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# Cerium(IV) Ammonium Nitrate Is an Excellent, General Catalyst for the Friedländer and Friedländer−Borsche Quinoline Syntheses: Very Efficient Access to the Antitumor Alkaloid Luotonin A

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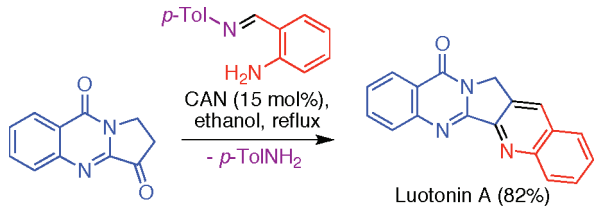


The use of cerium(IV) ammonium nitrate as a catalyst of the Friedländer reaction allows the synthesis of polysubstituted quinoline derivatives in excellent yields, avoiding the traditional harshly basic or acidic conditions. Unlike most other previously known reagents, CAN allows double condensations and is also an excellent catalyst for the Borsche variation of the Friedländer reaction, which has been applied to the very efficient synthesis of the antitumor alkaloid luotonin A.

The quinoline ring system is found in many pharmacologically significant compounds and in some bioactive natural products, exemplified by the natural topoisomerase I inhibitors luotonin A (**1**) and camptothecin (**2**) (Figure 1).[1] Many methods have been developed for the construction of quinoline building blocks, which include the classical Miller,[2] Combes,[2] Conrad−Limpach−Knorr,[2] Niementowski,[3] Pfitzinger,[3] and Friedländer reactions, and also more recent approaches.[1b]

The Friedländer quinoline synthesis involves the reaction between 2-aminoaryl aldehydes or ketones and carbonyl compounds containing an active methylene functionality under acidic or basic conditions. The reactions involving the use of 2-aminobenzaldehyde allow the synthesis of quinolines possessing an unsubstituted C-4 carbon, an important moiety that is present in many naturally occurring quinolines, including the ones in Figure 1, but have the problem of low stability of this reagent. This has prompted the development of some indirect Friedländer annulations involving the use of its synthetic equivalents, such as 2-aminobenzyl alcohols in the presence of metallic catalysts (Ru, Pd, Ir, Rh, Cu, etc.),[4] Schiff bases (known as the Borsche variation of the Friedländer reaction), or acetals of 2-aminobenzaldehyde.[5] While the Friedländer and Friedländer−Borsche reactions allow the creation of the quinoline moiety in a single operation, the presently known methods still have many limitations (see below), and the development of a mild, general, easily handled, and unexpensive catalyst for these important reactions remains challenging. We describe here that cerium(IV) ammonium nitrate (CAN) is an excellent catalyst for both the Friedländer and the Friedländer−Borsche reactions that allows the limitations inherent to previously studied catalysts to be circumvented. It is relevant to mention that the study of modern catalysts for the Friedländer−Borsche reaction has received very little attention in the literature.

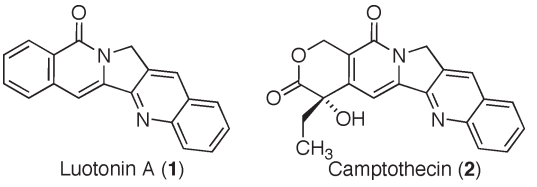


**FIGURE 1.** Structures of some bioactive alkaloids containing quinoline structural fragments.

Recently, many improved methodologies and new catalysts have been developed for the Friedländer annulation that avoid the use of the traditional strongly basic conditions.[6−8] Apart from conventional protic acids,[6] many other catalysts[7] and ionic liquids[7m] have also been used for the Friedländer synthesis. Microwave irradiation in the presence of several catalysts was also found to be effective.[8] In spite of this abundance of protocols, they lack generality since about 90% of the literature references quoted above are restricted

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(1) For selected reviews of quinolines, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166 and previous reviews of this series. (b) Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gomez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141. (c) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650.

