JOC The Journal of Organic Chemistry

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Aryl-Free Radical-Mediated Oxidative Arylation of Naphthoquinones Using *o*-Iodoxybenzoic Acid and Phenylhydrazines and Its Application toward the Synthesis of Benzocarbazoledione

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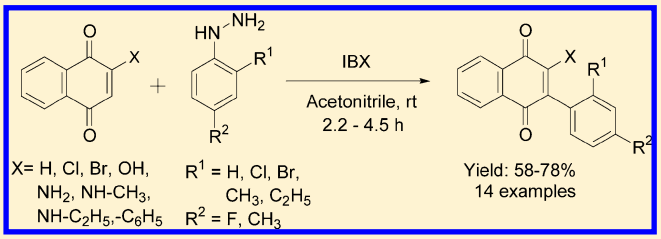
Supporting Information

ABSTRACT: Oxidative arylation of naphthoquinones has been developed through combination of *o*-iodoxybenzoic acid with arylhydrazines under mild conditions at open atmosphere. Arylated naphthoquinones with different electronic properties were obtained in moderate to good yields. The postulated radical mediated mechanism is supported by radical trapping experiments. Developed protocol for direct arylation of naphthoquinones has been extended toward short, high yielding, and an effective synthesis of antitumor−antibiotic precursor such as benzocarbazoledione.



Naphthoquinones are ubiquitous in nature and play significant roles in biological systems due to their electron and proton transfer properties. It articulates the spectrum of wide-ranging biological activities such as antibacterial, antifungal, anti-inflammatory, antithrombotic, antiplatelet, antibiotic, antiallergic, and apoptosis.[1] 1,4-Naphthoquinone derivatives have also been proven to be human DNA topoisomerase I and II inhibitors.[2] 1,4-Naphthoquinones and arylated naphthoquinones constitute an imperious class of natural products and found embedded in crisamicin A, microphyllaquinone, conocurvone and angelmicin B, δ-rubromycin, and in some other natural products.[3] Naphthoquinones have important applications in cosmetics,[4] dyes,[5] and pharmaceutical industries.[6] There are several drugs possessing wide-ranging activity such as parvaquone (antiprotozal), atovaquone (antimalerial), lapachol (antiproliferative), menadione (anticancer), and plumbagin (anticancer) constitute functionalized naphthoquinone as the basic core in them. Eventually, the applicability of naphthoquinones toward natural and synthetic materials has attracted the attention of researchers in preparative chemistry.

Despite pervasiveness of arylated naphthoquinones in several fields of science, they can be obtained by a few general methods such as oxidation of corresponding aromatics,[7] using a cycloaddition ring construction approach,[8] radical coupling reactions,[9] and by transition metal catalyzed coupling reactions through C−H bond activation. Out of these pathways, arylation via transition metal mediated cross-coupling has broader scope. Arylation of naphthoquinones can be accomplished by palladium(II) acetate mediated coupling of naphthoquinone to an arene with cosolvent,[10] palladium catalyzed coupling reaction of stannanes with naphthoquinones[11a] and naphthoquinone triflates,[11b] coupling of aryl chlorides with naphthoquinones using $HgCl_2/LiPdCl_2$,[12] and arylation via zwitterionic iodonium intermediates.[13] There are few reports[14] available on arylboronic acid mediated arylation in the presence of various oxidants.

The common limitations of most of these methods are inevitability of transition metals which possess high cost and toxicity, necessity of prefunctionalization of C−H bond at 2 or 3 positions of the starting naphthoquinones with a halogen or triflate group, use of expensive arylating counterparts such as boronic acid and stannanes, elevated temperature, and longer reaction time. Radical coupling of naphthoquinones can be accessed through aryldiazonium salts[1,9] which are difficult to synthesize, unstable, and give very poor yield with formation of azoproducts[9d] and known as explosive under certain circumstances. With the background of these inadequacies, the development of an adaptable method for arylation of naphthoquinones which is free from transition metal, relatively inexpensive, having short reaction time under mild reaction conditions is still a significant challenge.

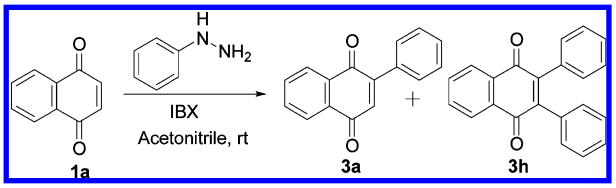
o-Iodoxybenzoic acid (IBX) is an imperative part of hypervalent iodine(V) reagents. Due to its chemoselectivity and mild oxidizing properties, its attractiveness is cumulative among synthetic chemists and it can be arbitrated from recent reports.[15] In persistence of our research contribution[16] toward exploring new-fangled applications of IBX, we recently discovered a new method for generation of arylating species for N-arylation of amines through combination of IBX and arylhydrazines.[17] Inspired by this outcome and considering the essential reactivity of naphthoquinones with nucleophilic species, it was of great interest to generate the same arylating species through combination of IBX and arylhydrazines as

Received: January 20, 2014
Published: February 10, 2014

arylating counterparts to react with electrophiles such as naphthoquinones.

To verify our hypothesis, we choose 1,4-naphthoquinone and phenylhydrazine as standard substrates as examples. When to a solution of 1,4-naphthoquinone **1a** and IBX in acetonitrile was added phenylhydrazine **2a** dropwise at room temperature, evolution of gas bubbles was observed during the course of the reaction. We surmised that the gas could be nitrogen generated by oxidation of phenylhydrazine **2a** by IBX. After completion of the reaction, products were analyzed and found as a mixture of 2-phenyl-1,4-naphthoquinone **3a** and 2,3-biphenyl-1,4-naphthoquinone **3h** in 60 and 15%, respectively (Scheme 1).

Scheme 1. Arylation of 1,4-Naphthoquinone Using IBX and Phenylhydrazine



To reduce the possibility of formation of diarylated product, reaction was carried out by using monosubstituted naphthoquinone. When 2-amino-1,4-naphthoquinone **1e** was subjected to the same reaction conditions, 2-amino-3-phenyl-1,4-naphthoquinone **3e** was obtained in good yield of 78%.

