JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

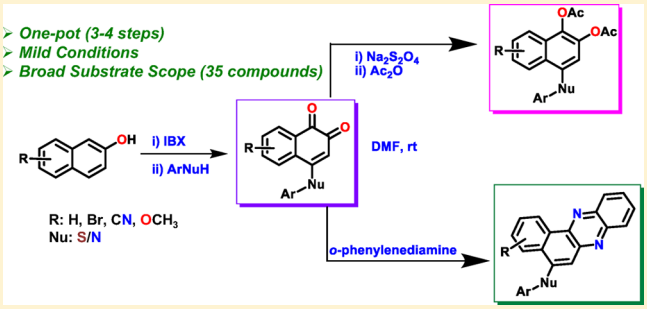
o-Iodoxybenzoic Acid-Initiated One-Pot Synthesis of 4-Arylthio-1,2-naphthoquinones, 4-Arylthio-1,2-diacetoxynaphthalenes, and 5-Arylthio-/5-Aminobenzo[*a*]phenazines

Abhaya Kumar Mishra and Jarugu Narasimha Moorthy*

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

Supporting Information

ABSTRACT: 1,2-Naphthoquiones and their derivatives constitute an important category of compounds of relevance in pharmaceutical and material chemistry. It is shown that 1,2-naphthoquinones generated by *o*-iodoxybenzoic acid-mediated oxidation of 2-naphthols can be subjected to a cascade of reactions, namely oxidation, Michael addition, reduction, acetylation, and cyclocondensation, in the same pot to afford diverse 4-arylthio-1,2-naphthoquinones **2**, 4-arylthio-1,2-diacetoxynaphthalenes **3**, and 5-arylthio-/5-aminobenzo[*a*]-phenazines **4** in very good isolated yields. The multistep single-pot synthesis occurs smoothly in DMF at rt.



INTRODUCTION

The derivatives of 1,2-naphthoquinones, 1,2-naphthalenediols, and phenazines are widely distributed in a variety of natural products[1] and organic functional materials.[1−6] Furthermore,1,2-naphthoquinone derivatives have been enormously explored for a range of biological activities[2,3] such as antidiabetic,[2b] anti-inflammatory,[2d,e] neuroprotection,[2d,e] anticancer,[2d,e] phosphatase inhibition,[2c] etc. (Figure 1).[4] The applications of 1,2-naphthoquinones, 1,2-diacetoxynaphthalenes,[5] and benzo[*a*]-phenazine derivatives derived therefrom have led to simplification of the synthetic procedures to access them.[2−6]

At present, there is a growing interest in the development of sustainable synthetic procedures that permit high efficiency, environmentally benign attributes, minimum reaction steps, good overall yield, short reaction times, low cost, etc. One-pot multistep synthesis has emerged as an important dimension in modern organic synthesis.[7] The one-pot multistep synthesis obviates isolation of products at the end of each step and allows "step economy"[8] as well as "pot economy".[9] This concept has been applied as a straightforward route that minimizes synthetic steps to access diverse molecular entities endowed with structural complexity in an atom economic manner.[10] We surmised that the electrophilic 1,2-naphthoquionones can be exploited to synthesize several derivatives that include 4-arylthio-1,2-naphthoquionones, 4-arylthio-1,2-diacetoxynaphthalenes, and 5-arylthio/5-aminobenzo[*a*]phenazines. 1,2-Naphthoquinones are generally accessed from commercially available 1- and 2-naphthols using several oxidation reagents,[11] with *o*-iodoxybenzoic acid (IBX) being one of the best reagents for oxidation under mild reaction conditions. The latter was indeed the motivation for our efforts to develop IBX-initiated one-pot multistep synthesis of napthoquinone-derived molecular entities mentioned at the outset. Of course, our own research interests for some time now have been concerned with development of IBX-mediated reactions, modified analogues of IBX, and catalytic oxidations with in situ-generated IBX.[12] Thus, our objective was to employ IBX as an oxidation reagent for in situ generation of 1,2-naphthoquionones and perform multistep reactions in a cascade manner in one pot, leading to several end products by judicious manipulation of the reagents (Scheme 1).[13] Herein, we report one-pot synthesis of libraries of 4-arylthio-1,2-naphthoquinones, 1,2-diacetoxynaphthalenes, and benzo[*a*]phenazines under mild reaction conditions. Notably, all of the steps involved in this methodology are known individually, but each step requires different reaction conditions in terms of solvent, reagent, temperature, and workup procedure. We have thus integrated operation of 3 to 4 reactions, namely oxidation, nucleophilic addition, reduction, acetylation, and condensation of 1,2-naphthoquionone with *o*-phenylenediamine in one pot, leading to different end products in respectable isolated yields (Scheme 1). To the best of our knowledge, one-pot syntheses of substituted 1,2-naphthoquinones, 1,2-diacetoxynaphthalenes, and benzo[*a*]phenazine derivatives are heretofore unknown.

RESULTS AND DISCUSSION

To begin, we considered the one-pot reaction cascade that leads to 4-arylthio-1,2-naphthoquinones. As a representative case, oxidation of 2-naphthol to 1,2-naphthoquinone by IBX was examined in different solvents such as acetonitrile, DMF, DCM, DCE, THF, and toluene at rt. While the reaction was found to be quite messy in acetonitrile, that in THF was found

Received: May 11, 2016
Published: July 13, 2016

DOI: 10.1021/acs.joc.6b01105
J. Org. Chem. 2016, 81, 6472−6480

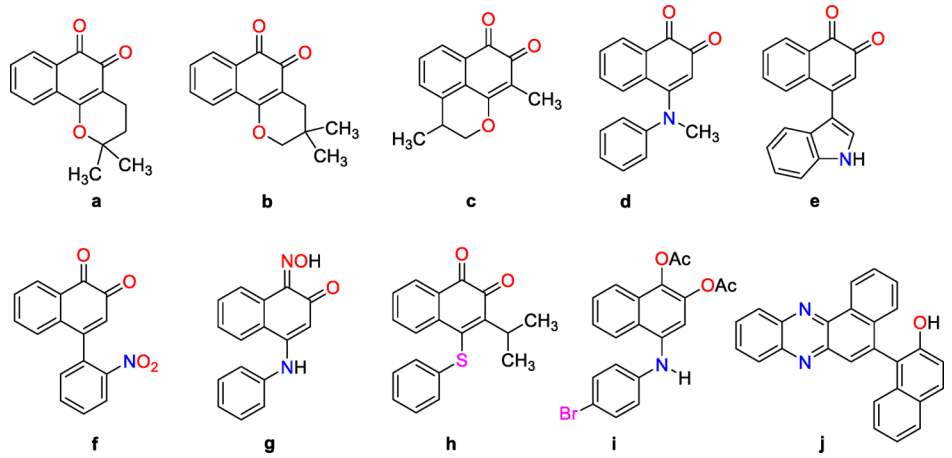
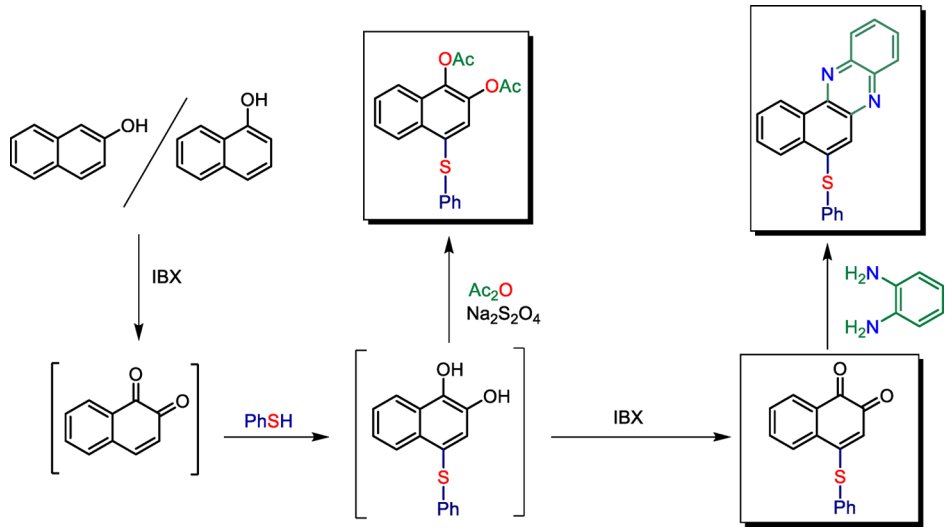


Figure 1. Selective examples of biologically active 1,2-naphthoquinones, diacetoxynaphthalenes, and phenazine derivatives: a–c (anticancer),[1d] d–f (antidiabetic),[2a] g (anti-inflammatory),[2d] h (Cdc25 phosphatase inhibitor),[2c] i (anticholinesterase),[5a] and j (antimicrobial).[2h]

Scheme 1. Envisaged One-Pot Cascade Leading to Phenylthionaphthalene-1,2-dione/diacetate and Phenylthiophenazine



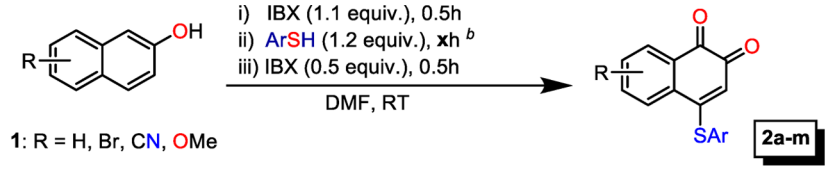
to occur in 3 h. In all other solvents except for DMF, the reaction was found to go to completion in 10–12 h, as monitored by TLC analysis. In DMF, oxidation was found to occur in 30 min, which is remarkably faster than that in the other solvents tested. Therefore, DMF was chosen as the solvent to generate 1,2-naphthoquinone by IBX-mediated oxidation of 2-naphthol. After complete disappearance of the naphthol, as monitored by TLC, thiophenol was introduced into the same pot as a nucleophile to perform Michael addition. The reaction was monitored by TLC until the disappearance of the colored naphthoquinone. As the oxidation is carried out in open air conditions, a mixture of 1,2-dione and 1,2-diol was obtained as the product of Michael addition. This is because naphthalene-1,2-diol is highly reactive to undergoing partial oxidation aerially. Introduction of 0.5 equiv of IBX was found to ensure complete oxidation within approximately 30 min to afford stable 4-phenylthionaphthalene-1,2-dione (**2a**, Scheme 2). The fact that the diol undergoes aerial oxidation was established in an independent reaction, wherein the dione was produced aerially in an isolated yield of 72% over a period of 9 h.

