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Synthetic Access to Poly-Substituted 6-Alkoxyindoles from 1,3-Cyclohexanediones and Nitroolefins through Facile Aromatization Reaction

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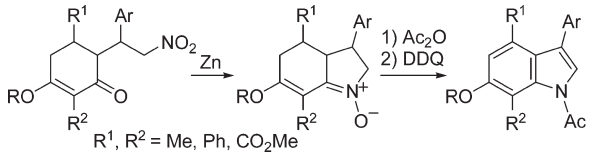

6-Alkoxy-3-arylindoles were efficiently prepared from 1,3-cyclohexanedione enol ethers and *β*-nitrostyrenes. Michael addition using the kinetically generated enolate, followed by Zn reduction of a nitro group of the resulting adducts produced the nitrones which were then treated with acetic anhydride to induce aromatization by dehydration and N-acetylation, which furnished the desired indoles by the DDQ oxidation. This methodology provides an easy entry toward various poly-substituted 6-alkoxyindoles.

The indole ring system is probably the most widespread heterocycle in nature.[1] Because of their structural diversity in biologically active indoles, it has been recognized that the indole ring system occupied an important structural unit in many pharmaceutical agents[2] and stimulated the development of new methods for synthesis and derivatization of indoles.[3]

Although numerous routes for preparation of indoles have been known, most of them are based on benzene derivatives as a starting material,[3c] and aliphatic starting materials are scarcely utilized presumably due to lack of an efficient aromatization method.[4] We envisioned that linking of 1,3-cyclohexanediones with a two-carbon chain bearing a nitrogen function followed by aromatization would be a useful tactic as a preparative method for biologically relevant indole derivatives.

Until now, approaches to indoles from 1,3-cyclohexanediones have mainly been examined by carbon-chain elongation at the position flanked by two carbonyl units, leading to 4-oxyindoles and their analogues.[5] On the other hand, to our knowledge, two-carbon homologation reaction at the kinetic enolates[6] from 1,3-cyclohexanedione enol ethers **1**, which would eventually reserve an alkoxy group at the C6 position of the indole ring after aromatization,[7] has never been attempted. We therefore report here facile access to poly-substituted 6-alkoxyindoles **6** by adopting Semmler−Wolff-type aromatization,[8,9] which involves intramolecular amination of 1,3-cyclohexanedione enol ethers with hydroxylamine and dehydration (Scheme 1).

The lithium enolates generated from 1,3-cyclohexanedione enol ether **1** upon treatment with LDA reacted smoothly with **2** at −78 to −50 °C, giving the adducts **3** installed with a two-carbon chain and a nitrogen function in good yields. In this addition, the adducts **3** were obtained as a mixture of diastereomers at the C6 in a six-membered ring and arylalkyl carbon of the side chain with no selectivity (ca. 1:1). However, the stereochemistry would be thoroughly erased in the aromatization step, and hence adducts **3** were used for the next step without separation of two isomers.

The subsequent reduction of **3** with zinc[10] in aqueous buffer solution (NH_4Cl) produced the corresponding nitrones **4** in moderate yields.[11] In this conversion, the reaction

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SCHEME 1. Synthesis of Indoles 6 from 1,3-Cyclohexanediones 1 and Nitroolefins 2

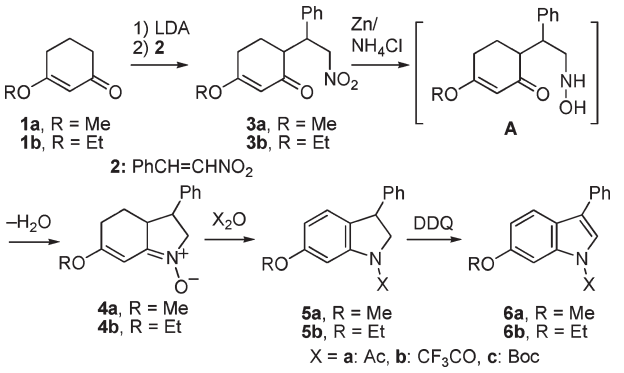
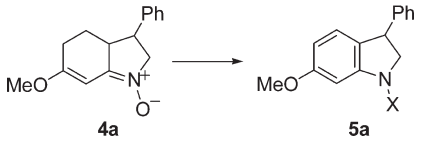