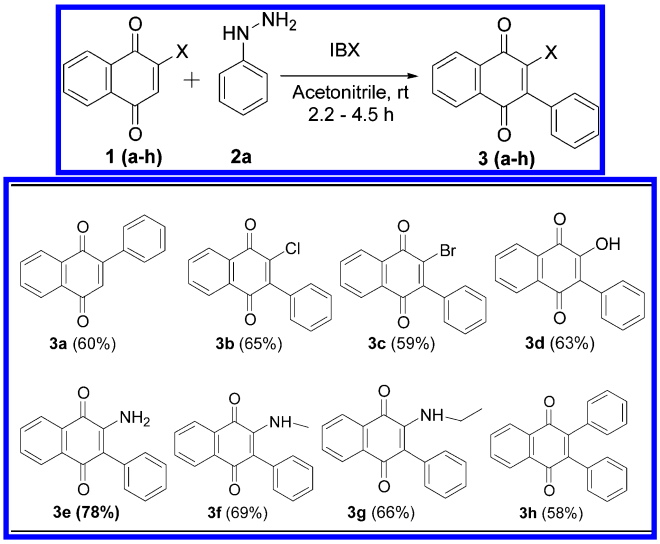
Further optimization was done with respect to feasibility of other hypervalent iodine(V) reagents, solvents, and mole ratio of reactants by keeping 2-amino-1,4-naphthoquinone **1e** as a constant substrate. Hypervalent iodine(V) reagents such as Dess-Martin periodinane (DMP) and iodic acid (HIO_3) were tested against IBX under the same set of reaction conditions. DMP and HIO_3 gave arylated naphthoquinones in 67 and 56%, respectively, in comparison with 78% by IBX. Among the listed solvents such as ACN, DMSO, THF, $CHCl_3$, and toluene, ACN was found to be the best solvent for the arylation. The reaction in DMSO was found to be vigorous and resulted in multiple side products with exothermicity. The inferior yield was observed with toluene (38%), and this might be due to the poor solubility of IBX in it. The best result was obtained with 1.2 equiv of phenylhydrazine and 2.0 equiv of IBX. Further exploration was carried out under optimized reaction conditions.

To demonstrate the substrate scope, a series of 1,4-naphthoquinones having different electronic properties were subjected to arylation and results are depicted in Table 1.

Most arylated naphthoquinones with different electronic properties were obtained in moderate to good yields. The best result was obtained with 2-amino-1,4-naphthoquinone **1e**, while reaction with 2-phenyl-1,4-naphthoquinone **1h** was found to be slower, and this may be due to steric hindrance caused by the phenyl ring present at the C-2 position. Although the substrate scope did not explicate decent chemoselectivity, the results with hydroxy and amino substituted naphthoquinones **1d** and **1e**, respectively, were encouraging while considering the radical quenching nature of hydroxy and amino groups. To illustrate the reactivity of differently substituted arylhydrazines, they were reacted with 2-amino-1,4-naphthoquinones. The reactions went smoothly, and the results are summarized in Table 2.

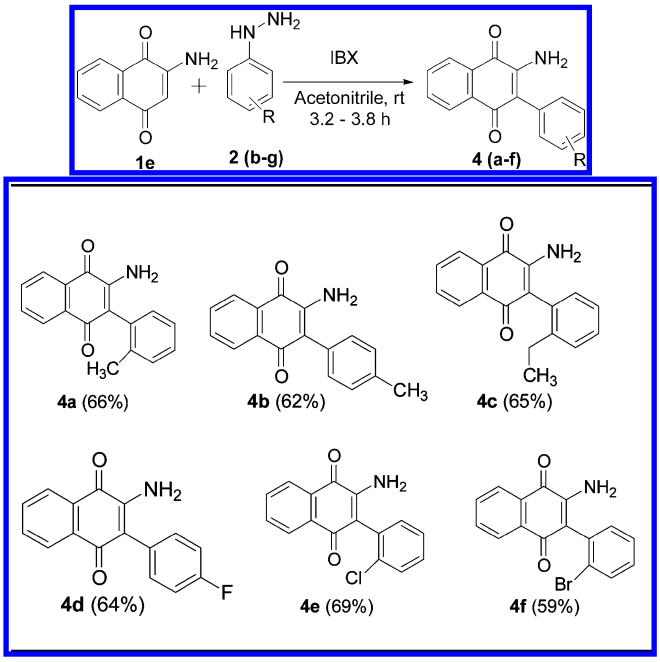
Reactions of 2-amino-1,4-naphthoquinone with differently substituted arylhydrazines provided 59−69% of arylated

Table 1. Arylation of Substituted Naphthoquinones Using IBX[a]



[a]Reaction conditions: naphthoquinones (1 equiv), phenylhydrazine **2a** (1.2 equiv), IBX (2 equiv) in 20 mL of acetonitrile at room temperature. Isolated yield mentioned after column chromatography (silica gel 60-120 mesh size and ethyl acetate/hexane as eluent).