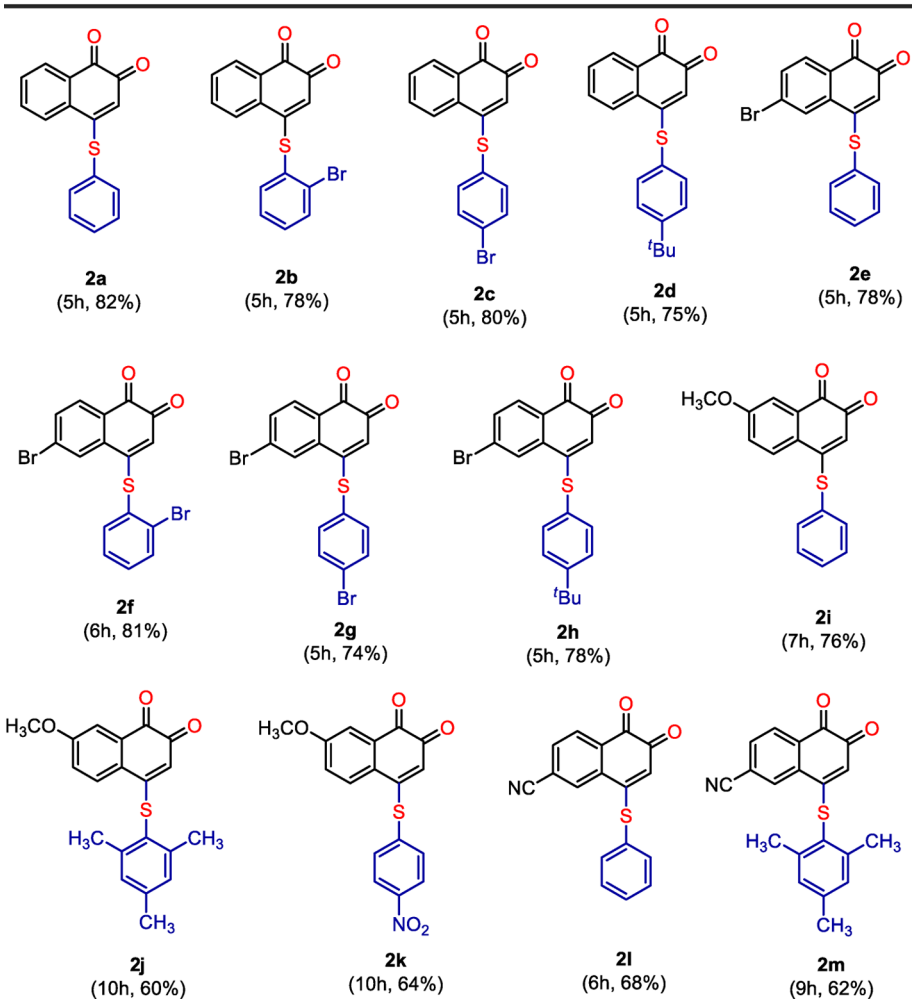
The initial and final oxidations were found to occur within 20–30 min, while the Michael addition reaction occurred over a period of 5 h; the latter is, therefore, the rate-determining step in the reaction cascade. Gratifyingly, the end product, i.e., 4-phenylthionaphthalene-1,2-dione **2a**, was isolated in 82% yield after silica gel column chromatography of the crude reaction mixture isolated after regular workup. Encouraged by this result, 2-naphthols substituted with electron-rich as well as electron-poor substitutents such as Br, OMe, and CN were subjected to a one-pot cascade with differently substituted thiophenols as nucleophiles, leading to a library of 4-arylthionaphthalene-1,2-diones **2a–m** in 60–82% isolated yields (Scheme 2). Lower yields were noted when naphthol is substituted with a cyano group and also when the nucleophilic thiophenol is either sterically hindered or substituted with an electron-withdrawing group. In these instances, monitoring of the reactions by TLC showed that Michael addition occurs over longer periods, approximately 5–10 h. Otherwise, three reactions, i.e., oxidation of 2-naphthol, Michael addition with arylthiols, and oxidation, occur at rt in DMF as the solvent leading to the end-products in respectable isolated yields.

In the same manner, we wondered if 4-phenylthionaphthalene-1,2-diol could be acetylated (Scheme 1). Because the addition of arylthiol in a Michael fashion occurred over a period

DOI: 10.1021/acs.joc.6b01105
J. Org. Chem. 2016, 81, 6472–6480

Scheme 2. IBX-Initiated One-Pot Synthesis of 4-Arylthio-1,2-naphthoquinones[a]





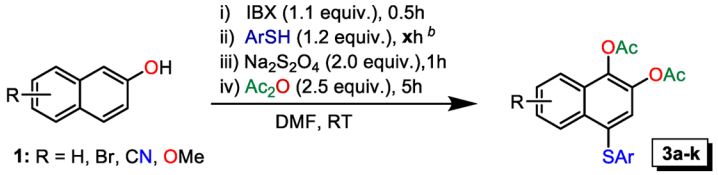
[a]All reactions were performed in DMF at rt without any precautions. Products were isolated by silica gel column chromatography. [b]Michael addition of thiol was found to be the slowest of all reactions. The reaction time given under each of the products in parentheses refers to this step.

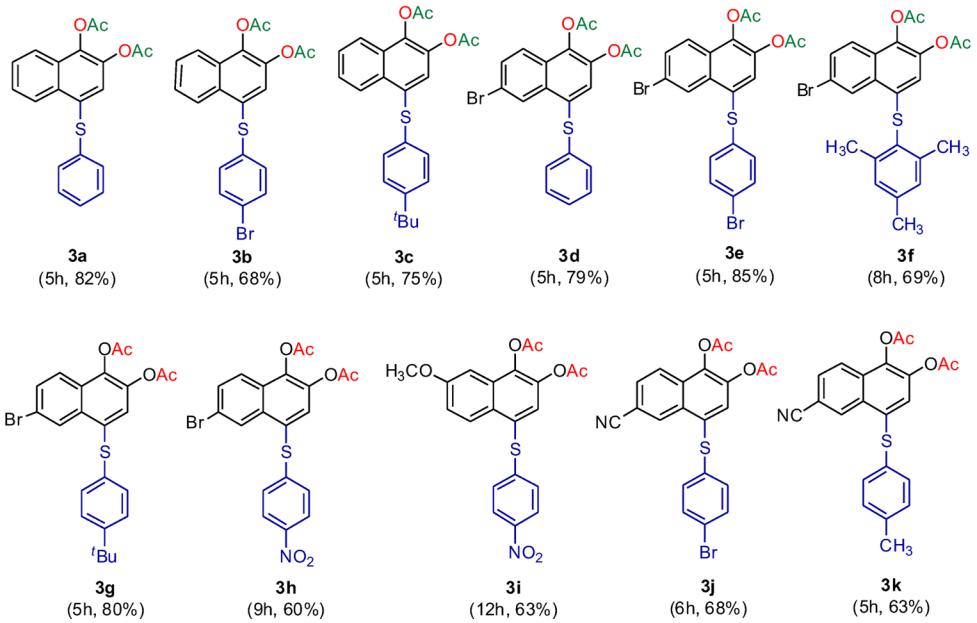
of 5−12 h, the initially produced diol was able to undergo oxidation partially to the dione. Therefore, before acylation with 2.5 equiv of Ac_2O, the mixture was reduced to the corresponding hydroquinone with 2 equiv of $Na_2S_2O_4$. The addition of $Na_2S_2O_4$ also facilitated the acetylation. We found in an independent experiment that addition of 1 equiv of $Na_2S_2O_4$ to catechol in DMF in the presence of 2.5 equiv Ac_2O leads to catechol diacetate almost quantitatively, while the acetylation was found to virtually not occur without the added $Na_2S_2O_4$. Presumably, the latter functions as a mild base to deprotonate the catechol, whereby acetylation with Ac_2O is promoted. Regular workup followed by silica gel chromatography of the reaction mixture led to 4-phenylthio-1,2-diacetoxynaphthalene (**3a**, Scheme 3) in a remarkable isolated yield of 82%. A variety of substituted 2-naphthols were thus subjected to oxidation-Michael addition-reduction-acetylation cascade in one pot to access diverse 4-arylthio-1,2-diacetoxynapthalenes in 60−85% isolated yields (Scheme 3); as in the previous case, rather lower yields of products were observed for cyano-substituted 2-naphthols and thiols that are sterically hindered and substituted with electron-withdrawing groups.

