)-4,5-dihydrothiophene-2-carboxylate (6b). According to the procedure similar to that for **6a**, the SmI_2-promoted three-component coupling reaction of methyl thiophene-2-carboxylate (142 mg, 1 mmol), 4-methoxybenzaldehyde (0.12 mL, 1.0 mmol), and 4-methoxyacetophenone (180 mg, 1.2 mmol) afforded **4b** (323 mg). Without further purification, a solution of **4b** (323 mg, 0.75 mmol) in CH_2Cl_2 (15 mL) was treated with pyridinium dichromate (376 mg, 1.0 mmol) at room temperature for 3 h in the presence of molecular sieves (4 Å, 2 g). The mixture was subjected to silica gel column chromatography by eluting with EtOAc/hexane (3:7) to give ketone **6b** (232 mg) in 54% overall yield.

Compound **6b**: oil; TLC (EtOAc/hexane, 3:7) R_f=0.17; IR (neat) 3492, 1708, 666, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.86 (2H, d, J=8.9 Hz), 7.37 (2H, d, J=8.8 Hz), 6.90 (2H, d, J=8.9 Hz), 6.84 (2H, d, J=8.8 Hz), 6.28 (1H, d, J=3.1 Hz), 5.34 (1H, d, J=7.0 Hz), 4.66 (1H, dd, J=7.0, 3.1 Hz), 3.82 (3H, s), 3.75 (3H, s), 3.64 (3H, s), 2.90 (1H, br s), 1.46 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 192.5, 163.9, 161.9, 158.6, 137.7, 134.6, 133.4, 131.0 (2×), 127.9, 126.1 (2×), 114.0 (2×), 113.7 (2×), 75.9, 61.1, 55.4, 55.1, 52.3, 50.4, 28.0; MS m/z (rel intensity) 428 (1, M^+), 151 (100); HRMS calcd for $C_{23}H_{24}O_6S$: 428.1294, found: m/z 428.1298 (M^+).

4.1.3. Methyl 4-[1-hydroxy-1-(4-methoxyphenyl)ethyl]-5-(4-methylbenzoyl)-4,5-dihydrothiophene-2-carboxylate (6c). According to the procedure similar to that for **6a**, the SmI_2-promoted three-component coupling reaction of methyl thiophene-2-carboxylate (142 mg, 1 mmol) with 4-methylbenzaldehyde (0.12 mL, 1.0 mmol) and 4-methoxyacetophenone (180 mg, 1.2 mmol) afforded **4c** (307 mg). Without further purification, a solution of **4c** (307 mg, 0.75 mmol) in CH_2Cl_2 (10 mL) was treated with pyridinium dichromate (420 mg, 1.12 mmol) at room temperature for 1 h in the presence of molecular sieves (4 Å, 1.5 g). The mixture was subjected to silica gel column chromatography by eluting with EtOAc/hexane (1:4) to give ketone **6c** (226 mg) in 54% overall yield.

Compound **6c**: oil; TLC (EtOAc/hexane, 3:7) R_f=0.23; IR (neat) 3494, 1711, 1671, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.78 (2H, d, J=8.2 Hz), 7.38 (2H, dd, J=8.9, 2.0 Hz), 7.24 (2H, d, J=8.2 Hz), 6.86 (2H, dd, J=8.9, 2.0 Hz), 6.29 (1H, d, J=3.1 Hz), 5.34 (1H, d, J=6.8 Hz), 4.67 (1H, dd, J=6.8, 3.1 Hz), 3.78 (3H, s), 3.67 (3H, s), 2.39 (3H, s), 2.14 (1H, br s), 1.48 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 193.4, 161.9, 158.6, 144.6, 137.6, 134.5, 133.4, 132.4, 129.4 (2×), 128.7 (2×), 126.1 (2×), 113.6 (2×), 75.9, 61.0, 55.1, 52.3, 50.6, 27.9, 21.6; MS m/z (rel intensity) 412 (7, M^+), 151 (100); HRMS calcd for $C_{23}H_{24}O_5S$: 412.1344, found: m/z 412.1340 (M^+).