Table 2. Reaction of 2-Amino-1,4-naphthoquinone with Substituted Arylhydrazines[a]



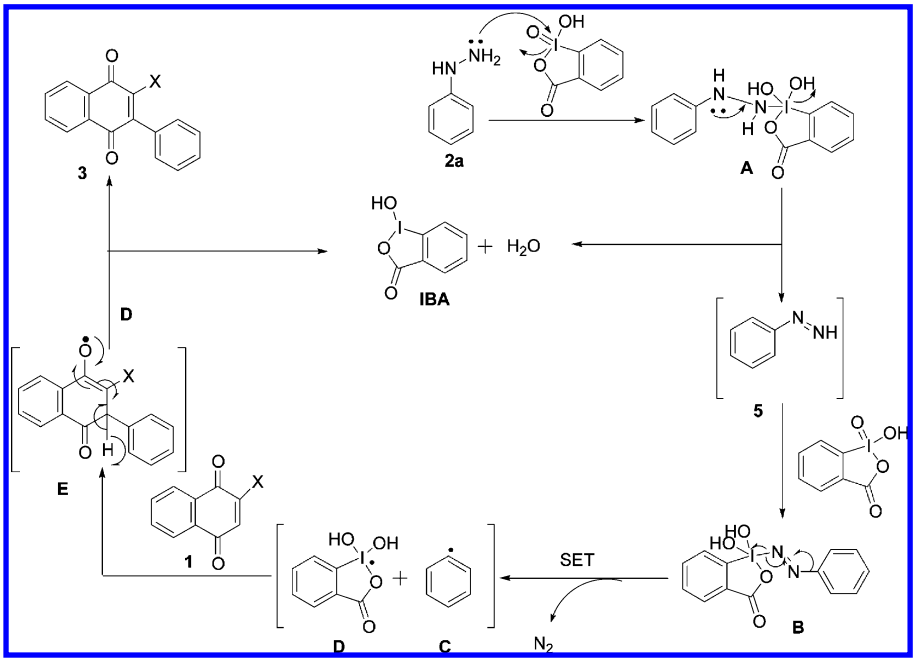
[a]Reaction conditions: 2-amino-1,4-naphthoquinone **1e** (1 equiv), substituted arylhydrazine (**2b−g**) (1.2 equiv), IBX (2 equiv) in 20 mL of acetonitrile at room temperature. Isolated yield mentioned after column chromatography (silica gel 60-120 mesh size and ethyl acetate/hexane as eluent).

naphthoquinones **4a−f**. We hypothesized that oxidative arylation of naphthoquinone could proceed through the intermediary of an aryl radical generated through oxidation of arylhydrazine by IBX. The plausible radical-mediated mechanism is shown in Scheme 2.

Phenylhydrazine **2a** may be attracted toward IBX due to the electrophilic nature of the iodine atom, and subsequent

dx.doi.org/10.1021/jo500131h | J. Org. Chem. 2014, 79, 2331−2336

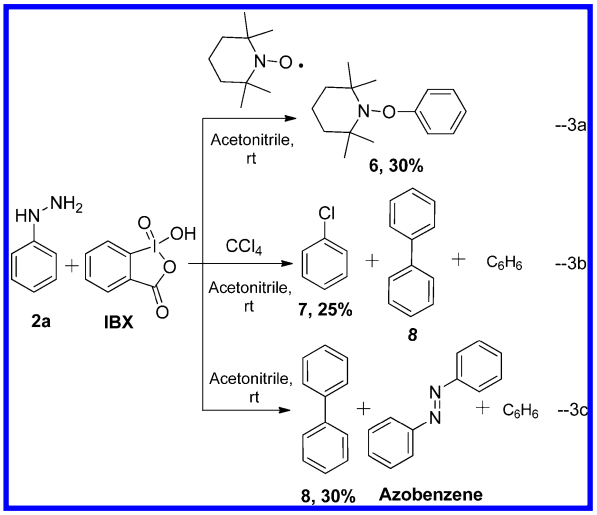
Scheme 2. Postulated Radical-Mediated Mechanism for the Arylation of Naphthoquinones



oxidation ensues, leading to loss of a water molecule from intermediate **A** to produce phenyldiazine **5** and *o*-iodosobenzoic acid (IBA). Being nucleophilic in nature, phenyldiazine would react with another molecule of IBX and form intermediate **B**, which undergoes oxidative cleavage through single electron transfer (SET) to form phenyl radical **C** along with species **D**. The characteristic SET mechanism by IBX was supported by literature.[18] Due to nucleophilic nature of the phenyl radical, it would be attracted to the electrophilic C-2 or C-3 positions of naphthoquinone, and subsequently, through the intermediate **E**, it would produce arylated naphthoquinones **3** along with another molecule of IBA and water. The reaction was carried out in open atmosphere and considered to tolerate a lower percentage of water molecules formed during the progress of the reaction. To understand the further role of IBA in the reaction sequence, a separate experiment was carried out on 2-amino-1,4-naphthoquinone **1e** under optimized reaction conditions but using IBA (prepared by literature method)[19] instead of IBX. It was found that the reaction between IBA and phenylhydrazine **2a** was slow and gave only 30% yield of corresponding arylated compound **3e** after 8 h. Based on this result, IBA would be considered to contribute a least partially to oxidation of arylhydrazine. To support the plausible radical mediated mechanism for arylation of naphthoquinones, experimental evidence was developed (Scheme 3).

Radical trapping experiment was carried out by using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). When phenylhydrazine **2a** was oxidized with IBX in the presence of TEMPO, it produced 1-(2,2,6,6-tetramethylpiperidinyloxy)-benzene **6** in 30% yield (Scheme 3a). When oxidation of phenylhydrazine was carried out using IBX in a mixture of solvents such as acetonitrile and CCl_4, it produced chlorobenzene **7** in 25% yield along with traces of biphenyl **8** and benzene (Scheme 3b). Formation of chlorobenzene **7** could be expected from abstraction of a Cl radical by a phenyl radical present in the reaction mixture. In another experiment, when phenylhydrazine **2a** was oxidized with IBX in acetonitrile in the absence of naphthoquinone, **1a** showed formation of

Scheme 3. Phenyl Radical Trapping Experiments



biphenyl **8** to the extent of 30% along with a small percentage of azobenzene and benzene (Scheme 3c). Formation of **6**, **7**, and **8** along with small percentages of azobenzene and benzene in corresponding radical trapping experiments strongly supports the presence of a phenyl radical as the reactive species in the reaction sequence.