The diketo compounds can be converted into phenazines by treatment with *o*-phenylenediamine.[4a] Therefore, the diketones **2** generated by a 3-step cascade in DMF were treated in the same pot with *o*-phenylenediamine at rt. TLC monitoring revealed gradual appearance of the products with reactions going to completion over a period of 6−24 h. At the end, the reaction mixtures were worked up in a regular manner and subjected to chromatographic purifications. Arylthiophenazines **4** were isolated in 73−88% yields for a variety of 2-naphthols and nucleophilic thiophenols (Scheme 4). What is noteworthy is the fact that the yields of phenazines after a 4-step cascade are

DOI: 10.1021/acs.joc.6b01105
J. Org. Chem. 2016, 81, 6472−6480

Scheme 3. IBX-Initiated One-Pot Synthesis of 4-Arylthio-1,2-diacetoxynaphthalenes[a]





[a]All reactions were performed in DMF at rt without any precautions. Products were isolated by silica gel column chromatography. [b]The addition of thiol was found to be the slowest of all reactions, and the time given under each of the products in parentheses refers to this step.

higher than diketones **2** isolated after a 3-step cascade. For example, the yield of methoxy-diketone **2j** (Scheme 2) is only 60%, while an additional step leads to 73% yield of the phenazine **4g** (Scheme 4). Evidently, the diketones appear to decompose during the course of their isolation, while their in situ trapping by condensation leading to phenazines precludes such losses. Notably, amines could also be employed as nucleophiles, whereby 5-aminosubstituted phenazines could be accessed in 40−78% isolated yields (Scheme 4). Thus, with primary aniline, the product **4h** was isolated in 56% yield, while secondary *N*-methylaniline and diphenylamine led to the products **4i** and **4j** in 78 and 40% yields, respectively. With tertiary *N*,*N*-diethylaniline, C−C bond formation occurred at the *para* position, leading to 5-(4-(*N*,*N*-diethylamino)phenyl)-benzo[*a*]phenazine **4k** in 72% isolated yield.

Mechanisms of Cascade Reactions. Overall, 3 to 4 reactions are sequentially involved in the one-pot syntheses. These are shown in Schemes 2, 3, and 4. Scheme 5 shows the pertinent mechanisms involved. It has long been established that the reaction of either 1- or 2-naphthol with one equiv of IBX yields 1,2-naphthoquinone quantitatively along with *o*-iodobenzoic acid.[14] Therefore, because 2-naphthols are inexpensive and readily available, they were employed for all cascade reactions initiated by IBX. It has also been well-established that 1,2-naphthoquinones are excellent Michael acceptors,[4a,15] so the conjugate addition of thiols was expected to occur smoothly. It has been reported that the 1,2-diols of the type formed are very sensitive to undergoing aerial oxidation to the corresponding naphthoquinones.[2c,4a,15] Because of this reason, it was necessary to use sodium dithionite[16,17] to reduce any quinone that was present before the acylation to form the diacetates **3** (Scheme 3). On the other hand, complete oxidation to the corresponding naphthoquinones was accomplished by the addition of 0.5 equiv of IBX before reaction with *o*-phenylenediamine to produce phenazines **4**. Presumably, the acidic conditions contributed by *o*-iodobenzoic acid facilitate the condensation.

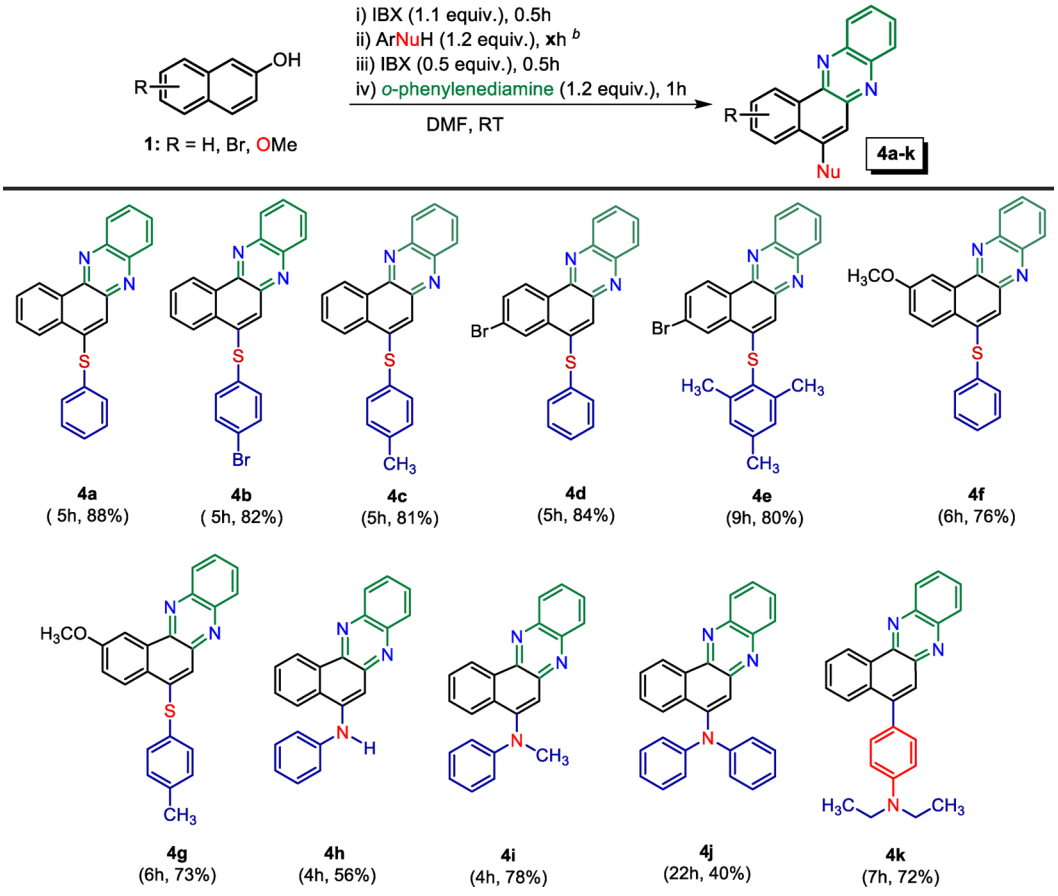
As mentioned at the outset, each of the reactions is independently known. Integration of 3 to 4 reactions into a one-pot operation, leading to respectable yields of the end-products with step economy, is a noteworthy development. The cascade reactions occur cleanly in DMF as the solvent at room temperature.

CONCLUSIONS

A convenient one-pot synthesis of a variety of naphthalene derivatives, namely arylthionaphthoquinones, arylthio-1,2-diacetoxynaphthalenes, and arylthiophenazines, which are relevant in pharmaceutical and materials chemistry, is demonstrated under mild conditions in DMF at room temperature. Although each of the reactions is independently known, a cascade of 3 to 4 reactions, i.e., oxidation of 2-naphthols to 1,2-napthoquinones, Michael addition, reduction, acetylation, and cyclocondensation, have been integrated into one-pot operation.

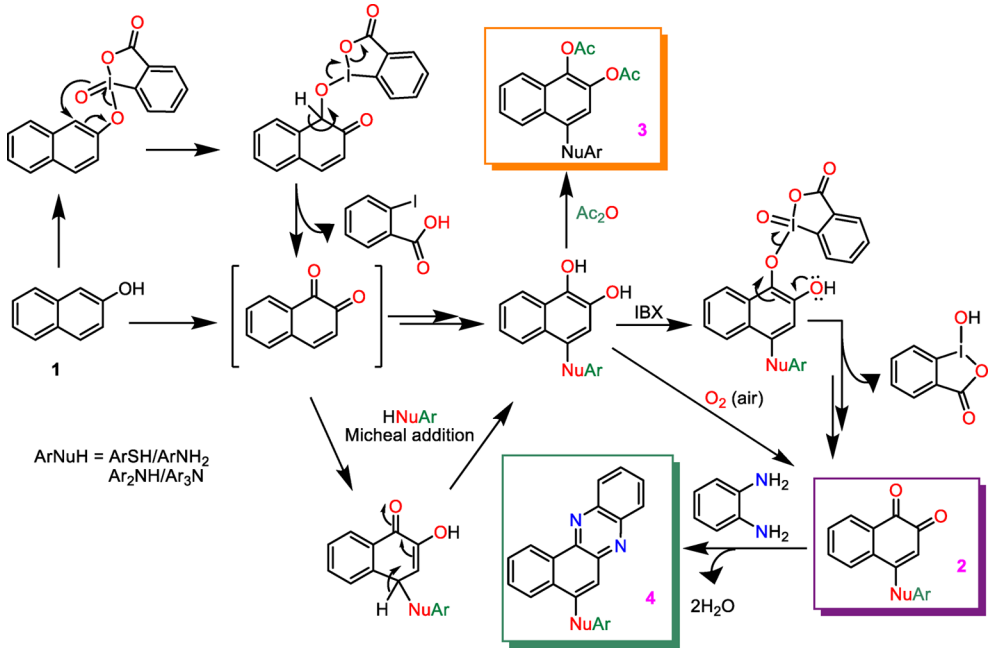
DOI: 10.1021/acs.joc.6b01105
J. Org. Chem. 2016, 81, 6472−6480

Scheme 4. One-Pot Synthesis of 5-Arylthio/5-Aminobenzo[*a*]phenazines Using IBX[a]



[a]All reactions were performed in DMF at rt without any precautions. Products were isolated by silica gel column chromatography. [b]The Michael addition of thiol was found to be the slowest of all reactions. The reaction time given under each of the products in parentheses refers to the Michael addition reaction.