TABLE 1. Aromatization of the Nitrones 4a to *N*-Acylindolines 5a[a]



entry	acid anhydride (equiv)	temp/time	product **5a** X, yield[b]
1	Ac_2O (1)	−15−0 °C/40 min	**a**, Ac, 22%
2	Ac_2O (3)	−15−0 °C/40 min	**a**, Ac, 75%
3	Ac_2O (5)	−15−0 °C/40 min	**a**, Ac, 72%
4	$(CF_3CO)_2O$ (3)	−15−0 °C/40 min	**b**, CF_3CO, 68%
5	Boc_2O (3)	−15 °C ∼ rt/12 h	**c**, Boc, 80%
6	Ac_2O (3)[c]	rt/40 min	**a**, Ac, 63%
7	Ac_2O (3)[d]	rt/40 min	**a**, Ac, 67%
8	Ac_2O (3)[e]	rt/40 min	**a**, Ac, 65%

[a]Carried out by reaction of **4a** (0.2 mmol) with acid anhydride in DMF (1 mL). [b]Based on isolated products. [c]Carried out in DMSO, and indole **6aa** (ca. 10%) was produced. [d]Run in CH_2Cl_2. [e]Run in Me_2CO.

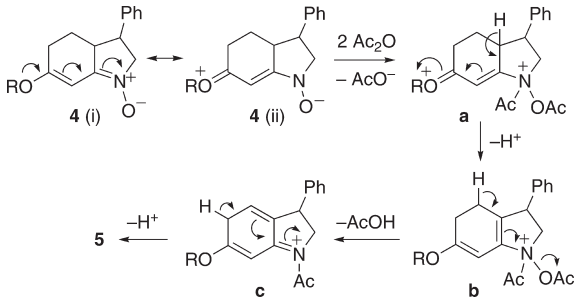
terminated at the four-electron reduction state of **A**, presumably due to formation of the zinc chelate, coordinated with carbonyl and amino groups. This hydroxylamine **A** would spontaneously undergo intramolecular addition and dehydration to form the nitrones **4**. Remarkable downfield shift of the ^1H absorption due to the vinylic proton in **4a** (5.93 and 5.96 ppm), compared with that in **3a** (5.46 ppm), may be ascribable to the anisotropic effect of the nitron oxide group, in agreement with the assigned structure.

We have succeeded in smooth aromatization by use of acetic anhydride as dehydrating and acetylating reagent of **4a**, giving the desired *N*-acetylindoline **5aa** (X = Ac) in a one-pot manner.[12]

Accordingly, we endeavored to optimize the conditions by examining the kind of anhydrides, its amounts, and suitable solvents. As shown in Table 1, the yield is improved to 72−75% by using excess Ac_2O (3 equiv) in DMF (entries 2 and 3), while the run with 1 equiv of Ac_2O is insufficient (22% yield, entry 1). Other acid anhydrides such as $(CF_3CO)_2O$ and Boc_2O are also effective to induce the aromatization to give the corresponding indolines **5ab** and

(12) Aromatization of nitrone in different structural core: El-Sheikh, M.; Cook, J. M. *J. Org. Chem.* **1980**, *45*, 2585–2587.

SCHEME 2. Mechanistic Assumption for Aromatization of 4 to 5



5ac protected with *N*-CF_3CO and *N*-Boc groups (entries 4 and 5). The aromatization in DMSO proceeds to give the desired **5aa** (X = Ac) along with **6aa** (X = Ac), the formation of which would presumably be caused by oxidation with DMSO (entry 6). The runs in CH_2Cl_2 and even in acetone also successfully afford the aromatized **5aa** (entries 7 and 8). Oxidation of **5aa** (X = Ac) with DDQ[13] produced the corresponding indole **6aa** (X = Ac) in 88% yield.

Since the aromatization of the nitrone **4** invoked the dehydration with acetic anhydride, the reaction mechanism for **5** from **4** can be rationalized as described in Scheme 2. Thus, treatment of the nitrone **4** with acetic anhydride would induce N- and O-acylation in the resonance form **4**(ii), which is accompanied by isomerization of the conjugated *exo*-cyclic azadiene to *endo*-cyclic cyclohexadiene as depicted in the structure **a** to form *N*-acylamine-*N*-oxide *O*-acetate **b**. The intermediate **b** would undergo 1,4-elimination of AcOH, leading to the cross-conjugated *N*-acetyliminium **c**, which can immediately form the aromatic ring of **5** by deprotonation.