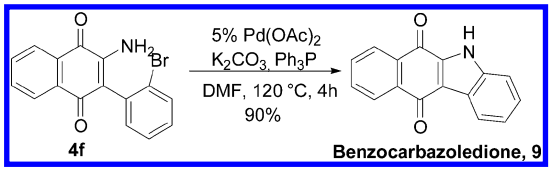
The results obtained during arylation of naphthoquinones particularly with 2-amino-1,4-naphthoquinone **1e** were found potentially applicable toward synthesis of benzocarbazoledione. Benzocarbazolediones are important precursors of anticancer and antibiotic molecules due to the "2-phenylnaphthalene-type" structural pattern.[20] The reported methods for the synthesis of these analogues have common scarcities such as multistep synthesis, use of hazardous reagents, and side product formation.[21] By applying newly developed protocols toward the synthesis of benzocarbazoledione, these limitations were effectively excluded.

When 2-amino-1,4-naphthoquinone **1e** was reacted with 2-bromophenylhydrazine **2g** in the presences of IBX, inter-

dx.doi.org/10.1021/jo500131h | J. Org. Chem. 2014, 79, 2331−2336

mediate **4f** was produced in 59% yield (Table 2), which underwent cyclization in the presence of 5% $Pd(OAc)_2$ in DMF and gave **9** in 90% yield (Scheme 4).

Scheme 4. Synthesis of Benzocarbazoledione



In conclusion, we demonstrated a new method for radical mediated arylation of naphthoquinones using the combination of IBX with arylhydrazines. It does not require transition metal catalysis and prefunctionalization on the naphthoquinone moiety. The reactions occurred under mild conditions in open atmosphere. Further, both 2-hydroxy and 2-amino groups were found to be tolerated under optimized reaction conditions. This fact could be attributed to rapid reaction between IBX and phenylhydrazine. A postulated radical mediated mechanism was supported by radical trapping experiments. Developed protocols were successfully extended toward an effective, short and high yielding synthesis of benzocarbazoledione. IBX-mediated developed protocols for arylation could open a new field in quinone chemistry as well as in the development of new procedures for arylation of electron-deficient molecules in the near future.

EXPERIMENTAL SECTION

General Methods. ^1H and ^{13}C NMR spectra were recorded on 300 and 75 MHz spectrometers, respectively. Chemical shifts are reported as δ values relative to internal chloroform (δ 7.26 for ^1H NMR and 77.0 for ^{13}C NMR), DMSO (δ 2.50 for ^1H NMR and 39.52 for ^{13}C NMR) in parts per million (ppm). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; t, triplet; q, quadruplet; m, multiplet; dt, doublet of triplet; br, broad; for proton spectra, coupling constants (J) are reported in hertz (Hz). Infrared spectra were recorded on an IR spectrometer, and absorption frequencies were reported in reciprocal centimeters (cm^{-1}).

Typical Procedure for Arylation of Naphthoquinones. To a stirred slurry of *o*-iodoxybenzoic acid (2 mmol) in 10 mL of acetonitrile was added naphthoquinones **1** (1 mmol) and stirred for 5 min. To this solution was slowly added a solution of phenylhydrazines **2** (1.2 mmol) dissolved in 10 mL of acetonitrile over a period of 30 min, and stirring was continued at room temperature for 2.2−4.5 h. Evolution of nitrogen gas bubbles was observed during the course of the reaction, and intensity of the same was decreased as the reaction proceeded. Progress of the reaction was monitored by TLC using hexane/EtOAc as a mobile phase. After completion of the reaction, acetonitrile was evaporated under vacuum to obtain residue. To this residue were added ethyl acetate (15 mL) and water (15 mL), followed by saturated sodium bicarbonate solution (10 mL). Separated organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum to obtain a yellow-orange residue, which was chromatographed on silica gel column using hexane/ethyl acetate mobile phase to afford the corresponding pure arylated naphthoquinones **3** and **4**.

2-Phenyl-1,4-naphthoquinone ***3a***.[22] Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc mobile phase (9:1) to give a yellowish solid (140 mg, 60% yield): mp 107−109 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18−8.10 (m, 2H), 7.86−7.75 (m, 2H), 7.56−7.48 (m, 5H), 7.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 185.1, 148.1, 135.2, 133.9, 133.8, 133.3, 132.4, 132.0, 130.5, 130.0, 128.4, 127.6, 125.9; FT-IR (ν) 3059, 1663, 1596, 1490, 1448, 758, and 696 cm^{-1}.

2-Chloro-3-phenyl-1,4-naphthoquinone ***3b***. Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give a yellowish solid (174 mg, 65% yield): mp 108−110 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 4.0 Hz, 1H), 8.15 (d, J = 4.0 Hz, 1H), 7.79 (t, J = 4.5 Hz, 2H), 7.48 (m, 3H), 7.37 (d, J = 4.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.1, 178.2, 145.9, 143.0, 134.4, 134.0, 131.7, 131.6, 131.2, 130.4, 129.5, 129.4, 128.0, 127.5, 127.3, 127.1; FT-IR (ν) 3060, 1671, 1594, 1491, 1443, 755, and 706 cm^{-1}. Anal. Calcd for $C_{16}H_9ClO_2$: C, 71.52; H, 3.38. Found: C, 71.68; H, 3.51.

2-Bromo-3-phenyl-1,4-naphthoquinone ***3c***.[23] Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give a yellowish orange solid (184 mg, 59% yield): mp 82−84 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (dd, J = 8.7 and 4.8 Hz, 1H), 8.16 (dd, J = 8.7 and 4.8 Hz, 1H), 7.80 (t, J = 4.5 Hz, 2H), 7.49 (t, J = 4.0 Hz, 3H), 7.33 (t, J = 4.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 173.8, 149.7, 145.7, 134.4, 134.1, 134.0, 131.5, 131.1, 130.5, 129.7, 129.3, 129.1, 128.0, 127.6, 127.3; FT-IR (ν) 3058, 1661, 1593, 1491, 1443, 755, and 700 cm^{-1}. Anal. Calcd for $C_{16}H_9BrO_2$: C, 61.37; H, 2.90. Found: C, 61.53; H, 3.08.