(2) For selected recent reports, see: (a) Horn, J.; Marsden, S. P.; Nelson, A.; House, D.; Weingarten, G. G. *Org. Lett.* **2008**, *10*, 4117. (b) Wu, Y.-C.; Liu, L.; Li, H.-J.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2006**, *71*, 6592. (c) Denmark, S. E.; Venkatraman, S. *J. Org. Chem.* **2006**, *71*, 1668. (d) Deady, L. W.; Devine, S. M. *Tetrahedron* **2006**, *62*, 2313.

(3) For some recent improvements of the Niementowski and Pfitzinger reactions, see: Laddha, S. S.; Bhatnagar, S. P. *Arkivoc* **2008**, *17*, 212 and references cited therein.

(4) For selected examples of Friedländer reactions with 2-aminobenzylalcohols, see: (a) Martínez, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2008**, *73*, 9778.(b) Cho, C. S.; Ren, W. X. *J. Organomet. Chem.* **2007**, *629*, 4182 and reference cited therein.

(5) For a recent example of a Friedländer reaction involving derivatives of 2-aminobenzaldehyde, see: Grillet, F.; Baumlová, B.; Prévost, G.; Constant, J.-G.; Chaumeron, S.; Bigg, D. C. H.; Greenea, A. E.; Kanazawa, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2143.

(6) For a recent example of a protic acid-catalyzed Friedländer reaction, see: Ghassamipour, S.; Sardarian, A. R. *Tetrahedron Lett.* **2009**, *50*, 514.

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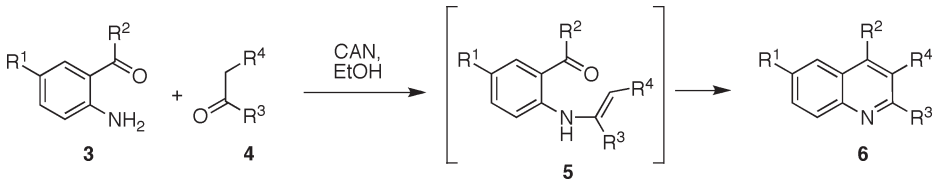
**SCHEME 1. CAN-Catalyzed Friedländer Reactions of 2-Aminophenones**




to the reaction between commercially available 2-aminoaryl ketones and active methylene carbonyl compounds and very few deal with reactions involving 2-aminobenzaldehyde or double reactions leading to polycyclic compounds.

CAN is a strong one-electron oxidant that is employed for carbon−carbon or carbon−heteroatom bond formation radical reactions, normally in stoichiometric quantities.[9] Because of its many advantages such as low cost, air and water stability, and low toxicity, Nair, one of the main contributors to CAN chemistry, has stated that the main goal to be achieved in this field is its use as a catalyst.[9a] Indeed, the Lewis acidity of CAN has recently allowed many synthetically important organic transformations using catalytic amounts of the reagent[10] to be carried out, and if this chemistry continues to be successfully implemented, CAN will become an alternative to the hygroscopic and highly expensive lanthanide triflate Lewis acids.

Our investigation started with an optimization study for the reaction between 2-aminoacetophenone (**3a**) and ethyl acetoacetate (**4a**) in the presence of a catalytic amount of CAN (Scheme 1 and Table 1, entries 1−4), which established that the best conditions involved 15 mol % of CAN in refluxing ethanol. Subsequently, we applied the optimized conditions to a variety of 2-aminoaryl ketones (**3**) and active methylene compounds (**4**), which furnished diversely substituted quinoline derivatives **6**, presumably with enaminones **5** as intermediates, since anilines and active methylene compounds are known to give enaminones in the presence of CAN, even at room temperature.[11] Yields of 91% and 88% were obtained for compounds **6b** and **6c** after a 13 h reflux (entries 6 and 8),