Scheme 5. Mechanisms of One-Pot Syntheses of Arylthio-1,2-naphthoquinones 2, Arylthio-1,2-diacetoxynaphthalenes 3, and Arylthiophenazines 4 Starting from 2-Naphthol



DOI: 10.1021/acs.joc.6b01105
J. Org. Chem. 2016, 81, 6472−6480

The reactions occur smoothly, leading to respectable yields of the end-products with pot economy.

EXPERIMENTAL SECTION

Solvents were distilled prior to use. All reactions were carried out in an open atmosphere without any precautions. The products were isolated by column chromatography with a silica gel of 100−200 μm particle size. NMR spectra were recorded with 400 and 500 MHz spectrometers. IR spectra were recorded on an FT-IR spectrophotometer. Mass spectral analyses were carried out with an ESI-QTOF instrument.

General Procedure for One-Pot Synthesis of 4-Arylthionaphthalene-1,2-diones (2a−m). A representative procedure is described below for 4-phenylthionaphthalene-1,2-dione **2a**. A similar procedure was employed for all other compounds, i.e., **2b−2m**.

To a solution of 2-naphthol (0.1 g, 0.69 mmol) in 3 mL of DMF, IBX (0.214 g, 0.76 mmol) was added and the resultant mixture was stirred in open atmosphere at rt for 0.5 h; the disappearance of 2-naphthol was monitored by thin layer chromatography (TLC). Subsequently, thiophenol (0.091 g, 0.82 mmol) was introduced into the reaction mixture and the contents were stirred at rt until naphthalene-1,2-dione was consumed. IBX (0.34 mmol) was introduced into the same reaction mixture and stirred for additional 0.5 h. The contents were extracted with 50 mL of ethyl acetate 2−3 times, and the organic extract was washed with saturated $NaHCO_3$ followed by brine. It was dried over anhyd Na_2SO_4 and the solvent removed in a rotary evaporator under reduced pressure. The residue was subjected to silica gel column chromatography to isolate 4-phenylthionaphthalene-1,2-dione (**2a**) as a reddish crystalline product using 20% ethyl acetate in pet. ether. Yield 82% (0.151 g); mp 168−170 °C; IR (KBr) cm^{-1} 1697 (m), 1641 (s), 1578 (m), 1544 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H), 7.49−7.75 (m, 6H), 7.73 (dt, J = 7.2, 1.4 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.3, 125.0, 126.3, 129.5, 130.3, 130.4, 131.1, 131.3, 133.4, 135.1, 136.0, 161.5, 176.6, 179.5; ESI-MS$^+$ m/z: exact mass calculated for $C_{16}H_{10}O_2SNa$ $[M + Na]^+$ 289.0299, found 289.0291.

*4-(2-Bromophenylthio)naphthalene-1,2-dione (**2b**).* Reddish solid; 0.185 g, yield 78%; mp 194−196 °C; IR (KBr) cm^{-1} 1690 (m), 1645 (s), 1579 (m), 1543 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (s, 1H), 7.40−7.49 (m, 2H), 7.62 (t, J = 7.8 Hz, 1H), 7.70−7.77 (m, 2H), 7.81 (dd, J = 1.8, 1.3 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 8.20 (d, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.2, 125.2, 127.9, 129.1, 129.6, 130.6, 130.8, 131.4, 132.8, 133.2, 134.7, 135.2, 138.2, 158.7, 176.6, 179.5; ESI-MS$^+$ m/z: exact mass calculated for $C_{16}H_{10}BrO_2S$ $[M + H]^+$ 344.9584, found 344.9582.

*4-(4-Bromophenylthio)naphthalene-1,2-dione (**2c**).* Reddish solid; 0.197 g, yield 80%; mp 204−206 °C; IR (KBr) cm^{-1} 1691 (m), 1639 (s) 1578 (m), 1544 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (s, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.61 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.74 (t, J = 7.8 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.4, 125.0, 125.4, 126.2, 129.6, 130.4, 131.5, 133.2, 133.7, 135.1, 137.4, 160.6, 176.6, 179.3; ESI-MS$^+$ m/z: exact mass calculated for $C_{16}H_{10}BrO_2S$ $[M + H]^+$ 344.9584, found 344.9590.

*4-(4-tert-Butylphenylthio)naphthalene-1,2-dione (**2d**).* Reddish solid; 0.167 g, yield 75%; mp 196−198 °C; IR (KBr) cm^{-1} 3069 (m), 2964 (s), 1695 (m), 1641 (s), 1578 (m), 1536 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 5.95 (s, 1H), 7.45−7.54 (AA'BB', 4H), 7.60 (dt, J = 7.8 Hz, 0.9 Hz, 1H), 7.73 (dt, J = 7.6, 1.8 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 8.18 (dd, J = 7.8, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 35.0, 121.2, 122.6, 125.0, 127.5, 129.5, 130.3, 131.3, 133.5, 135.0, 135.7, 154.7, 162.0, 176.7, 179.6; ESI-MS$^+$ m/z: exact mass calculated for $C_{20}H_{19}O_2S$ $[M + H]^+$ 323.1106, found 323.1100.

*6-Bromo-4-phenylthionaphthalene-1,2-dione (**2e**).* Reddish solid; 0.12 g, yield 78%; mp 188−190 °C; IR (KBr) cm^{-1} 1693 (m), 1643 (s), 1571 (m), 1545 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 1H), 7.51−7.59 (m, 5H), 7.75 (dd, J = 8.4, 1.3 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.2, 125.8, 128.2, 129.0, 130.5, 130.7, 130.8, 131.3, 134.3, 134.9, 136.0, 159.9, 176.2, 178.6; ESI-MS$^+$ m/z: exact mass calculated for $C_{16}H_{10}BrO_2S$ $[M + H]^+$ 344.9585, found 344.9579.

*6-Bromo-4-(2-bromophenylthio)naphthalene-1,2-dione (**2f**).* Reddish solid; 0.154 g, yield 81%; mp 192−194 °C; IR (KBr) cm^{-1} 1694 (m), 1638 (s), 1577 (m), 1542 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (s, 1H), 7.42−7.49 (m, 2H), 7.70 (d, J = 6.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.3 Hz, 1H), 8.04−8.07 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.0, 127.4, 128.2, 128.3, 129.1, 129.2, 130.8, 130.9, 133.0, 134.4, 134.5, 134.8, 138.2, 157.1, 176.2, 178.5; ESI-MS$^+$ m/z: exact mass calculated for $C_{16}H_9Br_2O_2S$ $[M + H]^+$ 422.8689, found 422.8685.

*6-Bromo-4-(4-bromophenylthio)naphthalene-1,2-dione (**2g**).* Reddish solid; 0.14 g, yield 74%; mp 184−186 °C; IR (KBr) cm^{-1} 1699 (m), 1645 (s), 1575 (m), 1542 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.76 (dd, J = 8.4, 1.4 Hz, 1H), 8.04 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.3, 124.9, 126.5, 128.2, 128.9, 130.8, 130.9, 133.9, 134.4, 134.6, 137.4, 159.0, 176.2, 178.4; ESI-MS$^+$ m/z: exact mass calculated for $C_{16}H_9Br_2O_2S$ $[M + H]^+$ 422.8689, found 422.8698.

*6-Bromo-4-(4-tert-butylphenylthio)naphthalene-1,2-dione (**2h**).* Reddish solid; 0.14 g, yield 78%; mp 188−189 °C; IR (KBr) cm^{-1} 2957 (s), 2890 (m), 1698 (m), 1659 (s), 1573 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.37(s, 9H), 5.97 (s, 1H), 7.48 d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.75 (dd, J = 8.2, 1.8 Hz, 1H), 8.03 (d, J = 8.3 Hz, 1H), 8.09 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 35.5, 122.0, 122.1,127.7, 128.2, 128.9, 130.6, 130.7, 134.2, 134.8, 135.6, 154.9, 160.4, 176.2, 178.8; ESI-MS$^+$ m/z: exact mass calculated for $C_{20}H_{18}BrO_2S$ $[M + H]^+$ 401.0211, found 401.0215.