2-Hydroxy-3-phenyl-1,4-naphthoquinone ***3d***.[24] Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give an orange red solid (157 mg, 63% yield): mp 142−144 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21−8.14 (m, 2H), 7.81−7.73 (m, 2H), 7.50−7.44 (m, 5H), 5.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.70, 181.8, 152.1, 135.2, 133.1, 132.7, 130.5, 129.8, 129.2, 128.6, 127.9, 127.2, 126.1; FT-IR (ν) 3289, 3071, 1674, 1600, 1562, 1512, 1441, 1256, 1162, 730, and 698 cm^{-1}.

2-Amino-3-phenyl-1,4-naphthoquinone ***3e***.[25] Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give an orange red solid (194 mg, 78% yield): mp 172−174 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, J = 16.0 and 6.6 Hz, 2H), 7.70 (dt, J = 12.0 and 8.0 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.41−7.22 (m, 3H), 5.20 (s br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 181.6, 145.0, 134.7, 134.6, 133.1, 132.4, 132.1, 130.4, 129.9, 128.9, 128.1, 126.6, 125.8, 116.8; FT-IR (ν) 3351, 3060, 1658, 1593, 1492, 1460, 1366, 1283, 757, and 693 cm^{-1}.

2-Methylamino-3-phenyl-1,4-naphthoquinone ***3f***.[26] Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give a reddish solid (181 mg, 69% yield): mp 160−162 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, J = 16.0 and 7.5 Hz, 2H), 7.72 (t, J = 7.2 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.36−7.26 (m, 5H), 6.06 (s br, 1H), 2.43 (d, J = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.8, 182.3, 145.1, 134.7, 134.1, 133.4, 131.9, 131.5, 130.1, 127.4, 126.5, 126.0, 114.9, 32.5; FT-IR (ν) 3284, 3060, 1673, 1599, 1555, 1482, 1397, 755, and 697 cm^{-1}.

2-Ethylamino-3-phenyl-1,4-naphthoquinone ***3g***. Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give a reddish solid (182 mg, 66% yield): mp 134−136 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.5 and 3.75 Hz, 1H), 8.07 (dd, J = 7.5 and 3.75 Hz, 1H), 7.72 (t, J = 10.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.38−7.29 (m, 5H), 5.84 (s, 1H), 2.63 (q, J = 6.6 and 6.0 Hz, 2H), 1.03 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.8, 182.3, 144.2, 134.7, 134.3, 133.4, 131.8, 131.2, 130.1, 127.5, 127.4, 126.4, 125.9, 114.9, 39.8, 15.1; FT-IR (ν) 3288, 3060, 1674, 1602, 1564, 1511, 1415, 1345, 728, and 693 cm^{-1}. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.79; H, 5.63; N, 5.27.

2,3-Diphenyl-1,4-naphthoquinone ***3h***.[27] Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give a yellowish solid (179 mg, 58% yield): mp 134−137 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (t, J = 3.3 Hz, 2H), 7.78 (t, J = 3.3 Hz, 2H), 7.22 (m, 6H), 7.08 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7, 145.6, 133.8, 133.1, 132.0, 130.4, 128.1, 127.5, 126.5; FT-IR (ν) 3060, 1671, 1593, 1491, 1443, 1284, 755, and 700 cm^{-1}.

dx.doi.org/10.1021/jo500131h | J. Org. Chem. 2014, 79, 2331−2336

2-Amino-3-(2-toluyl)-1,4-naphthoquinone ***4a***. Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give an orange solid (173 mg, 66% yield): mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (t, J = 8.0 Hz, 2H), 7.70 (dt, J = 10.5 and 7.5 Hz, 2H), 7.32−7.15 (m, 4H), 4.97 (s br, 2H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 181.5, 145.2, 137.3, 134.6, 133.2, 132.1, 131.7, 130.7, 130.5, 129.9, 128.6, 126.6, 126.4, 125.9, 117.2, 19.6; FT-IR (ν) 3449, 3338, 2928, 2854, 3052, 1680, 1601, 1560, 1383, 1280,758 and 721 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.71; H, 5.10; N, 5.53.

2-Amino-3-(4-toluyl)-1,4-naphthoquinone ***4b***. Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give a dark red solid (163 mg, 62% yield): mp 208−210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, J = 7.5 Hz, 2H), 7.69 (dt, J = 11.1 and 7.5 Hz, 2H), 7.27 (dd, J = 7.8 Hz, 4H), 5.19 (s br, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.1, 181.8, 145.0, 137.9, 134.5, 133.1, 132.1, 130.4, 129.8, 129.6, 129.3, 126.6, 125.8, 116.9, 21.3; FT-IR (ν) 3455, 3341, 3060, 2926, 2853, 1673, 1598, 1565, 1513, 1386, 1346, 1307, and 724 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.69; H, 5.16; N, 5.58.

2-Amino-3-(2-ethylphenyl)-1,4-naphthoquinone ***4c***. Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give an orange solid (180 mg, 65% yield): mp 136−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (t, J = 8.4 Hz, 2H), 7.70 (dt, J = 7.0 Hz, 2H), 7.37−7.26 (m, 3H), 7.13 (d, J = 9.0 Hz, 1H), 4.95 (s br, 2H), 2.50 (q, J = 4.2 and 3.0 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.8, 181.7, 145.5, 143.4, 134.6, 133.2, 132.1, 131.1, 130.5, 130.0, 128.9, 128.8, 126.6, 126.5, 125.9, 117.4, 26.4, 15.2; FT-IR (ν) 3414, 3303, 3063, 2964, 2926, 1682, 1596, 1560, 1479, 1397, 1351, 1226, 998, 758, and 723 cm^{-1}. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.83; H, 5.61; N, 5.23.

2-Amino-3-(4-fluorophenyl)-1,4-naphthoquinone ***4d***. Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give a reddish solid (170 mg, 64% yield): mp 134−137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, J = 7.5 and 6.6 Hz, 2H), 7.70 (dt, J = 12.6 and 7.5 Hz, 2H), 7.38−7.16 (m, 4H), 5.20 (s br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 181.0, 145.6, 134.7, 133.1, 132.3, 132.1, 132.0, 130.5, 130.4, 126.7, 126.0, 124.6, 124.5, 116.4, 116.1; FT-IR (ν) 3426, 3305, 3061, 1677, 1596, 1561, 1489, 1446, 1398, 1351, 1225, 1000, 759, and 721 cm^{-1}. Anal. Calcd for $C_{16}H_{10}FNO_2$: C, 71.91; H, 3.77; N, 5.24. Found: C, 71.70; H, 3.95; N, 5.09.