**TABLE 1. Synthesis of Quinoline Derivatives via CAN-Catalyzed Friedländer Annulations**

| entry | product | $R^1$ | $R^2$ | $R^3$ | $R^4$ | reaction time (h) | yield (%) | conditions[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | **6a** | H | $CH_3$ | $CH_3$ | $CO_2Et$ | 10 | 50 | A |
| 2 | **6a** | H | $CH_3$ | $CH_3$ | $CO_2Et$ | 10 | 89 | B |
| 3 | **6a** | H | $CH_3$ | $CH_3$ | $CO_2Et$ | 8 | 63 | C |
| 4 | **6a** | H | $CH_3$ | $CH_3$ | $CO_2Et$ | 8 | 98 | D |
| 5 | **6b** | H | $CH_3$ | $^n$Pr | $CO_2Et$ | 8 | 83 | D |
| 6 | **6b** | H | $CH_3$ | $^n$Pr | $CO_2Et$ | 13 | 91 | D |
| 7 | **6c** | H | $CH_3$ | $CH_3$ | COPh | 8 | 83 | D |
| 8 | **6c** | H | $CH_3$ | $CH_3$ | COPh | 13 | 88 | D |
| 9 | **6d** | H | $CH_3$ | $-(CH_2)_3-$ | | 16 | 97 | D, E |
| 10 | **6e** | H | Ph | $CH_3$ | $CO_2Et$ | 6 | 97 | D |
| 11 | **6f** | Cl | Ph | $CH_3$ | $CO_2Et$ | 6 | 98 | D |
| 12 | **6g** | H | Ph | $CH_3$ | COPh | 9 | 92 | D |
| 13 | **6h** | Cl | Ph | $CH_3$ | COPh | 7 | 90 | D |
| 14 | **6i** | H | Ph | $-(CH_2)_3-$ | | 6 | 98 | D, E |
| 15 | **6j** | H | Ph | $^n$Pr | $CO_2Et$ | 6 | 92 | D |
| 16 | **6k** | Cl | Ph | $^n$Pr | $CO_2Et$ | 4 | 94 | D |
| 17 | **6l** | Cl | Ph | $-(CH_2)_3-$ | | 4 | 97 | D, E |
| 18 | **6m** | H | $CH_3$ | $CH_3$ | COS$^t$Bu | 6 | 96 | D |
| 19 | **6n** | H | Ph | $CH_3$ | COS$^t$Bu | 2.5 | 98 | D |
| 20 | **6o** | Cl | Ph | $CH_3$ | COS$^t$Bu | 2.5 | 98 | D |
| 21 | **6p** | H | Ph | $-(CH_2)_4-$ | | 8 | 98 | D, E |
| 22 | **6q** | H | Ph | $-(CH_2)_5-$ | | 8 | 89 | D, E |
| 23 | **6r** | H | Ph | $-(CH_2)_{10}-$ | | 8 | 50 | D |
| 24 | **6r** | H | Ph | $-(CH_2)_{10}-$ | | 24 | 62 | D |

[a] Conditions: (A) 5 mol % of CAN, rt; (B) 5 mol % of CAN, reflux; (C) 15 mol % of CAN, rt; (D) 15 mol % of CAN, reflux; (E) 1.5 equiv of **4** was used.

while 16 h was required for cyclopentanone (entry 9) to achieve quantitative yield. In contrast to 2-aminoacetophenones, 2-aminobenzophenone derivatives were more reactive (entries 10−20) and gave the expected products in excellent yields and shorter reaction times. The reaction of 2-aminobenzophenone with cyclohexanone and cycloheptanone proceeded well, while cyclododecanone was less reactive and gave only 62% yield after a 24 h reflux (entries 21−24).

Due to the existence of very little literature precedent for the catalysis by Lewis acids of double Friedländer processes, we treated two 2-aminobenzophenones and 1,2-cyclohexanedione, in a 2:1 ratio, under our previously determined optimal conditions. These three-component reactions led to fast and efficient double annulations that afforded compounds **7**, derived from the pentacyclic dibenzo[*b*, *j*][1,10]-phenanthroline system, in 85−90% yields after 2 h (Scheme 2). The framework of compounds **7** is of interest because of its chelating properties.[12]

Our initial attempts to synthesize quinolines with an unsubstituted C-4 position using the challenging 2-aminobenzaldehyde were complicated by the isolation of a side product **8**, arising from a diastereoselective four-component

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(9) For reviews of CAN-promoted synthetic transformations, see: (a) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res*. **2004**, *37*, 21. (b) Nair, V.; Deepthi, A. *Chem. Rev*. **2007**, *107*, 1862.

