A Mild and Simple Method for the Synthesis of Substituted Phenazines

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Abstract: A mild, simple, and general method has been developed for the synthesis of phenazines by cross-coupling of benzoquinones with *o*-phenylenediamines. Benzoquinones and *o*-phenylenediamines reacted smoothly to give the corresponding cross-coupled products in good to excellent yields. 1,4-Naphthoquinone also coupled with *o*-phenylenediamines in the presence of copper acetate at 50 °C to give the corresponding benzo[*a*]phenazines. All reactions could be carried out under air.

Key words: cross-coupling, quinones, amines, heterocycles, cyclization, polycycles, catalysis, copper

Phenazines are an important class of compounds with diverse biological activities, such as antibacterial, antifungal, antiviral, antiparasitic, antimalarial, neuroprotectant, and antitumor properties.[1] In addition, phenazines are used in dyes, as building blocks for the synthesis of organic semiconductors, and as chemically controllable switches, cavitands, DNA-cleaving agents, and dehydroannulenes.[2] In nature, phenazines are generally produced by microorganisms,[3] and their role in the virulence and competitive fitness of such organisms has been reviewed by Kerr.[4] In 2004, Laursen and Nielsen reviewed natural and synthetic phenazines, including their biosynthesis and biological activity.[5] Six methods for synthesizing these systems have been developed (Scheme 1);[6] however, most of these methods have severe limitations with respect to the substrates, and no efficient and general method for the synthesis of phenazine derivatives has been reported in the literature.

Our interest in the synthesis of bioactive heterocycles,[7] together with a recent report by Garden and co-workers on a copper-catalyzed oxidative coupling of anilines with 1,4-naphthoquinone through C–H activation,[8] prompted us to consider that coupling of quinones with *o*-phenylenediamines might provide an alternative route for the synthesis of phenazine scaffolds. We have therefore developed a general, mild, and efficient method for the synthesis of phenazine derivatives by the direct coupling of *o*-phenylenediamines with quinones. We found that 1,4-benzoquinone couples efficiently with *o*-phenylenediamines to give good to excellent yields of the corresponding products, whereas the corresponding coupling reactions of 1,4-naphthoquinone required the presence of copper(II) acetate as a catalyst.

Initially, when we attempt the reaction of 1,4-benzoquinone (**1a**) with benzene-1,2-diamine (**2a**) in the presence of copper(II) acetate as catalyst under air at room temperature, coupling occurred rapidly to give phenazin-2-ol (**3a**) and 5,12-dihydroquinoxalino[2,3-*b*]phenazine (**4a**) (Table 1, entry 1). In a control experiment, we found that coupling occurred even in the absence of copper(II) acetate (entry 2). Further optimization towards the predominant formation of either product **3a** or **4a** was studied (entries 3–5). At a low temperature and with one equivalent of diamine **2a**, phenazin-2-ol (**3a**) was obtained as the major product together with minor amounts of **4a** (entry 4). When 1,4-benzoquinone was coupled with two equivalents of diamine **2a** at room temperature, quinoxalinophenazine **4a** was obtained as the major product (entry 5), together with traces of phenazin-2-ol (**3a**). The use of other solvents, such as methanol, ethanol, tetrahydrofuran, dichloromethane, and *N*,*N*′-dimethylformamide was also examined (entries 6–10). Coupling in polar solvents such as methanol, ethanol, tetrahydrofuran, or *N*,*N*-dimethylformamide occurred with almost equal efficiency to that observed in acetic acid. The optimal conditions for the synthesis of phenazine (**3a**) involve treating 1,4-benzoquinone (**1a**) with one equivalent of diamine **2a** in acetic acid at –10 °C (entry 4), whereas the reaction of **1a** with two equivalents **2a** at room temperature in acetic acid gave 5,12-dihydroquinoxalino[2,3-*b*]phenazine (**4a**) (entry 5).

The structure of product **3a** (enol-imine) was confirmed by NMR spectroscopy (^{1}H, ^{13}C DEPT, ^{1}H–^{1}H COSY; see SI) and by comparison with values reported in the literature.[1c] The possibility of a keto-amine structure of product **3a** was ruled out based on the ^{13}C NMR signal at δ = 160.94 ppm, which showed the presence of a hydroxyl group at the 2-position. Moreover, Zendah et al.[1c] have isolated closely related keto-amine phenazine derivatives, viz. chromophenazines, where the carbonyl-containing phenazine **7** and **8** showed a chemical shift at δ = 183.9 and 181.9 ppm in the ^{13}C NMR spectra corresponding to the C=O group (Fig. 1). Gomez et al.[1d] studied the tautomerism of quinoxalines derivatives **9** and **10**, where the hydroxyl-containing phenazine **10** showed a signal at δ = 151 ppm in the ^{13}C NMR spectrum corresponding to a carbon attached to a hydroxyl group (normally expected in the range of 160–170 ppm). In the ^{13}C NMR, there is no