2-Amino-3-(2-chlorophenyl)-1,4-naphthoquinone ***4e***. Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give an orange solid (195 mg, 69% yield): mp 182−185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, J = 7.8 and 3.6 Hz, 2H), 7.71 (dt, J = 11.4 and 7.5 Hz, 2H), 7.53 (t, J = 6.3 Hz, 2H), 7.38−7.28 (m, 2H), 5.06 (s br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.5, 181.0, 145.4, 145.3, 134.7, 133.1, 132.3, 132.0, 131.3, 130.4, 130.1, 129.9, 127.4, 126.7, 126.0, 117.4; FT-IR (ν) 3476, 3331, 3083, 1684, 1607, 1565, 1472, 1398, 844, 792, 757, and 726 cm^{-1}. Anal. Calcd for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; N, 4.94. Found: C, 67.53; H, 3.63; N, 5.06.

2-Amino-3-(2-bromophenyl)-1,4-naphthoquinone ***4f***. Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (7:3) to give an orange-brown solid (192 mg, 59% yield): mp 196−199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13−8.07 (m, 2H), 7.75−7.74 (m, 2H), 7.49−7.34 (m, 4H), 5.21 (s br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.5, 180.9, 145.0, 134.9, 134.7, 133.6, 133.3, 132.7, 132.3, 131.9, 130.1, 128.0, 127.2, 126.7, 126.0, 116.9. FT-IR (ν) 3339, 1683, 1605, 1571, 1458, 1399, 1351, 1276, 757, and 721 cm^{-1}. Anal. Calcd for $C_{16}H_{10}BrNO_2$: C, 58.56; H, 3.07; N, 4.27. Found: C, 58.43; H, 3.19; N, 4.42.

5H-Benzo[b]carbazole-6,11-dione ***9***.[28] A mixture of **4f** (1.0 mmol), Pd $(OAc)_2$ (0.05 mmol), Ph_3P (0.1 mmol), and K_2CO_3 (3.0 mmol) in dry DMF (15 mL) under N_2 atmosphere was heated to 120 °C for 4 h. Reaction mixture was cooled to room temperature. The reaction mixture was partitioned between EtOAc (30 mL) and H_2O (30 mL). Separated aqueous phase was extracted with EtOAc (2 × 25 mL) and combined with the previous fraction. The combined organic extracts washed with brine (25 mL), dried (Na_2SO_4), and filtered. The solvents were evaporated. The obtained residue was purified by column chromatography to afford an orange solid (222 mg, 90% yield): mp 311−313 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.09 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.14−8.10 (m, 2H), 7.89−7.81 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.46 (ddd, J = 8.0 Hz, 1H), 7.38 (ddd, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 181.7, 144.1, 135.03, 134.6, 133.1, 132.6, 130.5, 130.4, 127.8, 126.7, 126.2, 123.1, 104.4; FT-IR (ν) 3307, 3038, 1672, 1620, 1589, 1531, 1343, and 739 cm^{-1}.

Preparation of Starting Compounds. Compounds 1,4-naphthoquinone **1a** and 2-hydroxy-1,4-naphthoquinone **1d** were purchased from commercial sources and used as received. 2-Phenyl-1,4-naphthoquinone **1h** was synthesized by the method described in this paper and used as a starting material after characterization. Remaining starting compounds were synthesized using literature procedures.

2-Chloro-1,4-naphthoquinone ***1b***:[29] Yellowish solid (83% yield); mp 114−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (t, J = 4.8 Hz, 1H), 8.09 (t, J = 4.8 Hz, 1H), 7.79 (t, J = 4.5 Hz, 2H), 7.23 (s, 1H); FT-IR (ν) 1678, 1654, 1585, 1559, 1273, and 701 cm^{-1}.

2-Bromo-1,4-naphthoquinone ***1c***:[30] Brown solid (78% yield); mp 130−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20−8.17 (m, 1H), 8.10−8.08 (m, 1H), 7.81−7.75 (m, 2H), 7.53 (s, 1H); FT-IR (ν) 1678, 1658, 1589, 1569, 1292, 1244, and 694 cm^{-1}.

2-Amino-1,4-naphthoquinone ***1e***:[31] Reddish solid (68% yield); mp 205−206 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.96 (t, J = 7.8 Hz, 2H), 7.74 (t, J = 7.2 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 6.94 (s br, 2H), 5.89 (s, 1H); FT-IR (ν) 3410, 3178, 1612, 1557, 1495, 1418, 1269, 984, and 723 cm^{-1}.

2-Methylamino-1,4-naphthoquinone ***1f***:[32] Reddish solid (65% yield); mp 232−234 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J = 12.3 and 7.5 Hz, 2H), 7.73 (t, J = 7.2 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 5.95 (s, 1H), 5.72 (s, 1H), 2.93 (d, J = 5.1 Hz, 3H). FT-IR (ν) 3380, 2856, 1613, 1598, 1586, and 1420 cm^{-1}.

2-Ethylamino-1,4-naphthoquinone ***1g***:[33] Reddish solid (72% yield); mp 140−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J = 10.2 and 7.5 Hz, 2H), 7.72 (t, J = 7.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 5.84 (s, 1H), 5.73 (s, 1H), 3.27−3.18 (m, 2H), 1.34 (t, J = 7.5 Hz, 3H); FT-IR (ν) 3378, 2928, 2859, 1623, 1608, 1578, and 1450 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the TEQIP (P.P.) and CSIR (A.N.) for financial support of this research. We are also thankful to M/s Omkar Speciality Chemicals Ltd., Badlapur, Mumbai, for the generous gift of IBX.