(10) For examples of CAN-catalyzed reactions, taken from our work, see: (a) Sridharan, V.; Maiti, S.; Menéndez, J. C. *Chem.—Eur. J*. **2009**, *15*, 4565. (b) Sridharan, V.; Menéndez, J. C. *Org. Lett*. **2008**, *10*, 4303. (c) Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **2007**, *63*, 673. For proof of the Lewis acidity of CAN, see: (d) Maulide, N.; Vanherck, J.-C.; Gautier, A.; Markó, I. E. *Acc. Chem. Res*. **2007**, *40*, 381.

(11) Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Synlett* **2007**, 881.

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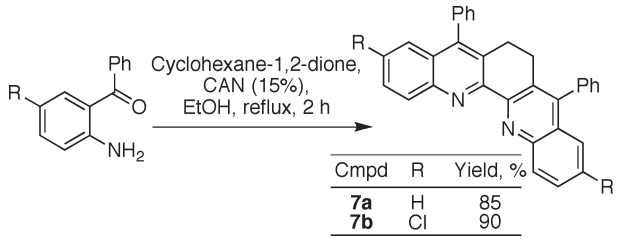
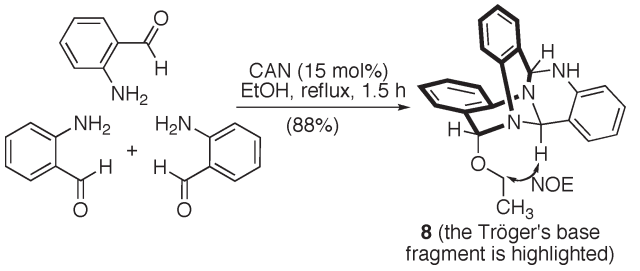
**SCHEME 2. CAN-Catalyzed Double Friedländer Reactions of 2-Aminobenzophenones**

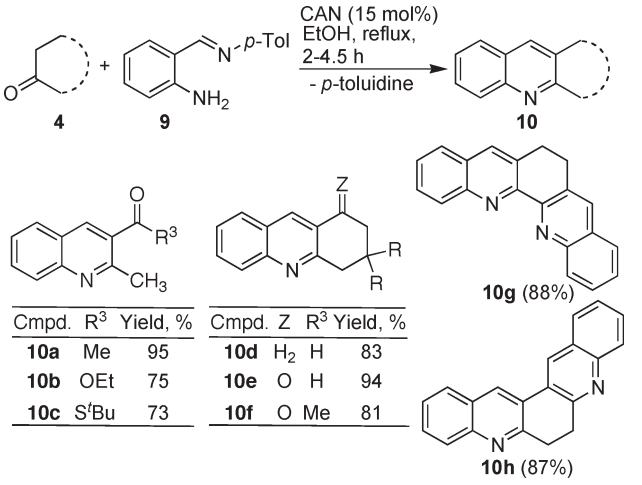



**SCHEME 3. CAN-Catalyzed Four-Component Synthesis of 8**




reaction between three molecules of 2-aminobenzaldehyde and a molecule of ethanol. This was confirmed by conducting the reaction in the absence of the active methylene substrate. Although the unstable hydroxy analogue of **8** is a known compound, which is obtained in low yield via the trimerization of 2-aminobenzaldehyde in the presence of acids,[13] our synthesis of compound **8** is noteworthy for its mildness and excellent yield (Scheme 3). Although **8** may be of interest because of its structural relationship with Tröger's base, which has multiple applications in supramolecular chemistry that have led to a surge of interest in its analogues,[14] we needed to suppress its formation in order to optimize our quinoline synthesis. To this end, we applied the Borsche modification of the Friedländer reaction, using *N*-(2-aminobenzylidene)-4-methylaniline (**9**) as a 2-aminobenzaldehyde equivalent. Treatment of mixtures of imine **9** and carbonyl compounds **4** in the presence of 15 mol % of CAN under our previously established conditions furnished the desired quinolines **10** in excellent yields (Scheme 4). Our first experiments confirmed the feasibility of preparing simple quinoline systems unsubstituted at C-4 (compounds **10a**−**c**). We also carried out the synthesis of tetrahydroacridines from imine **9** and cyclohexanone or 1,3-cyclohexanediones, the latter of which afforded only monocondensation derivatives **10e**,**f**, even when excess imine was used. These reactions are completely regioselective, and proceeded via the most stable conjugated enaminone, as proved by HMBC correlations. Double condensations were possible for both 1,2-cyclohexanedione and 1,4-cyclohexanedione, which furnished products **10g** (related to **7**) and **10h**, the latter of which is interesting because its skeleton is almost unknown in the literature. The proposed angular structure for **10h** was