*7-Methoxy-4-phenylthionaphthalene-1,2-dione (**2i**).* Reddish solid; 0.129 g, yield 76%; mp 190−192 °C; IR (KBr) cm^{-1} 3027 (m), 2944 (s), 1697 (m), 1641 (s), 1594 (m), 1533 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 5.76 (s, 1H), 7.19 (dd, J = 8.9, 2.7 Hz, 1H), 7.48−7.58 (m, 5H), 7.66 (d, J = 2.7 Hz, 1H), 7.86 (d, J = 9.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.9, 113.6, 119.0, 121.0, 126.4, 126.5, 126.8, 130.3, 131.0, 132.0, 136.0, 161.9, 162.1, 176.8, 179.6; ESI-MS$^+$ m/z: exact mass calculated for $C_{17}H_{13}O_3S$ $[M + H]^+$ 297.0585, found 297.0580.

*7-Methoxy-4-(2,4,6-trimethylphenylthio)naphthalene-1,2-dione (**2j**).* Reddish solid; 0.116 g, yield 60%; mp 196−198 °C; IR (KBr) cm^{-1} 2922 (m), 3030 (m), 1698 (m), 1642 (s), 1597 (m), 1577 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.37 (s, 6H), 3.93 (s, 3H), 5.60 (s, 1H), 7.04 (s, 2H), 7.21 (dd, J = 8.7, 2.7 Hz, 1H), 7.66 (d, J = 2.7 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.3, 55.9, 113.3, 117.3, 121.0, 121.7, 126.5, 127.2, 130.1, 132.2, 141.5, 143.5, 160.5, 162.0, 176.7, 179.9; ESI-MS$^+$ m/z: exact mass calculated for $C_{20}H_{19}O_3S$ $[M + H]^+$ 339.1055, found 339.1054.

*7-Methoxy-4-(4-nitrophenylthio)naphthalene-1,2-dione (**2k**).* Reddish solid; 0.125 g, yield 64%; mp 198−200 °C; FT- IR (KBr) cm^{-1} 3029 (m), 2978 (m), 1699 (m), 1648 (s), 1596 (m), 1575 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 5.76 (s, 1H), 7.20 (dd, J = 8.9, 2.9 Hz, 1H), 7.67 (d, J = 2.7 Hz, 1H), 7.77−7.82 (m, 3H), 8.34 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 114.2, 120.0, 121.1, 125.0, 125.7, 127.1, 132.1, 135.3, 136.4, 149.1, 159.0, 162.4, 176.9, 178.9; ESI-MS$^+$ m/z: exact mass calculated for $C_{17}H_{12}NO_5S$ $[M + H]^+$ 342.0436, found 342.0430.

*6-Cyano-4-phenylthionaphthalene-1,2-dione (**2l**).* Reddish solid; 0.135 g, yield 68%; mp 199−201 °C; IR (KBr) cm^{-1} 2232 (m), 1700 (m), 1644 (s), 1566 (m), 1542 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 (s, 1H), 7.53−7.59 (m, 5H), 7.90 (dd, J = 8.0, 1.4 Hz, 1H), 8.23 (d, J = 0.9 Hz, 1H), 8.27 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.9, 118.5, 122.7, 125.3, 125.4, 128.5, 129.7, 130.7, 131.5, 132.5, 134.3, 135.9, 159.2, 175.4, 178.1; ESI-MS$^+$ m/z: exact mass calculated for $C_{17}H_{10}NO_2S$ $[M + H]^+$ 292.0432, found 292.0435.

*6-Cyano-4-(2,4,6-trimethylphenylthio)naphthalene-1,2-dione (**2m**).* Reddish solid; 0.121 g, yield 62%; mp 202−204 °C; IR (KBr) cm^{-1} 2920 (m), 2234 (m), 1720 (m), 1649 (s), 1599 (m), 1567 (m);

DOI: 10.1021/acs.joc.6b01105
J. Org. Chem. 2016, 81, 6472−6480

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.38 (s, 6H), 5.83 (s, 1H), 7.08 (s, 2H), 7.89 (dd, J = 8.2, 1.4 Hz, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.33 (d, J = 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 21.3, 117.0, 118.5, 120.7, 121.1, 129.0, 129.6, 130.4, 132.7, 134.2, 134.4, 142.2, 143.4, 157.8, 175.2, 175.6; ESI-MS$^+$ m/z: exact mass calculated for $C_{20}H_{16}NO_2S$ $[M + H]^+$ 334.0902, found 334.0900.

General Procedure for One-Pot Synthesis of 4-Arylthio-1,2-diacetoxynaphthalenes (3a−k). A typical procedure is described below for 4-phenylthio-1,2-diacetoxynaphthalene **3a**. A similar procedure was adopted for the synthesis of all others, i.e., **3b−3k**.

To a solution of 2-naphthol (0.1 g, 0.69 mmol) in 4 mL of DMF, IBX (0.214 g, 0.76 mmol) was added and stirred in an open atmosphere for 0.5 h at rt. The disappearance of 2-naphthol was followed by TLC analysis. At the end of complete oxidation, thiophenol (0.091 g, 0.82 mmol) was added to the reaction mixture at rt. After complete consumption of naphthalene-1,2-dione, as monitored by TLC analysis, $Na_2S_2O_4$ (0.241 g, 1.38 mmol) was introduced into the same pot followed by acetic anhydride (0.177 g, 1.72 mmol) to afford 4-phenylthio-1,2-diacetoxynaphthalene (**3a**); it should be noted that the reaction flask was kept stoppered during acetylation. At the end of the reaction, 60 mL of ethyl acetate was added to the reaction mixture, and the mixture was washed thoroughly with saturated $NaHCO_3$ followed by brine. The ethyl acetate extract was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography to isolate 4-phenylthio-1,2-diacetoxynaphthalene (**3a**) as a colorless semisolid material using 10% ethyl acetate in PE. Yield 82% (0.2 g); IR (KBr) cm^{-1} 3070 (m), 1774 (s), 1601 (m), 1582 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.47 (s, 3H), 7.22−7.31 (m, 5H), 7.44 (s, 1H), 7.52−7.59 (m, 2H), 7.89 (dd, J = 7.5, 1.5 Hz, 1H), 8.38 (dd, J = 9.0, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.6, 121.7, 125.7, 126.7, 126.8, 126.9, 127.4, 128.2, 129.2, 130.0, 131.1, 131.9, 135.2, 137.2, 138.7, 167.9, 168.1; ESI-MS$^+$ m/z: exact mass calculated for $C_{20}H_{16}O_4SNH_4$ $[M+NH_4]^+$ 370.1113, found 370.1116.

*4-(4-Bromophenylthio)-1,2-diacetoxynaphthalene (**3b**).* White crystalline material, 0.202 g, yield 68%; mp 88−90 °C; IR (KBr) cm^{-1} 3074 (m), 1770 (s), 1632 (m), 1600 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.47 (s, 3H), 7.09 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 7.48 (s, 1H), 7.56 (m, 2H), 7.88 (d, J = 7.4 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.7, 120.6, 121.8, 125.7, 127.2, 127.5, 127.6, 128.4, 129.8, 130.9, 132.0, 132.3, 134.9, 137.7, 138.7, 167.9, 168.1; ESI-MS$^+$ m/z: exact mass calculated for $C_{20}H_{15}BrO_4SNH_4$ $[M+NH_4]^+$ 448.0218, found 448.0214.

*4-(4-tert-Butylphenylthio)-1,2-diacetoxynaphthalene (**3c**).* White solid, 0.212 g, yield 75%; mp 92−94 °C; IR (KBr) cm^{-1} 2962 (s), 2868 (m), 1778 (s), 1600 (m), 1570 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H), 2.30 (s, 3H), 2.46 (s, 3H), 7.27 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 7.38 (s, 1H), 7.54−7.58 (m, 2H), 7.88 (dd, J = 8.9, 2.3 Hz, 1H), 8.40 (dd, J = 7.1, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.6, 31.2, 34.5, 121.7, 125.7, 125.9, 126.4, 126.9, 127.4, 128.2, 130.4, 131.2, 131.8, 132.0, 136.9, 138.8, 150.4, 167.9, 168.1; ESI-MS$^+$ m/z: exact mass calculated for $C_{24}H_{24}O_4SNH_4$ $[M+NH_4]^+$ 426.1739, found 426.1730.

*6-Bromo-4-phenylthio-1,2-diacetoxynaphthalene (**3d**).* White solid, 0.152 g, yield 79%; mp 96−98 °C; IR (KBr) cm^{-1} 3045 (m), 1763 (s), 1586 (m), 1479 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.45 (s, 3H), 7.23−7.31 (m, 5H), 7.39 (s, 1H), 7.63 (dd, J = 9.1, 1.8 Hz, 1H), 7.73 (d, J = 9.1 Hz, 1H), 8.56 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.6, 121.7, 123.5, 126.9, 127.3, 127.6, 128.0, 129.5, 130.5, 130.7, 130.9, 132.9, 134.5, 137.2, 139.0, 167.8, 167.9; ESI-MS$^+$ m/z: exact mass calculated for $C_{20}H_{15}BrO_4SNa$ $[M + Na]^+$ 452.9772, found 452.9774.