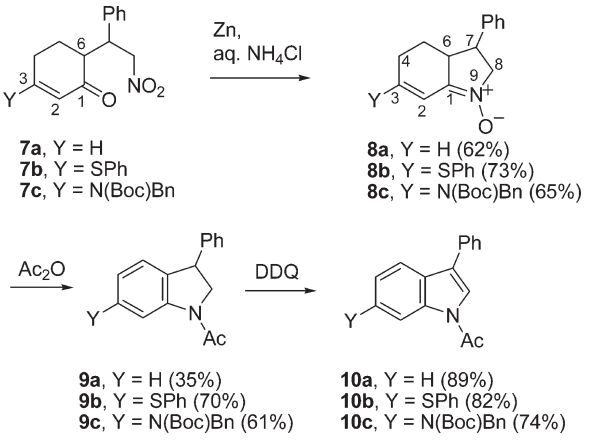
Having succeeded in aromatization of cyclohexane-1,3-dione enol ether moiety, we extended this aromatization reaction to the nitrones **8a**−**c** (Scheme 3), bearing H, PhS, and Bn(Boc)N at the C3 position of 9-azabicyclo[4.3.0]-nonadiene core. These nitrones **8a**−**c** were prepared in a similar manner as described above from the respective precursor 2-cyclohexenones by Michael addition of regioselectively generated kinetic Li enolates to the nitroolefin **2**,[14] followed by Zn reduction of the nitroketones **7a**−**c**. Thus, the treatment of **8a** with acetic anhydride (3 equiv) produced the corresponding indoline **9a** in lesser yield (35%), compared with the case of the 3-methoxy derivative **4a**. On the other hand, aromatization of the 3-phenylthio and 3-carbamoylamino derivatives **8b** and **8c** by treatment with acetic anhydride produced the corresponding indolines **9b** and **9c** in 70 and 61% yields, respectively. Thus, the substituents of electron-donating ability at the C3 of the starting 2-cyclohexenones turned out favorable for smooth aromatization, in agreement with the proposed mechanism. Oxidation of **9a**−**c** with DDQ produced the corresponding indoles **10a**−**c** in good yields.

On the other hand, the treatment of the 5,5-dimethyl derivative **12**, accessible from dimedone enol ether through the Michael adducts **11**, with acetic anhydride caused aromatization in the N-hetero ring, giving the fused pyrrole **13** in

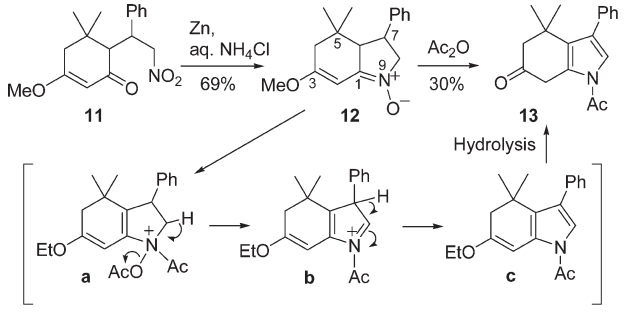
(13) Buckle, D. R. *Encyclopedia of Reagents for Organic Syntheses*; John Wiley & Sons: New York, 1995; Vol. 3, pp 1699−1704.

(14) Cory, R. M.; Anderson, P. C.; Bailey, M. D.; McLaren, F. R.; Renneboog, R. M.; Yamamoto, B. R. *Can. J. Chem.* **1985**, *63*, 2618–2627.