**SCHEME 4. CAN-Catalyzed Friedländer−Borsche Reactions**




deduced from the large chemical shift value for the proton $\gamma$ with respect to the pyridine nitrogen, which is characteristic for 1,8-phenanthroline derivatives,[15] and corresponds to the generation of the most conjugated intermediate.

To further validate our protocol, we decided to apply it to the synthesis of the naturally occurring cytotoxic alkaloid luotonin A (**1**), which is of considerable interest because of its ability to stabilize the binary complex between human DNA and topoisomerase I.[16] Following its first total synthesis by Ganesan,[17] a number of routes have been developed for the synthesis of luotonin A and its analogues.[18] Some of these methods involve the use of the Friedländer reaction as a key step to generate the quinoline framework[19] from the known[20] compound **12** and 2-aminobenzaldehyde or its synthetic equivalents. However, the reported conditions, such as Triton B (ethanol, reflux, 2 h, 36%)[19a] and *p*-toluenesulfonic acid (xylene, reflux, 20 h, 30%),[19b] gave very poor yields. Derivatives of luotonin A have also been synthesized by using the Friedländer reaction, and here again the yields were poor (32−36%).[19c] With this precedent in mind, we applied our conditions to the cyclocondensation between **12** and 2-aminobenzaldehyde and found that the reaction was complete in 1.5 h and gave 66% of luotonin A, along with a small amount of compound **8**. The fact that the expected Friedländer product is the major one contrasts with the results obtained in our initial studies with simple ketones as substrates. This different behavior can be explained through the expected higher reactivity of the carbonyl group in compound **12**, due to the presence of a neighboring electron-withdrawing substituent, leading to a shorter reaction time. Use of the Borsche protocol afforded 82% of luotonin A from compound **12** and imine **9** (Scheme 5).

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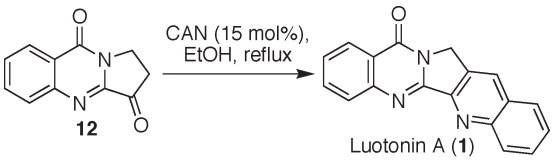
**SCHEME 5. CAN-Catalyzed Synthesis of Luotonin A**




| Conditions | Yield, % |
|---|---|
| 2-Aminobenzaldehyde, 1.5 h | 66 |
| Compound **9**, 3 h | 82 |

In conclusion, we have developed a mild, environmentally friendly, and very efficient protocol for the Friedländer and Friedländer−Borsche reactions under CAN catalysis, avoiding the need for harsh basic or acidic conditions and allowing double condensations. This method significantly increases the scope of the traditional one and has led to an exceptionally general synthesis of polysubstituted and polycyclic quinoline derivatives in excellent yields. It has also led to a much improved synthesis of the alkaloid luotonin A, which can be readily adapted to the preparation of luotonin analogues modified at the quinoline structural fragment in order to contribute to the study of structure−activity relationships in this family of antitumor agents.

## Experimental Section

**General Procedure for the CAN-Catalyzed Friedländer and Friedländer−Borsche Reactions.** A solution of the suitable 2-aminoketone, aldehyde, or imine (2 mmol) and active methylene compound (2 to 4 mmol), together with CAN (15 mol %), in ethanol (5 mL) was refluxed for the time periods specified in Table 1 and in the Supporting Information. After completion of the reaction (TLC), the mixture was cooled, diluted with $CH_2Cl_2$, washed with water followed by brine, and dried (anhydrous $Na_2SO_4$). The solvent was evaporated under reduced pressure and the crude reaction mixture was purified by silica column chromatography eluting with a suitable petroleum ether−ethyl acetate mixture. Characterization data for some representative cases are given below, and data for all other compounds can be found in the Supporting Information.