*6-Bromo-4-(4-bromophenylthio)-1,2-diacetoxynaphthalene (**3e**).* White solid, 0.195 g, yield 85%; mp 131−133 °C; IR (KBr) cm^{-1} 3068 (m), 2937 (m), 1762 (s), 1589 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.45 (s, 3H), 7.12 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.44 (s, 1H), 7.64 (dd, J = 8.7, 1.8 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 8.51 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.7, 121.2, 122.0, 123.6, 127.0, 127.9, 128.5, 129.4, 131.0, 131.4, 132.5, 133.0, 134.2, 137.7, 139.0, 167.7, 168.0; ESI-MS$^+$ m/z: exact mass calculated for $C_{20}H_{14}Br_2O_4SNH_4$ $[M+NH_4]^+$ 525.9323, found 525.9327.

*6-Bromo-4-(2,4,6-trimethylphenylthio)-1,2-diacetoxynaphthalene (**3f**).* White solid, 0.146 g, yield 69%; mp 188−190 °C; IR (KBr) cm^{-1} 2920 (w), 1776 (s), 1588 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.35 (s, 3H), 2.39 (s, 6H), 2.40 (s, 3H), 6.36 (s, 1H), 7.06 (s, 2H), 7.62−7.69 (m, 2H), 8.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.7, 21.2, 21.5, 117.7, 120.6, 123.6, 124.8, 126.6, 126.7, 129.7 (2), 130.2, 130.6, 134.3, 139.6, 140.0, 144.1, 167.9, 168.1; ESI-MS$^+$ m/z: exact mass calculated for $C_{23}H_{21}BrO_4SNH_4$ $[M+NH_4]^+$ 490.0687, found 490.0683.

*6-Bromo-4-(4-tert-butylphenylthio)-1,2-diacetoxynaphthalene (**3g**).* White solid, 0.174 g, yield 80%; mp 190−194 °C; IR (KBr) cm^{-1} 2965 (m), 2904 (w), 2867 (w), 1774 (s), 1589 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H), 2.28 (s, 3H), 2.44 (s, 3H), 7.27 (d, J = 7.6 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.35 (s, 1H), 7.63 (dd, J = 9.1, 1.8 Hz, 1H), 7.12 (d, J = 9.1 Hz, 1H), 8.59 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.7, 31.2, 34.6, 121.5, 123.5, 126.6 (2), 126.9, 127.9, 130.5, 130.8 (2), 131.6, 132.8, 136.9, 139.1, 150.8, 167.8, 167.9; ESI-MS$^+$ m/z: exact mass calculated for $C_{24}H_{23}BrO_4SNH_4$ $[M+NH_4]^+$ 504.0844, found 504.0842.

*6-Bromo-4-(4-nitrophenylthio)-1,2-diacetoxynaphthalene (**3h**).* White solid, 0.127 g, yield 60%; mp 171−173 °C; IR (KBr) cm^{-1} 3102 (w), 1775 (s), 1662 (m), 1590 (s), 1336 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.50 (s, 3H), 7.14 (d, J = 9.1 Hz, 2H), 7.68 (dd, J = 9.1, 1.8 Hz, 1H), 7.79 (s, 1H) 7.82 (d, J = 9.1 Hz, 1H), 8.06 (d, J = 9.1 Hz, 2H), 8.45 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.7, 123.9, 124.3, 124.9, 126.6 (2), 127.4, 127.8, 128.1, 132.4, 134.1, 139.0, 139.4, 145.7, 146.5, 167.5, 167.9; ESI-MS$^-$ m/z exact mass calculated for $C_{16}H_9BrNO_4S$ $[M - (2CH_3CO + H)]^-$ 389.94356, found 389.9444.

*7-Methoxy-4-(4-nitrophenylthio)-1,2-diacetoxynaphthalene (**3i**).* White solid, 0.157 g, yield 63%; mp 97−99 °C; IR (KBr) cm^{-1} 3070 (w), 2893 (w), 1769 (s), 1625 (m), 1595 (m), 1578 (s), 1507 (s), 1337 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.50 (s, 3H), 3.92 (s, 3H), 7.11 (d, J = 8.7 Hz, 2H), 7.17−1.20 (m, 2H), 7.62 (s, 1H), 8.02 (d, J = 8.7 Hz, 2H), 8.13 (s, J = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 20.7, 55.4, 100.7, 120.3, 124.1, 125.3, 126.3, 127.7, 128.3, 128.4, 130.2, 138.4, 139.4, 145.4, 147.4, 159.2, 167.7, 168.0; ESI-MS$^+$ m/z exact mass calculated for $C_{21}H_{17}NO_7SNH_4$ $[M + NH_4]^+$ 445.1069, found 445.1070.

*6-Cyano-4-(4-bromophenylthio)-1,2-diacetoxynaphthalene (**3j**).* White solid; 0.183 g, yield 68%; mp 156−158 °C; FT- IR (KBr) cm^{-1} 3074 (w), 2227 (m), 1778 (s), 1605 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.47 (s, 3H), 7.16 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.48 (s, 1H), 7.70 (dd, J = 8.7, 1.3 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 8.73 (d, J = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.7, 110.8, 118.5, 121.9, 123.4, 128..0, 128.4, 130.1. 130.6, 131.6, 132.1, 132.2, 132.8, 133.1, 137.2, 141.3, 167.6, 167.7; ESI-MS$^+$ m/z: exact mass calculated for $C_{21}H_{14}BrNO_4SNH_4$ $[M + NH_4]^+$ 473.0171, found 473.0172.

*6-Cyano-4-(4-methylphenylthio)-1,2-diacetoxynaphthalene (**3k**).* White solid, 0.145 g, yield 63%; mp 140−143 °C; FT- IR (KBr) cm^{-1} 3071 (w), 2937 (w), 2231 (m), 1774 (s), 1604 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29, (s, 3H), 2.35 (s, 3H), 2.46 (s, 3H) 7.17 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 6.8 Hz, 3H), 7.68 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 9.1 Hz, 1H), 8.76 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.7, 21.2, 110.3, 118.7, 123.3, 126.1, 127.9, 129.1, 129.9, 130.1, 130.5, 131.5, 132.3, 134.9, 136.2, 138.7, 141.4, 167.6, 167.7; ESI-MS$^+$ m/z: exact mass calculated for $C_{22}H_{17}NO_4SNH_4$ $[M + NH_4]^+$ 409.1222, found 409.1221.

General Procedure for One-Pot Synthesis of 5-Arylthio-/5-Arylaminobenzo[*a*]phenazines (4a−k). A representative procedure is described below for 5-phenylthiobenzo[*a*]phenazine **4a**. A similar procedure was followed for all other phenazines **4b−4k**.

To a solution of 4-phenylthionaphthalene-1,2-dione prepared by above procedure starting from 2-naphthol (0.1 g, 0.69 mmol), *o*-phenylenediamine (0.09 g, 0.82 mmol) was added at rt and stirred for

DOI: 10.1021/acs.joc.6b01105
J. Org. Chem. 2016, 81, 6472−6480

1 h in open air. The disappearance of 4-arylthionaphthalene-1,2-diones was monitored by TLC. At the end of the reaction, the reaction mixture was diluted with DCM, and the organic layer was washed with saturated $NaHCO_3$ followed by brine. It was later dried over Na_2SO_4, and the solvent was removed in rotary evaporator under reduced pressure. Silica gel column chromatography was performed to isolate 5-phenylthiobenzo[*a*]phenazine (**4a**) as a yellow colored solid material using 25% DCM in PE. Yield 88% (0.206 g); mp 192−194 °C; IR (KBr) cm^{-1} 1608 (s), 1584 (m), 1497 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.47 (m, 3H), 7.54 (s, 1H), 7.63−7.65 (m, 2H), 7.80−7.88 (m, 4H), 8.14−8.16 (m, 1H), 8.30−8.33 (m, 1H), 8.41−8.43 (m, 1H), 9.48 (dd, 7.0, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.5, 124.6, 125.6, 128.4, 128.8, 129.4, 129.4, 129.6, 130.0 (2), 130.1, 130.8, 131.5, 134.6 (2), 141.6, 141.9, 142.6, 142.9, 143.2; ESI-MS$^+$ *m*/*z* exact mass calculated for $C_{22}H_{14}N_2S$ $[M]^+$ 338.0878, found 338.0877.

5-(4-Bromophenylthio)benzo[a]phenazine (**4b**). Yellow solid, 0.237 g, yield 82%; mp 220−220 °C; IR (KBr) cm^{-1} 1616 (m), 1580 (m), 1489 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 3H), 7.82−7.88 (m, 4H), 8.16−8.19 (m, 1H), 8.31−8.38 (m, 2H), 9.48 (dd, *J* = 7.6, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.5, 124.6, 125.7, 125.8, 128.6, 128.9, 129.7 (2), 130.1, 130.3, 130.5, 131.5, 131.5, 133.2, 135.5, 141.5, 141.8, 142.0, 142.9, 143.0; ESI-MS$^+$ *m*/*z*: exact mass calculated for $C_{22}H_{14}BrN_2S$ $[M + H]^+$ 417.0062, found 417.0066.

5-(4-Methylphenylthio)benzo[a]phenazine (**4c**). Yellow solid, 0.197 g, yield 81%; mp 196−198 °C; IR (KBr) cm^{-1} 3032 (w), 2919 (w), 1616 (w), 1580 (m), 1490 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.39 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.76−7.80 (m, 2H), 7.82−7.85 (m, 2H), 8.11−8.13 (m, 1H), 8.27−8.29 (m, 1H), 8.38−8.39 (m, 1H), 9.44 (dd, *J* = 7.2, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 123.2, 124.3, 125.6, 126.5, 128.3, 128.7, 129.2, 129.7, 129.9, 130.0, 130.7, 130.9, 131.4, 135.2, 139.8, 141.5, 141.9, 142.9, 143.3, 143.8; ESI-MS$^+$ *m*/*z*: exact mass calculated for $C_{23}H_{16}N_2S$ $[M]^+$ 352.1034, found 352.1036.