4.1.4. Methyl 5-(3,4-dimethoxybenzoyl)-4-[1-(4-methoxyphenyl)ethenyl]-4,5-dihydrothiophene-2-carboxylate (7). Under an atmosphere of nitrogen, a mixture of alcohol **6a** (25 mg, 0.054 mmol) and p-TsOH monohydrate (catalytic amount, ca. 1 mg) in benzene (20 mL) was heated at reflux for 5 h, while the generated water was removed by a Dean–Stark apparatus. The reaction mixture was concentrated under reduced pressure, and chromatographed on a silica gel column by eluting with EtOAc/hexane (1:9) to afford the corresponding alkene **7** (23 mg, 94% yield) as an oil. TLC (EtOAc/hexane, 3:7) R_f=0.12; IR (neat) 1710, 1663, 1599, 1262, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.46 (1H, d, J=1.9 Hz), 7.32 (2H, d, J=8.7 Hz), 7.28 (1H, dd, J=8.5, 1.9 Hz), 6.81 (2H, d, J=8.7 Hz), 6.80 (1H, d, J=8.5 Hz), 6.66 (1H, d, J=3.4 Hz), 5.44 (1H, s), 5.23 (1H, dd, J=4.3, 3.4 Hz), 5.15 (1H, s), 4.87 (1H, d, J=4.3 Hz), 3.89 (6H, s), 3.75 (3H, s), 3.74 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 191.9, 162.1, 159.5, 153.7, 149.2, 145.5, 136.5, 133.0, 131.5, 127.8, 127.5 (2×), 123.0, 114.0 (2×), 113.2,

110.9, 110.0, 56.1, 56.0, 55.2, 54.6, 52.4, 52.3; MS *m/z* (rel intensity) 440 (58, M^+), 165 (100); HRMS calcd for $C_{24}H_{24}O_6S$: 440.1294, found: *m/z* 440.1289 (M^+).

4.1.5. Methyl 5-(3,4-dimethoxybenzoyl)-4-[1-(4-methoxyphenyl)ethenyl]thiophene-2-carboxylate (8). A solution of alkene **7** (150 mg, 0.34 mmol) in degassed anhydrous acetonitrile (7 mL) was stirred with $Pd(OAc)_2$ (153 mg, 0.68 mmol) and K_2CO_3 (142 mg, 1.02 mmol) at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure, and chromatographed on a silica gel column by eluting with EtOAc/hexane (1:9) to give compound **8** (136 mg, 91% yield) as an oil. TLC (CH_2Cl_2) R_f=0.35; IR (neat) 1718, 1637, 1594, 1511, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (1H, s), 7.14 (1H, dd, *J*=8.2, 2.0 Hz), 6.93 (1H, d, *J*=2.0 Hz), 6.85 (2H, dd, *J*=8.8, 2.0 Hz), 6.65 (1H, d, *J*=8.2 Hz), 6.60 (2H, dd, *J*=8.8, 2.0 Hz), 5.29 (1H, s), 5.20 (1H, s), 3.86 (3H, s), 3.84 (3H, s), 3.71 (3H, s), 3.69 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.1, 161.9, 159.1, 153.2, 148.5, 144.8, 143.6, 142.9, 135.4, 134.9, 132.9, 130.1, 127.9 (2×), 124.4, 115.3, 113.4 (2×), 110.4, 109.4, 55.9, 55.6, 55.0, 52.4; MS *m/z* (rel intensity) 438 (31, M^+), 55 (100); HRMS calcd for $C_{24}H_{22}O_6S$: 438.1137, found: *m/z* 438.1140 (M^+).