■ REFERENCES

(1) (a) *The Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988; Vol. 2, Parts 1 and 2. (b) Thomson, R. H. *Naturally Occuring Quinones IV*; Blackie Academic: London,

1997. (c) Verma, R. P. *Anti-Cancer Agents Med. Chem.* **2006**, *6*, 489 and references cited therein.
(2) (a) Foye, M. O. *Cancer Chemotherapeutic Agents*; American Chemical Society: Washington, DC, 1995. (b) Leopold, W. R.; Shillis, J. L.; Mertus, A. E.; Nelson, J. M.; Roberts, B. J.; Jackson, R. C. *Cancer Res.* **1984**, *44*, 1928.
(3) (a) Li, Z.; Gao, Y.; Tang, Y.; Dai, M.; Wang, G.; Wang, Z.; Yang, Z. *Org. Lett.* **2008**, *10*, 3017. (b) Lumb, G.; Trauner, D. *Org. Lett.* **2005**, *7*, 5865. (c) Yin, J.; Liebeskind, L. S. *J. Org. Chem.* **1998**, *63*, 5726 and references cited therein. (d) Narayan, S.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3789. (e) Wang, W.; Xue, J.; Tian, T.; Zhang, J.; Wei, L.; Shao, J.; Xie, Z.; Li, Y. *Org. Lett.* **2013**, *15*, 2402. (f) Maruo, S.; Nishio, K.; Sasamori, T.; Tokitoh, N.; Kuramochi, K.; Tsubaki, K. *Org. Lett.* **2013**, *15*, 1556. (g) Kuttruff, C. A.; Geiger, S.; Cakmak, M.; Mayer, P.; Trauner, D. *Org. Lett.* **2012**, *14*, 1070.
(4) Babich, H.; Stern, A.; Munday, R. *Toxicol. Lett.* **1993**, *69*, 69.
(5) Bechtold, T. In *Handbook of Natural Colorants*; Bechtold, T., Mussakm, R., Eds.; Wiley: New York, 2009; pp 151−182.
(6) (a) Harrity, J. P. A.; Kerr, W. J.; Middlemiss, D.; Scott, J. S. *J. Organomet. Chem.* **1997**, *532*, 219 and references cited therein. (b) El Hage, S.; Ane, M.; Stigliani, J. L.; Marjorie, M.; Vial, H.; Baziard-Mouysset, G.; Payard, M. *Eur. J. Med. Chem.* **2009**, *44*, 4778. (c) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1998**, *39*, 7629. (d) Bonifazi, E. L.; Ríos-Luci, C.; León, L. G.; Burton, G.; Padrón, J. M.; Misico, R. I. *Bioorg. Med. Chem.* **2010**, *18*, 2621. (e) Akman, S. A.; Dietrich, M.; Chlebowski, R.; Limberg, P.; Block, J. B. *Cancer Res.* **1985**, *45*, 5257. (f) Rajendra Prasad, K.; Suresh Babu, K.; Ranga Rao, R.; Suresh, G.; Rekha, K.; Madhusudana Murthy, J.; Usha Rani, P.; Madhusudana Rao, J. *Med. Chem. Res.* **2012**, *21*, 578 and references cited therein.
(7) (a) Corson, B. B.; Heintzelman, W. J.; Moe, H.; Rousseau, C. R. *J. Org. Chem.* **1962**, *27*, 1636. (b) Pluim, H.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 2498. (c) Janowski, W. K.; Prager, R. H. *Aust. J. Chem.* **1985**, *38*, 921.
(8) (a) Hutchinson, E. J.; Kerr, W. J.; Magennis, E. J. *Chem. Commun.* **2002**, *19*, 2262. (b) Liebeskind, L. S.; Baysdon, S. L.; South, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7397.
(9) (a) Coppa, F.; Fontana, F.; Minisci, F.; Nogueira Barbosa, M. C.; Vismara, E. *Tetrahedron* **1991**, *47*, 7343. (b) Lin, A. J.; Sartorelli, A. T. *J. Med. Chem.* **1976**, *19*, 1336. (c) Wurm, G.; Gurka, H. J. *Pharmazie* **1997**, *52*, 739. (d) Fieser, L. F.; Berliner, E.; Bondhus, F. J.; Chang, F. C.; Dauben, W. G.; Ettlinger, M. G.; Fawaz, G.; Fields, M.; Heidelberger, C.; Heymann, H.; Vaughan, W. R.; Wilson, A. G.; Wilson, E.; Wu, M.; Leffler, M. T.; Hamlin, K. E.; Matson, E. J.; Moore, E. E.; Moore, M. B.; Zaugg, H. E. *J. Am. Chem. Soc.* **1948**, *70*, 3174.
(10) (a) Itahara, T. *J. Chem. Soc., Chem. Commun.* **1981**, 859. (b) Itahara, T. *J. Org. Chem.* **1985**, *50*, 5546. (c) Itahara, T. *Chem. Ind.* **1982**, *16*, 599.
(11) (a) Tamayo, N.; Echavarren, A. M.; Carmen Pardes, M. *J. Org. Chem.* **1991**, *56*, 6488. (b) Echavarren, A. M.; de Frutos, O.; Tamayo, N.; Noheda, P.; Calle, P. *J. Org. Chem.* **1997**, *62*, 4524.
(12) Singh, P. K.; Rohtagi, B. K.; Khanna, R. N. *Synth. Commun.* **1992**, *22*, 987.
(13) (a) Papoutsis, I.; Spyroudis, S.; Varvoglis, A.; Raptopoulou, C. A. *Tetrahedron* **1997**, *53*, 6097. (b) Papoutsis, I.; Spyroudis, S.; Varvoglis, A. *Tetrahedron Lett.* **1996**, *37*, 913. (c) Kazantzi, G.; Malamidou-Xenikaki, E.; Spyroudis, S. *Synlett* **2006**, 2597. (d) Glinis, E.; Malamidou-Xenikaki, E.; Skouros, H.; Spyroudis, S.; Tsanakopoulou, M. *Tetrahedron* **2010**, *66*, 5786.