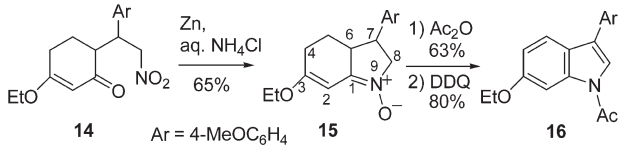
SCHEME 3. Aromatization of Nitrones 8 in Comparison with 4



SCHEME 4. Aromatization of Nitrone 12 Derived from Dimedone



SCHEME 5. Indole with a Different Aromatic Substituent

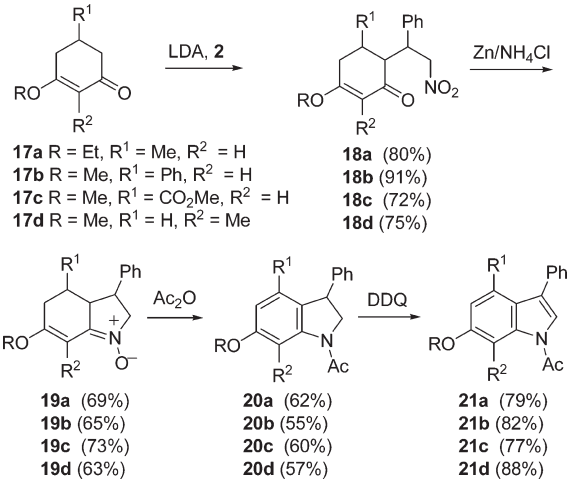


30% yield. The formation of **13** can be explained by aromatization in the azacyclopentane ring accompanied by hydrolysis of the methyl enol ether in the six-membered ring as described in Scheme 4.

We examined the synthesis of indole with a different aromatic substituent at the C3 position. Thus, the nitrone **15** (Ar = 4-$MeOC_6H_4$) was obtained in 65% yield by Zn reduction of **14**, derived from **1b** and β-nitro-4-methoxystyrene. The aromatization of **15** on treatment with acetic anhydride followed by DDQ oxidation afforded the corresponding indole **16** in 50% yield from **15** (Scheme 5).[15]

To extend the scope of this reaction further, we investigated the synthesis of indoles with additional substitutents at the C5 or C7 position, which might easily be realized by employing appropriate starting materials. Thus, cyclohexane-1,3-dione enol ethers **17a**−**d**, bearing either an Me, Ph, or ester[16] group at the C5 and an Me group at the C2, were installed with an phenylalkylnitro side chain by using Michael addition of the kinetically generated enolates to nitroolefin **2**, giving the corresponding **18a**−**d** in 72−91% yields. Adducts **18a**−**d** were converted to the corresponding nitrones **19a**−**d** by reduction with zinc buffered with NH_4Cl in moderate yields. Treatment of **19a**−**d** with acetic anhydride produced the corresponding *N*-acetylindolines **20a**−**d**, which were finally oxidized with DDQ to give the corresponding *N*-acetylindoles **21a**−**d** in good yields (Scheme 6).

SCHEME 6. Synthesis of Poly-Substituted 6-Alkoxyindoles 21 from 1,3-Cyclohexanediones 17



In summary, we have shown a novel preparative protocol for 6-alkoxyindoles from cyclohexane-1,3-dione enol ethers and nitroolefins via four steps which involves Michael addition, Zn reduction of the nitro group, aromatization and acylation, and DDQ oxidation. Aromatization of the nitrone intermediates such as **4** was effected smoothly by treatment with acetic anhydride. It is presumable that the present protocol might be of wide utility for the preparation of variously substituted 6-alkoxy-3-arylindoles as well as indolines from appropriate 1,3-cyclohexanediones which are commercially available or easily accessible according to reported methods.[16,17]

Experimental Section

3-Methoxy-6-(2-nitro-1-phenylethyl)-2-cyclohexenone (3a). To a cooled (−78 °C) solution of LDA, prepared from *n*-BuLi (3.2 mmol) and *i*-Pr_2NH (3.2 mmol) in THF (5 mL) at −78 °C under N_2 was added dropwise a solution of **1a** (252 mg, 2.0 mmol) in THF (3 mL). After being stirred at −78 °C for 30 min, a solution of **2a** (328 mg, 2.2 mmol) in THF (3 mL) was added dropwise, and the resulting mixture was stirred for an additional 1 h at the same temperature. The reaction was quenched with aqueous saturated NH_4Cl, the products were extracted with EtOAc (20 mL × 2), and the extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude products were purified by column chromatography (SiO_2, hexane/ethyl acetate, by increasing the gradient from 10:1 to 1:1 v/v) to give 446 mg (81% yield) of **3a** (R_f = 0.34, hexane/ethyl acetate 2:1) as a ca. 1:1 inseparable mixture of two diastereomers: ^{1}H NMR (300 MHz) δ 1.46 + 1.61 (m, 1H), 1.75 + 1.95 (m, 1H), 2.20−2.61 (m, 3H), 3.60 + 3.65 (s, 3H), 3.83 + 4.07 (m, 1H), 4.69 + 4.88 (m, 1H), 5.02−5.11 (m, 1H), 5.32 (s, 1H), 7.16−7.31 (m, 5H). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N,