3-Bromo-5-phenylthiobenzo[a]phenazine (**4d**). Yellow solid, 0.157 g, yield 84%; mp 238−240; IR (KBr) cm^{-1} 1616 (w), 1591 (m), 1354 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47−7.49 (m, 3H), 7.55 (s, 1H), 7.63−7.65 (m, 2H), 7.81−7.83 (m, 2H), 7.94 (d, *J* = 8.7 Hz, 1H), 8.14 (m, 1H), 8.27−8.30 (m, 1H), 8.56 (s, 1H), 9.31 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.6, 124.9, 125.2, 125.8, 127.4, 128.9, 129.5, 129.7, 129.8, 130.1 (2), 130.4, 130.5, 131.6, 133.0, 134.7, 141.5, 141.8, 142.9, 143.1; ESI-MS$^+$ *m*/*z*: exact mass calculated for $C_{22}H_{14}BrN_2S$ $[M + H]^+$ 417.0062, found 417.0065.

3-Bromo-5-(2,4,6-trimethylphenylthio)benzo[a]phenazine (**4e**). Yellow solid, 0.164 g, yield 80%; mp 237−239 °C; IR (KBr) cm^{-1} 2955 (m), 1590 (m), 1481 (m), 1354 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 2.39, (s, 3H), 2.44 (s, 6H), 7.03 (s, 1H), 7.12 (s, 2H), 7.78−78 (m, 2H), 7.95 (dd, *J* = 8.9, 1.8 Hz, 1H), 8.08−8.10 (m, 1H), 8.26−8.28 (m, 1H), 8.62 (d, *J* = 1.4 Hz, 1H), 9.32 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 21.5, 120.3, 123.7, 124.8, 127.0, 127.4, 128.7, 129.4, 129.6, 129.7, 130.1, 130.3, 131.4, 132.9, 140.6, 141.2, 141.4, 141.5, 143.0, 143.2, 144.1; ESI-MS$^+$ *m*/*z*: exact mass calculated for $C_{25}H_{20}BrN_2S$ $[M + H]^+$ 459.0530, found 459.0537.

2-Methoxy-5-phenylthiobenzo[a]phenazine (**4f**). Yellow solid, 0.16 g, yield 76%; mp 224−226 °C; IR (KBr) cm^{-1} 3053 (m), 2955 (m), 1608 (s), 1584 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 3H), 7.40−7.48 (m, 5H), 7.61−7.63 (m, 2H), 7.79−7.82 (m, 2H), 8.13−8.15 (m, 1H), 8.30−8.33 (m, 2H), 8.90 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 106.8, 119.5, 122.5, 125.6, 126.3, 128.8, 129.1, 129.3, 129.6, 129.9, 130.2, 131.1, 132.7, 134.4, 141.3, 141.7, 142.4, 143.0, 143.7, 159.9; ESI-MS$^+$ *m*/*z*: exact mass calculated for $C_{23}H_{17}N_2OS$ $[M + H]^+$ 369.1062, found 369.1061.

2-Methoxy-5-(4-methylphenylthio)benzo[a]phenazine (**4g**). Yellow solid, 0.16 g, yield 73%; mp 218−220; IR (KBr) cm^{-1} 3050 (m), 2958 (m), 1610 (m), 1583 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.12 (s, 3H), 7.28 (d, *J* = 7.2 Hz, 3H), 7.41 (dd, *J* = 7.2, 2.7 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.77−7.80 (m, 2H), 8.11−8.13 (m, 1H), 8.29−8.31 (m, 2H), 8.78 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 55.8, 106.8, 119.4, 120.9, 125.9, 125.6, 126.6, 128.7, 129.0, 129.6, 130.1, 130.8, 132.6, 135.2, 139.7, 141.2, 141.5, 142.9, 143.6, 143.7, 159.8; ESI-MS$^+$ *m*/*z*: exact mass calculated for $C_{24}H_{19}N_2OS$ $[M + H]^+$ 383.1218, found 383.1219.

5-(N-Phenylamino)benzo[a]phenazine (**4h**).[4a] Yellow solid, 0.124 g, yield 56%; IR (KBr) cm^{-1} 3420 (s), 1620 (m), 1590 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 6.48 (s, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 8.5 Hz, 2H), 7.53 (s, 1H), 7.71−7.79 (m, 2H), 7.84−7.88 (m, 2H), 8.09−8.11(m, 2H), 8.28 (dd, *J* = 8.3, 1.1 Hz, 1H), 9.51 (dd, *J* = 7.5, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.5, 120.4, 122.6 (2), 124.1, 126.3, 127.8, 127.9, 128.2, 128.4, 129.6, 129.7 (2), 129.9, 131.9, 140.5, 140.7, 143.3, 143.7, 145.3.

5-(N-Methyl-N-phenylamino)benzo[a]phenazine (**4i**). Yellow solid, 0.181 g, yield 78%; mp 140−142 °C; IR (KBr) cm^{-1} 3056 (w), 1619 (w), 1587 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H), 6.90−6.93 (m, 3H), 7.72 (t, *J* = 7.8 Hz, 2H), 7.62 (dt, *J* = 8.2, 1.4 Hz, 1H), 7.67 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.79 (s, 1H), 7.83−7.86 (m, 2H), 7.89 (d, *J* = 8.2 Hz, 1H), 8.22−8.25 (m, 1H), 8.34−8.37 (m, 1H), 9.46 (dd, *J* = 8.2, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.8, 118.2, 120.4, 120.5, 125.4, 125.7, 127.9, 128.7, 128.7, 129.3, 129.3, 129.5, 130.1, 131.4, 132.2, 133.2, 141.5, 141.8, 144.5, 149.9, 150.3; ESI-MS$^+$ *m*/*z*: exact mass calculated for $C_{23}H_{18}N_3$ $[M + H]^+$ 336.1501, found 336.1502.

5-(N,N-Diphenylamino)benzo[a]phenazine (**4j**).[4a] Yellow solid, 0.11 g, yield 40%; IR (KBr) cm^{-1} 1623 (w), 1590 (s), 1488 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (t, *J* = 7.4 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 4H), 7.28 (d, *J* = 8.0 Hz, 4H), 7.61 (dt, *J* = 6.8, 1.1 Hz, 1H), 7.67 (s, 1H), 7.77 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.82−7.85 (m, 2H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.15−8.18 (m, 1H), 8.34−8.37 (m, 1H), 9.49 (dd, *J* = 8.0, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.2, 123.7, 124.6, 125.7, 128.0, 128.7, 129.3, 129.4 (2), 129.6, 129.7, 130.1, 131.7, 132.4, 141.5, 141.9, 143.0, 144.3, 148.3, 140.1.

5-(4-(N,N-Diethylamino)phenyl)benzo[a]phenazine (**4k**). Yellow solid, 0.188 g, yield 72%; mp 143−145; IR (KBr) cm^{-1} 3055 (w), 2971 (m), 2933 (w), 1606 (s), 1518 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 6.9 Hz, 6H), 3.46 (q, *J* = 6.9 Hz, 4H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.72 (t, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.82−7.85 (m, 2H), 8.15(d, *J* = 7.8 Hz, 1H), 8.25−8.27 (m, 1H), 8.35−8.37 (m, 1H), 9.52 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 44.4, 111.2, 125.6, 125.8, 126.2, 127.3, 127.5, 128.9, 129.2, 129.4, 129.7, 129.8, 130.9, 131.5, 133.2, 141.7, 142.3, 143.1, 143.6, 145.7, 147.7; ESI-MS$^+$ *m*/*z*: exact mass calculated for $C_{26}H_{24}N_3$ $[M + H]^+$ 378.1970, found 378. 1970.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01105.

^1H and ^{13}C NMR spectral reproductions for all products of the multistep synthesis (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: moorthy@iitk.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.N.M. is thankful to the CSIR, India for generous financial support. A.K.M. gratefully acknowledges the senior research fellowship from UGC, New Delhi.

■ DEDICATION

This paper is dedicated to Prof. Hiryakkanavar Junjappa on the occasion of his 80th birthday.

DOI: 10.1021/acs.joc.6b01105
J. Org. Chem. 2016, 81, 6472−6480

REFERENCES

(1) (a) Turner, J. M.; Messenger, A. N. Occurrence, Biochemistry and Physiology of Phenazine Pigment Production. In *Advances in Microbial Physiology*; Rose, A. H., Tempest, D. W., Eds.; Academic Press: London, 1986; pp 211−275. (b) Papageorgiou, V. P.; Assimopoulou, A. N.; Couladouros, E. A.; Hepworth, D.; Nicolaou, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 270−301. (c) Meazza, G.; Scheffler, B. E.; Tellez, M. R.; Rimando, A. M.; Romagni, J. G.; Duke, S. O.; Nanayakkara, D.; Ehab, I. A. K.; Abourashed, A.; Dayan, F. E. *Phytochemistry* **2002**, *59*, 281−288. (d) Laursen, J. B.; Nielsen, J. *Chem. Rev.* **2004**, *104*, 1663−1685. (e) Pinto, A. V.; Castro, S. L. *Molecules* **2009**, *14*, 4570−4590. (f) Pierson, L. S., III; Pierson, E. A. *Appl. Microbiol. Biotechnol.* **2010**, *86*, 1659−1670.