4.1.6. Methyl 6,7-dimethoxy-4-(4-methoxyphenyl)-4-methyl-9-oxo-4,9-dihydronaphtho[2,3-*b*]thiophene-2-carboxylate (9). Compound **8** (55 mg, 0.125 mmol) and catalytic amount of *p*-TsOH monohydrate in CH_2Cl_2 solution (15 mL) were stirred at room temperature for 2 h. The reaction mixture was filtered, concentrated under reduced pressure, and chromatographed on a silica gel column by eluting with EtOAc/hexane (1:9) to give compound **9** (53 mg, 97% yield) as an oil; TLC (EtOAc/hexane, 3:7) R_f=0.23; IR (neat) 1719, 645, 1279 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.73 (1H, s), 7.39 (1H, s), 7.07 (2H, dd, *J*=8.6, 2.1 Hz), 6.77 (2H, dd, *J*=8.6, 2.1 Hz), 6.47 (1H, s), 3.95 (3H, s), 3.83 (3H, s), 3.74 (3H, s), 3.73 (3H, s), 1.94 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.0, 162.2, 158.4, 157.3, 153.7, 148.3, 146.2, 139.3, 139.1, 136.2, 133.3, 128.1 (2×), 123.9, 114.0 (2×), 110.2, 107.3, 56.0, 55.9, 55.1, 52.5, 46.2, 30.4; MS *m/z* (rel intensity) 438 (75, M^+), 423 (100); HRMS calcd for $C_{24}H_{22}O_6S$: 438.1137, found: *m/z* 438.1142 (M^+).

4.1.7. Methyl 4-[1-hydroxy-1-(4-methoxyphenyl)ethyl]-5-(1-methylindole-2-carbonyl)-4,5-dihydrothiophene-2-carboxylate (11). According to the procedure similar to that for **4a**, the SmI_2-promoted three-component coupling reaction of methyl thiophene-2-carboxylate (142 mg, 1 mmol) with *N*-methylindole-2-carboxaldehyde (159 mg, 1 mmol) and 4-methoxyacetophenone (180 mg, 1.2 mmol) afforded **10** (349 mg) containing two isomers (65:35) as shown by the ^1H NMR analysis. Without further purification, **10** (349 mg, 0.77 mmol) was treated with DDQ (216 mg, 0.94 mmol) by a procedure similar to that for **6a** to give ketone **11** (306 mg) in 65% overall yield. Compound **11**: oil; TLC (EtOAc/hexane, 3:7) R_f=0.23; IR (neat) 3502, 1717, 1661, 1613, 1251, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (1H, d, *J*=8.0 Hz), 7.41 (2H, d, *J*=8.7 Hz), 7.38–7.33 (2H, m), 7.20 (1H, s), 7.13 (1H, td, *J*=8.0, 2.0 Hz), 6.86 (2H, d, *J*=8.7 Hz), 6.34 (1H, d, *J*=3.0 Hz), 5.42 (1H, d, *J*=7.2 Hz), 4.64 (1H, dd, *J*=7.2, 3.0 Hz), 4.03 (3H, s), 3.74 (3H, s), 3.67 (3H, s), 2.40 (1H, br s, OH), 1.54 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.6, 162.0, 158.6, 140.6, 137.6, 134.3, 133.8, 133.1, 126.4, 126.1 (2×), 125.6, 123.1, 120.9, 113.7 (2×), 112.1, 110.3, 75.9, 61.0, 55.1, 52.3, 52.0, 32.1, 27.7; FABMS *m/z* 452.1 (M^+-H_2O+H); HRMS calcd for $C_{25}H_{25}NO_5S$: 451.1453, found: *m/z* 451.1463 (M^+).

4.1.8. Methyl 4-[1-(4-methoxyphenyl)ethenyl]-5-(1-methylindole-2-carbonyl)-4,5-dihydrothiophene-2-carboxylate (12). By a procedure similar to that for **7**, treatment of **11** (95 mg, 0.21 mmol) with catalytic amount of *p*-TsOH monohydrate (ca. 3 mg) in refluxing benzene for 5 h gave the dehydration product **12** (87 mg, 95%) as an oil; TLC (EtOAc/hexane, 3:7) R_f=0.13; IR (neat) 1720, 1660, 1607, 1511, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.59 (1H, d, *J*=8.0 Hz), 7.36–7.32 (4H, m), 7.14–7.08 (1H, m), 6.97 (1H, s), 6.83 (2H, d, *J*=8.7 Hz), 6.69 (1H, d, *J*=3.5 Hz), 5.47 (1H, s), 5.20 (1H, dd, *J*=4.6, 3.5 Hz), 5.19 (1H, s), 4.98 (1H, d, *J*=4.6 Hz), 4.06 (3H, s), 3.77 (3H, s), 3.74 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.3, 162.1, 159.4, 145.6, 140.5, 136.1, 133.4, 132.8, 131.5, 127.5 (2×), 126.3, 125.6, 122.9, 120.9, 113.9 (2×), 113.2, 111.5, 110.3, 56.2, 55.1, 52.4, 52.3, 32.1; MS *m/z* (rel intensity) 433 (57, M^+), 374 (13), 275 (100), 158 (88), 133 (32); HRMS calcd for $C_{25}H_{23}NO_4S$: 433.1348, found: *m/z* 433.1346 (M^+).