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5.09. Found: C, 65.21; H, 6.40; N, 4.97. The same reaction of 3-ethoxy-2-cyclohexenone (**1b**) and **2** as above produced the corresponding Michael adducts **3b** as a separable mixture (ca. 1:1) of diastereomers in 76%. **3-Ethoxy-6-(2-nitro-1-phenylethyl)-2-cyclohexenone (3b):** (less polar component) R_f = 0.43, hexane/ethyl acetate 2:1; mp 86.5−88.0 °C (from hexane/ethyl acetate); ^{1}H NMR (600 MHz) δ 1.33 (t, J = 7.1 Hz, 3H), 1.66 (m, 1H), 1.97 (m, 1H), 2.28 (m, 1H), 2.40 (m, 1H), 2.62 (m, 1H), 3.85 (m, 2H), 4.08 (m, 1H), 4.94 (dd, J = 13.4, 5.4 Hz, 1H), 5.09 (dd, J = 13.4, 10.0 Hz, 1H), 5.33 (d, J = 1.5 Hz, 1H), 7.25 (m, 3H), 7.29 (m, 2H); ^{13}C NMR (150.8 MHz) δ 14.0, 24.4, 28.9, 44.3, 48.7, 64.5, 76.9, 102.9, 127.5, 128.5 (2C), 128.6 (2C), 137.7, 177.3, 198.2. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.47; H, 6.54; N, 4.87. **3b:** (polar component) R_f = 0.42, hexane/ethyl acetate 2:1; mp 101.0−102.5 °C (from hexane/ethyl acetate); ^{1}H NMR (600 MHz) δ 1.37 (t, J = 7.1 Hz, 3H), 1.50 (m, 1H), 1.82 (m, 1H), 2.28 (m, 1H), 2.42 (m, 1H), 2.50 (m, 1H), 3.84 (m, 1H), 3.92 (m, 2H), 4.70 (dd, J = 12.9, 10.2 Hz, 1H), 5.05 (dd, J = 12.9, 5.1 Hz, 1H), 5.34 (s, 1H), 7.21 (m, 2H), 7.28 (m, 1H), 7.33 (m, 2H); ^{13}C NMR (150.8 MHz) δ 14.1, 24.2, 26.8, 43.4, 47.2, 64.6, 79.5, 102.0, 127.9, 128.0 (2C), 129.0 (2C), 137.8, 177.2, 199.3. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.43; H, 6.70; N, 4.81.

3-Methoxy-7-phenyl-9-azabicyclo[4.3.0]nona-2,9-diene *N*-Oxide (4a): To a solution of **3a** (275 mg, 1.0 mmol) in methanol (8 mL) containing water (0.7 mL) were added zinc powder (262 mg, 4.0 mmol) and ammonium chloride (107 mg, 2.0 mmol). After heating at reflux for 6 h, the mixture was filtered and the filtrate was concentrated in vacuo. The crude products were purified by column chromatography (SiO_2, EtOAc/ethanol, by increasing the gradient from 5:1 to 2:1 v/v) to afford 159 mg (combined amount of two diastereoisomers, 67% yield) of **4a** as pale-yellow solids. **4a:** (less polar component) R_f = 0.41, ethyl acetate/ethanol 1:1; mp 168.0−169.5 °C (from EtOAc/CH_2Cl_2); ^{1}H NMR (300 MHz) δ 1.50−1.65 (m, 1H), 2.00 (m, 1H), 2.12−2.42 (m, 2H), 2.99 (m, 1H), 3.27 (q, J = 9.7 Hz, 1H), 3.70 (s, 3H), 4.27 (d, J = 9.7 Hz, 2H), 5.96 (s, 1H), 7.21−7.34 (m, 5H); ^{13}C NMR (75.5 MHz) δ 26.2, 28.9, 46.1, 47.6, 56.1, 67.6, 88.3, 127.4 (2C), 127.5, 128.9 (2C), 138.2, 147.0, 170.1. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.64; H, 6.80; N, 5.76; EI-MS m/z 225 ($M^+ - H_2O$). **4a:** (polar component) R_f = 0.33, ethyl acetate/ethanol 1:1; mp 185.0−187.0 °C (from EtOAc/CH_2Cl_2); ^{1}H NMR (600 MHz) δ 0.95 (m, 1H), 1.52 (m, 1H), 2.20 (m, 1H), 2.42 (m, 1H), 3.35 (m, 1H), 3.64 (t, J = 7.6 Hz, 1H), 3.72 (s, 3H), 4.13 (d, J = 13.9 Hz, 1H), 4.59 (m, 1H), 5.93 (d, J = 1.7 Hz, 1H), 7.12 (m, 2H), 7.25 (m, 1H), 7.30 (m, 2H); ^{13}C NMR (150.8 MHz) δ 23.1, 29.1, 40.9, 44.2, 55.9, 68.4, 88.6, 127.32 (2C), 127.33, 128.8 (2C), 139.7, 145.9, 170.2.