(14) (a) Komeyama, K.; Kashihara, T.; Takaki, K. *Tetrahedron Lett.* **2013**, *54*, 1084. (b) Wang, J.; Wang, S.; Wang, G.; Zhang, J.; Yu, X. *Chem. Commun.* **2012**, *48*, 11769. (c) Mai, W.-P.; Yuan, J.-W.; Li, Z.-C.; Sun, G.-C.; Qu, L.-B. *Synlett* **2012**, 145. (d) Lockner, J. W.; Dixon, D. D; Risgaard, R.; Baran, P. S. *Org. Lett.* **2011**, *13*, 5628. (e) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Bel, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292. (f) Uchiyama, N.; Shirakawa, E.; Nishikawa, R.; Hayashi, T. *Chem. Commun.* **2011**, *47*, 11671. (g) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194.
(15) (a) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524 and references cited therein. (b) Satam, V.; Harad, A.; Rajule, R.; Pati, H. *Tetrahedron* **2010**, *66*, 7659 and references cited therein. (c) Granger, B. A.; Jewett, I. T.; Butler, J. D.; Hua, B.; Knezevic, C. E; Parkinson, E. I.; Hergenrother, P. J.; Martin, S. F. *J. Am. Chem. Soc.* **2013**, *135*, 12984. (d) Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 13964. (e) Yadav, J. S.; Rajendar, G.; Rao, R. S.; Pabbaraja, S. *J. Org. Chem.* **2013**, *78*, 8524. (f) Abed, H.; Mammoliti, O.; Bande, O.; Lommen, G.; Herdewijn, P. *J. Org. Chem.* **2013**, *78*, 7845. (g) Zhu, L.; Zhou, C.; Yang, W.; He, S.; Cheng, G.; Zhang, X.; Lee, C. *J. Org. Chem.* **2013**, *78*, 7912. (h) Yadav, J. S.; Goreti, R.; Pabbaraja, S.; Sridhar, B. *Org. Lett.* **2013**, *15*, 3782.
(16) (a) Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G. *J. Org. Chem.* **2003**, *68*, 5422. (b) Bhalerao, D. S.; Mahajan, U. S.; Chaudhari, K. H.; Akamanchi, K. G. *J. Org. Chem.* **2007**, *72*, 662. (c) Bellale, E. V.; Bhalerao, D. S.; Akamanchi, K. G. *J. Org. Chem.* **2008**, *73*, 9473. (d) Patil, P. C.; Bhalerao, D. S.; Dangate, P. S.; Akamanchi, K. G. *Tetrahedron Lett.* **2009**, *50*, 5820. (e) Chaudhari, P. S.; Pathare, S. P.; Akamanchi, K. G. *J. Org. Chem.* **2012**, *77*, 3716.
(17) Jadhav, R. R.; Huddar, S. N.; Akamanchi, K. G. *Eur. J. Org. Chem.* **2013**, *30*, 6779.
(18) (a) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 2245. (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233. (d) Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y. L.; Sugita, K.; Zou, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 202.
(19) Shefter, E.; Wolf, W. *J. Pharm. Sci.* **1965**, *54*, 104.
(20) (a) Cheng, C. C.; Dong, Q.; Liu, D.-F.; Luo, Y.-L.; Liu, L. F.; Chen, A. Y.; Yu, C.; Savaraj, N.; Chou, T.-C. *J. Med. Chem.* **1993**, *36*, 4108. (b) Cheng, C. C. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elsevier (Biomedical Division): Amsterdam, 1988; Vol. 25, pp 35−83. (c) Choi, T. A.; Czerwonka, R.; Frchner, W.; Krahl, M. P.; Reddy, K. R.; Franzblau, S. G.; Knolker, H.-J. *ChemMedChem* **2006**, *1*, 812.
(21) (a) Knölker, H.-J.; O'Sullivan, N. *Tetrahedron Lett.* **1994**, *35*, 1695. (b) Alves, G. B. C.; Azevedo, M. S.; Lopes, R. S. C.; Lopes, C. C.; Cardoso, J. N. *Beilstein J. Org. Chem.* **2006**, *2*, No. 1. (c) Bernardo, P. H.; Chai, C. L.; Heath, G. A.; Mahon, P. J.; Smith, G. D.; Waring, P.; Wilkes, B. A. *J. Med. Chem.* **2004**, *47*, 4958. (d) Knölker, H.-J.; O'Sullivan, N. *Tetrahedron* **1994**, *50*, 10893. (e) Kobayashi, K.; Taki, T.; Kawakita, M.; Uchida, M.; Morikawa, O.; Konishi, H. *Heterocycles* **1999**, *51*, 349.
(22) Dawood, K. M. *Tetrahedron* **2007**, *63*, 9642.
(23) Fieser, L. F.; Bader, A. R. *J. Am. Chem. Soc.* **1951**, *73*, 681.
(24) Martínez, A.; Fernández, M.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **2005**, *61*, 485.
(25) Hadden, M. K.; Hill, S. A.; Davenport, J.; Matts, R. L.; Blagg, B. S. J. *Bioorg. Med. Chem.* **2009**, *17*, 634.
(26) Forrester, A. R.; Ingram, A. S.; John, L.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1115.
(27) Irvine, S.; Kerr, W. J.; McPherson, A. R.; Pearson, C. M. *Tetrahedron* **2007**, *64*, 926.
(28) Liegault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022.
(29) Perumal, P. T.; Bhatt, M. V. *Tetrahedron Lett.* **1979**, *33*, 3099.
(30) Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91.
(31) Zhang, J.; Chang, C.-W. T. *J. Org. Chem.* **2009**, *74*, 4414.
(32) Valente, C.; Moreira, R.; Guedes, R. C.; Lley, J.; Jaffar, M.; Douglas, K. T. *Bioorg. Med. Chem.* **2007**, *15*, 5340.
(33) Lohmann, U.; Hartke, K. *Arch. Pharm.* **1984**, *317*, 313.