4.1.9. Methyl 4-[1-(4-methoxyphenyl)ethenyl]-5-(1-methylindole-2-carbonyl)thiophene-2-carboxylate (13). By a procedure similar to that for **8**, alkene **12** (70 mg, 0.16 mmol) was treated with $Pd(OAc)_2$ (70 mg, 0.31 mmol) and K_2CO_3 (130 mg, 0.94 mmol) at room temperature for 12 h to give compound **13** (65 mg, 93%) as an oil. TLC (EtOAc/hexane, 1:9) R_f=0.13; IR (neat) 1719, 1626, 1510, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 (1H, s), 7.59 (1H, d, *J*=8.0 Hz), 7.35 (1H, t, *J*=8.0 Hz), 7.24 (1H, d, *J*=8.0 Hz), 7.11 (1H, t, *J*=8.0 Hz), 6.99 (1H, s), 6.82 (2H, d, *J*=8.5 Hz), 6.59 (2H, d, *J*=8.5 Hz), 5.34 (1H, s), 5.33 (1H, s), 3.92 (3H, s), 3.70 (3H, s), 3.57 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 162.2, 159.2, 145.6, 143.9, 143.5, 140.3, 135.7, 135.2, 135.0, 133.5, 128.0 (2×), 126.2, 125.7, 123.0, 120.7, 115.1, 114.9, 113.3 (2×), 110.1, 55.2, 52.5, 31.1; FABMS *m/z* 431 (M^+); HRMS calcd for $C_{25}H_{21}NO_4S$: 431.1191, found: *m/z* 431.1183 (M^+).

4.1.10. Methyl 4,9-dimethyl-4-(4-methoxyphenyl)-10-oxo-4,10-dihydrocarbazolo[2,3-*b*]thiophene-2-carboxylate (14). By a procedure similar to that for **9**, treatment of **13** (50 mg, 0.12 mmol) with a catalytic amount of *p*-TsOH monohydrate in CH_2Cl_2 solution at room temperature for 2 h afforded the acid-catalyzed cyclization product **14** (49 mg, 98%) as colorless solid, mp 113–114 °C. TLC (EtOAc/hexane, 1:9) R_f=0.13; IR (KBr) 1716, 1637, 1510, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.53 (1H, s), 7.38–7.30 (2H, m), 7.23–7.16 (3H, m), 6.97 (1H, m), 6.77 (2H, dd, *J*=8.8, 2.1 Hz), 4.26 (3H, s), 3.85 (3H, s), 3.73 (3H, s), 2.08 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7, 162.3, 158.4, 158.0, 141.8, 140.5, 138.4, 135.6, 134.9, 132.7, 128.8, 127.8 (2×), 126.5, 123.2, 122.2, 120.4, 114.1 (2×), 110.5, 55.1, 52.5, 44.4, 31.6, 28.1; FABMS *m/z* 431 (M^+); HRMS calcd for $C_{25}H_{21}NO_4S$: 431.1191, found: *m/z*

431.1192 (M^+). Anal. Calcd for $C_{25}H_{21}NO_4S$: C, 69.59; H, 4.91; N, 3.25. Found: C, 69.42; H, 4.98; N, 3.14.