***N*-Acetyl-6-methoxy-3-phenylindoline (5aa):.** To a solution of **4a** (49 mg, 0.2 mmol) in dry DMF (1 mL) was added dropwise acetic anhydride (61 mg, 0.6 mmol) at 0 °C. After being stirred at 0 °C for 40 min, the reaction was quenched with aqueous saturated $NaHCO_3$ and the products were extracted with EtOAc (10 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude products were purified by column chromatography (SiO_2, hexane/EtOAc, by increasing the gradient from 10:1 to 2:1 v/v) to afford 38 mg (75% yield) of **5aa** (R_f = 0.37, hexane/ethyl acetate 2:1) as a light-blue gum: ^{1}H NMR (600 MHz) δ 2.21 (s, 3H), 3.82 (s, 3H), 3.94 (dd, J = 10.3, 6.4 Hz, 1H), 4.47 (t, J = 10.3 Hz, 1H), 4.55 (dd, J = 10.0, 6.6 Hz, 1H), 6.57 (dd, J = 8.3, 2.4 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 7.18 (m, 2H), 7.26 (m, 1H), 7.32 (m, 2H), 7.96 (d, J = 2.4 Hz, 1H); ^{13}C NMR (150.8 MHz) δ 24.2, 45.8, 55.5, 58.8, 102.6, 110.4, 125.2, 126.4, 127.2, 127.6 (2C), 128.9 (2C), 143.4, 144.0, 159.8, 168.7; HRMS (ESI) calcd for $C_{17}H_{18}NO_2$ (MH^+) 268.1338, found 268.1334 (MH^+).

***N*-Acetyl-6-methoxy-3-phenylindole (6aa):.** To a solution of indoline **5aa** (32 mg, 0.12 mmol) in dichloromethane (2 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 41 mg, 0.18 mmol). The mixture was stirred at 0 °C for 2 h before being quenched with aqueous saturated $NaHCO_3$. Products were extracted with EtOAc (10 mL × 3), and extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate, by increasing the gradient from 10:1 to 3:1 v/v) to afford 28 mg (88% yield) of **6aa** (R_f = 0.48, hexane/ethyl acetate 5:1) as a light-blue gum: ^{1}H NMR (300 MHz) δ 2.67 (s, 3H), 3.91 (s, 3H), 6.97 (dd, J = 8.6, 2.3 Hz, 1H), 7.39 (m, 2H), 7.44−7.51 (m, 2H), 7.60−7.69 (m, 3H), 8.14 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 24.1, 55.7, 100.9, 113.1, 120.3, 120.6, 122.6, 124.0, 127.5, 127.8 (2C), 128.9 (2C), 133.4, 137.3, 158.6, 168.8.

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Supporting Information Available: Spectral data including IR, ^{1}H NMR, and ^{13}C NMR spectra of **3a**,**b**, **7a**−**c**, **11**, **14**, **18a**−**d**, **4a**, **8a**−**c**, **15**, **19a**−**d**, **12**, **5aa**−**ac**, **9a**−**c**, **20a**−**d**, **13**, 6aa−**ac**, **10a**−**c**, **16**, and **21a**−**d**, and products in the conversion of **15** to **16** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.