**Ethyl 4-Methyl-2-propylquinoline-3-carboxylate (6b).** Starting from *o*-aminoacetophenone (270 mg, 2.0 mmol) and ethyl 3-oxohexanoate (316 mg, 2.0 mmol), a yield of 468 mg (91%) of compound **6b** was obtained, as a colorless viscous liquid. IR (neat) 3069.7, 2962.9, 1726.4, 1587.5, 1454.6, 1233.5, 1055.2 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 1.05 (t, $J$ = 7.4 Hz, 3H), 1.47 (t, $J$ = 7.2 Hz, 3H), 1.82−1.91 (m, 2H), 2.67 (s, 3H), 2.90−2.96 (m, 2H), 4.51 (q, $J$ = 7.2 Hz, 2H), 7.55 (td, $J$ = 8.2, 1.3 Hz, 1H), 7.73 (td, $J$ = 8.2, 1.3 Hz, 1H), 8.02 (dd, $J$ = 8.4, 0.8 Hz, 1H), 8.06 (dd, $J$ = 8.4, 0.8 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 63 MHz) $\delta$ 14.7, 16.2, 23.5, 39.8, 62.1, 124.4, 126.2, 126.7, 128.3, 129.9, 130.3, 141.8, 147.6, 158.4, 169.8. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.37; H, 7.57; N, 5.59.

**6,7-Dihydrodibenzo[*b*,*j*][1,10]phenanthroline (10g).** Starting from 1,2-cyclohexanedione (80 mg, 0.72 mmol) and compound **9** (300 mg, 1.44 mmol), a yield of 179 mg (88%) of compound **10g**, as a brown solid, was obtained. Mp 177−179 °C (lit.[21] mp 185 °C); IR (neat) 1601.2, 1494.7 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 3.30 (s, 4H), 7.59 (td, $J$ = 7.0, 1.2 Hz, 2H), 7.75 (td, $J$ = 7.0, 1.5 Hz, 2H), 7.84 (dd, $J$ = 8.0, 1.0 Hz, 2H), 8.12 (s, 2H), 8.49 (d, $J$ = 8.5 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 63 MHz) $\delta$ 29.1, 127.2, 127.7, 128.8, 129.4, 131.4, 133.0, 135.1, 148.6, 152.8. Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.79; H, 5.16; N, 9.71.

**Luotonin A (1). Method A:** Starting from compound **12**[22] (120 mg, 0.60 mmol) and 2-aminobenzaldehyde (73 mg, 0.60 mmol), a yield of 112 mg (66%) of luotonin A was obtained, as a pale brown solid. **Method B:** Starting from compound **12**[20] (110 mg, 0.55 mmol) and compound **9** (77 mg, 0.37 mmol), a yield of 86.4 mg (82%) of luotonin A was obtained, as a pale brown solid. Mp 253 °C dec (lit.[22] mp 252 °C dec); IR (neat) 3052.1, 2929.1, 1678.6, 1629.6, 1606.6, 1467.0, 1359.1, 1326.8 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 5.40 (s, 2H), 7.62 (td, $J$ = 8.1, 1.1 Hz, 1H), 7.74 (td, $J$ = 7.9, 1.1 Hz, 1H), 7.86−7.93 (m, 2H), 8.01 (dd, $J$ = 8.0, 1.0 Hz, 1H), 8.17 (d, $J$ = 7.7 Hz, 1H), 8.46−8.54 (m, 3H); $^{13}C$ NMR ($CDCl_3$, 63 MHz) $\delta$ 47.7, 121.7, 126.9, 127.6, 128.4, 128.9, 129.2, 129.8, 131.1, 132.0, 135.0, 149.7, 149.8, 151.6, 152.9, 161.1. Anal. Calcd for $C_{18}H_{11}N_3O$: C, 75.78; H, 3.89; N, 14.73. Found: C, 75.47; H, 4.08; N, 14.39.

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**Supporting Information Available:** Experimental procedures and spectra of all final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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