4.1.11. Methyl 5-(3,4-dimethoxybenzoyl)-4-[1-(4-methoxyphenyl)ethylidene]-5*H*-thiophene-2-carboxylate (15a). Under an atmosphere of nitrogen, a mixture of **6a** (263 mg, 0.59 mmol) and *p*-TsOH monohydrate (57 mg, 0.30 mmol) in benzene (20 mL) was heated at reflux for 1 h. The mixture was then subjected to silica gel column chromatography by eluting with EtOAc/hexane (1:4) to give alkene **15a** (204 mg, 79% yield) as a solid; mp 156–158 °C; TLC (EtOAc/hexane, 1:4) R_f=0.14; IR (KBr) 1701, 1669, 1245, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57 (1H, s), 7.56 (1H, d, J=8.1 Hz), 7.21 (2H, d, J=8.5 Hz), 7.04 (1H, s), 6.91 (1H, d, J=8.1 Hz), 6.88 (2H, d, J=8.5 Hz), 5.86 (1H, s), 3.95 (3H, s), 3.92 (3H, s), 3.81 (3H, s), 3.70 (3H, s), 1.90 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.3, 162.9, 159.2, 153.8, 149.3, 141.6, 138.3, 134.9, 134.4, 133.7, 129.2 (2×), 128.0, 122.8, 113.7 (2×), 110.9, 110.1, 56.1, 55.9, 55.3, 54.1, 52.3, 22.6; MS *m*/*z* (rel intensity) 440 (55, M^+), 165 (100); HRMS calcd for $C_{24}H_{24}O_6S$: 440.1293, found: *m*/*z* 440.1294 (M^+). Anal. Calcd for $C_{24}H_{24}O_6S$: C, 65.44; H, 5.49. Found: C, 65.68; H, 5.42.

4.1.12. Methyl 4-acetyl-5-(3,4-dimethoxybenzoyl)thiophene-2-carboxylate (5a). A mixture of **15a** (30 mg, 0.07 mmol) and stoichiometric amount of *p*-TsOH monohydrate (19 mg, 0.1 mmol) in $CHCl_3$ (10 mL) was placed in a round-bottomed flask without capping. The mixture was stirred in air for 2.5 h at room temperature, and then subjected to a short silica gel column to remove *p*-TsOH. The crude product eluted by EtOAc/hexane (1:1) was concentrated, and purified by chromatography by eluting with EtOAc/hexane (1:4) to give 4-methoxyphenol (**16**, 8.1 mg, 95%) and diacylthiophene **5a** (23 mg, 95%).

Compound **5a**: solid; mp 125–127 °C; TLC (EtOAc/hexane, 1:4) R_f=0.07; IR (KBr) 1716, 1678, 1650, 1267, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.03 (1H, s), 7.52 (1H, d, J=2.0 Hz), 7.21 (1H, dd, J=8.4, 2.0 Hz), 6.78 (1H, d, J=8.4 Hz), 3.90 (6H, s), 3.89 (3H, s), 2.38 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 192.3, 187.7, 161.4, 154.3, 150.0, 149.3, 141.4, 134.3, 132.8, 129.7, 125.4, 110.5, 109.9, 56.1, 56.0, 52.7, 28.8; MS *m*/*z* (rel intensity) 348 (100, M^+); HRMS calcd for $C_{17}H_{16}O_6S$: 348.0667, found: *m*/*z* 348.0670 (M^+). Anal. Calcd for $C_{17}H_{16}O_6S$: C, 58.61; H, 4.63. Found: C, 58.72; H, 4.56.

4.1.13. Methyl 4-acetyl-5-(4-methoxybenzoyl)thiophene-2-carboxylate (5b). By a procedure similar to that for **15a**, alcohol **6b** (182 mg, 0.42 mmol) was first treated with 0.5 equiv of *p*-TsOH (40 mg, 0.21 mmol) in refluxing benzene under an atmosphere of nitrogen to give a crude product of alkene **15b** (148 mg). Without further purification, the crude product was stirred with excess amount of *p*-TsOH (100 mg, 0.53 mmol) in $CHCl_3$ for 2 h under an atmosphere of air to give **5b** (113 mg) in 85% overall yield.