(2) (a) Bolton, J. L.; Trush, M. A. T.; Penning, M.; Dryhurst, G.; Monks, T. J. *Chem. Res. Toxicol.* **2000**, *13*, 135−160. (b) Ahn, J. H.; Cho, S. Y.; Ha, J. D.; Chu, S. Y.; Jung, S. H.; Jung, Y. S.; Baek, J. Y.; Choi, I. K.; Shin, E. Y.; Kang, S. K.; Kim, S. S.; Cheon, H. G.; Yang, S.-D.; Choi, J.-K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1941−1946. (c) Huang, W.; Li, J.; Zhang, W.; Zhou, Y.; Xie, C.; Luo, Y.; Li, Y.; Wang, J.; Li, J.; Lu, W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1905−1908. (d) Tseng, C.-H.; Cheng, C.-M.; Tzeng, C.-C.; Peng, S.-I.; Yang, C.-L.; Chen, Y.-L. *Bioorg. Med. Chem.* **2013**, *21*, 523−531. (e) Wellington, K. W. *RSC Adv.* **2015**, *5*, 20309−20338. (f) de Andrade-Neto, V. F.; Goulart, M. O. F.; da Filho, J. F. S.; da Silva, M. J.; Pinto, M. C. F. R.; Pinto, A. V.; Zalis, M. G.; Carvalho, L. H.; Krettli, A. U. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1145−1149. (g) Price-Whelan, A.; Dietrich, L. E. P.; Newman, D. K. *Nat. Chem. Biol.* **2006**, *2*, 71−78. (h) Hussain, H.; Specht, S.; Sarite, S. R.; Saeftel, M.; Hoerauf, A.; Schulz, B.; Krohn, K. *J. Med. Chem.* **2011**, *54*, 4913−4917.

(3) (a) Shukla, S.; Srivastava, R. S.; Shrivastava, S. K.; Sodhi, A.; Kumar, P. *Appl. Biochem. Biotechnol.* **2012**, *167*, 1430−1445. (b) Nishida, M.; Sawa, T.; Kitajima, N.; Ono, K.; Inoue, H.; Ihara, H.; Motohashi, H.; Yamamoto, M.; Suematsu, M.; Kurose, H.; van der Vliet, A.; Freeman, B. A.; Shibata, T.; Uchida, K.; Kumagai, Y.; Akaike, T. *Nat. Chem. Biol.* **2012**, *8*, 714−724. (c) Shukla, S.; Srivastava, R. S.; Shrivastava, S. K.; Sodhi, A.; Kumar, P. *J. Enzyme Inhib. Med. Chem.* **2013**, *28*, 1192−1198.

(4) (a) Singh, P.; Baheti, A.; Thomas, K. R. J. *J. Org. Chem.* **2011**, *76*, 6134−6145. (b) York, M. *Tetrahedron Lett.* **2012**, *53*, 2226−2230. (c) Kim, J.-H.; Kim, H. U.; Song, C. E.; Park, M.-J.; Kang, I.-N.; Shin, W. S.; Hwang, D.-H. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 2354−2365. (d) Jali, B. R.; Baruah, J. B. *Dyes Pigm.* **2014**, *110*, 56−66.

(5) (a) Guilbault, G. G.; Kramer, D. N. *Anal. Chem.* **1965**, *37*, 1675−1680. (b) Foti, M. C.; Johnson, E. R.; Vinqvist, M. R.; Wright, J. S. L.; Barclay, R. C.; Ingold, K. U. *J. Org. Chem.* **2002**, *67*, 5190−5196. (c) Molinari, A.; Oliva, A.; Ojeda, C.; del Corral, J. M.; Castro, M. A.; Cuevas, C.; San Feliciano, A. S. *Bioorg. Med. Chem.* **2005**, *13*, 6645−6650. (d) Flueraru, M.; So, R.; Willmore, W. G.; Poulter, M. O.; Durst, T.; Charron, M.; Wright, J. S. *Chem. Res. Toxicol.* **2006**, *19*, 1221−1227. (e) Thorson, M. K.; Puerta, D. T.; Cohen, S. M.; Barrios, A. M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4019−4022. (f) Zhou, Y.; Dahl, J.; Carlson, R.; Liang, H. *Carbon* **2015**, *86*, 132−138.

(6) (a) Sun, P.-P.; Duan, J.-P.; Lih, J.-J.; Cheng, C.-H. *Adv. Funct. Mater.* **2003**, *13*, 683−691. (b) Bunz, U. H. F. *Chem. - Eur. J.* **2009**, *15*, 6780−6789. (c) Richards, G. J.; Hill, J. P.; Mori, T.; Ariga, K. *Org. Biomol. Chem.* **2011**, *9*, 5005−5017. (d) Miao, Q. *Synlett* **2012**, *23*, 326−336. (e) Bunz, U. H. F.; Engelhart, J. U.; Lindner, B. D.; Schaffroth, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3810−3821. (f) Gu, P.-Y.; Zhao, Y.; He, J.-H.; Zhang, J.; Wang, C.; Xu, Q.-F.; Lu, J.-M.; Sun, X. W.; Zhang, Q. *J. Org. Chem.* **2015**, *80*, 3030−3035.

(7) (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (b) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605−3607.

(8) (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40−49. (b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010−3021. (c) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657−4673.

(9) Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438−440.

(10) (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Hall, N. *Science* **1994**, *266*, 32−34.

(11) (a) Sukumaran, K. B.; Harvey, R. G. *J. Org. Chem.* **1980**, *45*, 4407−4413. (b) Egusquiza, M. G.; Romanelli, G. P.; Cabello, C. I.; Botto, I. L.; Thomas, H. J. *Catal. Commun.* **2008**, *9*, 45−50. (c) Wu, A.; Duan, Y.; Xu, D.; Penning, T. M.; Harvey, R. G. *Tetrahedron* **2010**, *66*, 2111−2118. (d) Ratnikov, M. O.; Farkas, L. E.; McLaughlin, E. C.; Chiou, G.; Choi, H.; El-Khalafy, S. H.; Doyle, M. P. *J. Org. Chem.* **2011**, *76*, 2585−2593. (e) Uyanik, M.; Mutsuga, T.; Ishihara, K. *Molecules* **2012**, *17*, 8604−8616.

(12) (a) Moorthy, J. N.; Singhal, N.; Senapati, K. *Tetrahedron Lett.* **2006**, *47*, 1757−1761. (b) Moorthy, J. N.; Singhal, N.; Senapati, K. *Tetrahedron Lett.* **2008**, *49*, 80−84. (c) Moorthy, J. N.; Senapati, K.; Singhal, N. *Tetrahedron Lett.* **2009**, *50*, 2493−2496. (d) Moorthy, J. N.; Senapati, K.; Parida, K. N. *J. Org. Chem.* **2010**, *75*, 8416−8421. (e) Moorthy, J. N.; Senapati, K.; Parida, K. N.; Jhulki, S.; Sooraj, K.; Nair, N. N. *J. Org. Chem.* **2011**, *76*, 9593−9601. (f) Moorthy, J. N.; Neogi, I. *Tetrahedron Lett.* **2011**, *52*, 3868−3871. (g) Seth, S.; Jhulki, S.; Moorthy, J. N. *Eur. J. Org. Chem.* **2013**, *2013*, 2445−2452. (h) Moorthy, J. N.; Parida, K. N. *J. Org. Chem.* **2014**, *79*, 11431−11439.

(13) For our recent contributions to the one-pot multistep mechanochemical synthesis of important heterocyclic compounds, see: Nagarajaiah, H.; Mishra, A. K.; Moorthy, J. N. *Org. Biomol. Chem.* **2016**, *14*, 4129−4135.

(14) (a) Magdziak, D.; Rodriguez, A. A.; Van de Water, W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285−288. (b) Ladziata, U.; Zhdankin, V. V. *ARKIVOC* **2006**, *9*, 26−58. (c) Satam, V.; Harad, A.; Rajule, R.; Pati, H. *Tetrahedron* **2010**, *66*, 7659−7706.

(15) Biggs, I. D.; Tedder, J. M. *Tetrahedron* **1978**, *34*, 1377−1380.

(16) (a) Platt, K. L.; Oesch, F. *J. Org. Chem.* **1983**, *48*, 265−268. (b) Verga, D.; Doria, F.; Mella, M.; Freccero, M. *J. Org. Chem.* **2009**, *74*, 5311−5319. (c) Francke, R.; Little, R. D. *J. Am. Chem. Soc.* **2014**, *136*, 427−435.

(17) (a) Mayhew, S. G.; Massey, V. *Biochim. Biophys. Acta* **1973**, *315*, 181−190. (b) Gassman, P. G.; Rasmy, O. M.; Murdock, T. O.; Saito, K. *J. Org. Chem.* **1981**, *46*, 5457−5458.

DOI: 10.1021/acs.joc.6b01105
J. Org. Chem. 2016, 81, 6472−6480