Compound **5b**: oil; TLC (EtOAc/hexane, 1:4) R_f=0.09; IR (neat) 1713, 1678, 1649, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.03 (1H, s), 7.45 (2H, dd, J=8.9, 2.0 Hz), 6.88 (2H, dd, J=8.9, 2.0 Hz), 3.89 (3H, s), 3.82 (3H, s), 2.38 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 192.2, 187.7, 164.3, 161.4, 150.2, 141.2, 134.2, 132.9, 131.9 (2×), 129.4, 114.0 (2×), 55.5, 52.6, 28.8; MS *m*/*z* (rel intensity) 318 (54, M^+), 135 (100); HRMS calcd for $C_{16}H_{14}O_5S$: 318.0562, found: *m*/*z* 318.0564 (M^+).

4.1.14. 6-(2,3-Diaza-4-methyl-1-oxo-3-penten-1-yl)-1-methyl-4-(3,4-dimethoxyphenyl)thieno[2,3-*d*]pyridazine (17a). A mixture of **5a** (20 mg, 0.06 mmol) and excess amount of hydrazine monohydrate (9 mg, 0.18 mmol) in EtOH (15 mL) was stirred at room temperature for 10 min. The mixture was concentrated, acetone was added (20 mL), and concentrated again under reduced pressure. This procedure was repeated twice to give the desired product **17a** (23 mg) in 99% yield. Solid; mp 209–211 °C; TLC ($MeOH/CH_2Cl_2$, 1:19) R_f=0.13; IR (KBr) 3423, 1642, 1415, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.69 (1H, br s), 8.53 (1H, s), 7.71 (1H, s), 7.69 (1H, d, J=8.1 Hz), 7.00 (1H, d, J=8.1 Hz), 3.59 (3H, s), 3.94 (3H, s), 2.99 (3H, s), 2.13 (3H, s), 2.03 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.5, 154.3, 153.9, 152.3, 150.8, 149.3, 141.0, 139.8, 134.9, 129.8, 128.8, 121.1, 111.3, 110.9, 55.9 (2×), 25.1, 19.9, 16.2; MS *m*/*z* (rel intensity) 384 (70, M^+), 285 (100); HRMS calcd for $C_{19}H_{20}N_4O_3S$: 384.1256, found: *m*/*z* 384.1259 (M^+). Anal. Calcd for $C_{19}H_{20}N_4O_3S$: C, 59.36; H, 5.24; N, 14.57. Found: C, 59.46; H, 5.12; N, 14.62.

4.1.15. 6-(2,3-Diaza-4-methyl-1-oxo-3-penten-1-yl)-1-methyl-4-(4-methylphenyl)thieno[2,3-*d*]pyridazine (17c). By a procedure similar to that for **5b**, compound **6c** (200 mg, 0.51 mmol) was first treated with 0.5 equiv of *p*-TsOH in refluxing benzene under an atmosphere of nitrogen to give a crude product **15c**. The crude product was subsequently stirred with stoichiometric amount of *p*-TsOH in $CHCl_3$ for 2.5 h under an atmosphere of air to give a mixture of 4-methoxyphenol and **5c**, which were inseparable by silica gel column chromatography. By a procedure similar to that for **17a**, the mixture was treated with excess amounts of hydrazine and acetone to afford a crude product, which was purified on a silica gel column by eluting with MeOH/CH_2Cl_2 (1:19) to give **17c** (168 mg) in 97% overall yield. Solid; mp 262–264 °C; TLC ($MeOH/CH_2Cl_2$, 1:19) R_f=0.17; IR (KBr) 3447, 1648, 1390, 1259 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$=4:1, 200 MHz) δ 8.39 (1H, s), 7.80 (2H, J=8.0 Hz), 7.23 (2H, d, J=8.0 Hz), 2.83 (3H, s), 2.32 (3H, s), 1.98 (3H, s), 1.87 (3H, s); ^{13}C NMR ($CDCl_3$/CD_3OD=3:1), 75 MHz) δ 161.5, 154.8, 154.1, 152.7, 141.3, 140.4, 140.0, 132.9, 134.7, 129.4 (2×), 129.2, 127.9 (2×), 24.6, 21.0, 19.3, 16.3; MS *m*/*z* (rel intensity) 338 (42, M^+), 239 (100); HRMS calcd for $C_{18}H_{18}N_4OS$: 338.1202, found: *m*/*z* 338.1199 (M^+). Anal. Calcd for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.56. Found: C, 63.82; H, 5.40; N, 16.42.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.11.080.

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