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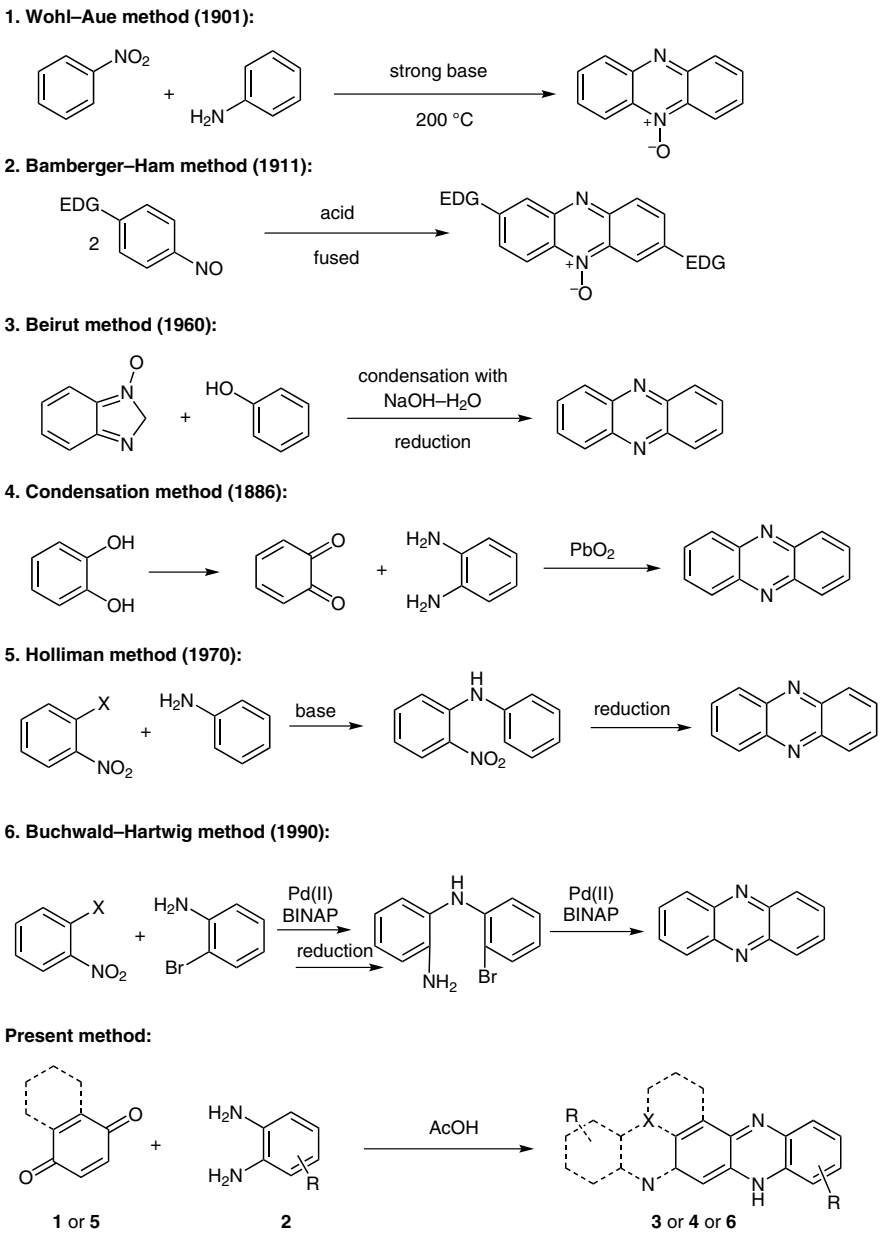

Scheme 1 Methods (reported and present) for the synthesis of phenazine and its derivatives (EDG = electron-donating group)

signal beyond 180 ppm and the presence of signal at δ = 161 ppm shows the existence of an enol-imine structure for the synthesized phenazine derivatives **3**.

To assess the scope of the present method, we examined the reactions of various 1,4-benzoquinones **1a**–**c** with various *ortho*-phenylenediamines **2a**–**c**, and we obtained excellent results (Table 2). *o*-Phenylenediamines containing electron-withdrawing groups (**2b**, R = NO_2, **2c**, R = CO_2H) coupled efficiently with 1,4-benzoquinone (**1a**) to give the corresponding phenazine derivatives **3b** and **3c** in 75% and 74% yields respectively (Table 2, entries 1 and 2). Mono- and disubstituted-1,4-benzoquinones **1b** and **1c** also coupled smoothly with phenylenediamines to give the corresponding phenazine derivatives **3d**–**h** (entries 3–7). In the case of benzoquinone **1b**, higher yields of the coupled phenazines **3d** and **3e** were obtained (entries 3 and 4), presumably due to suppression of double coupling to give the corresponding quinoxalino[2,3-*b*]phenazine product **4**.

When 1,4-naphthoquinone (**5**) was used as the coupling partner under the optimized conditions, no coupling reaction was observed. However, when we attempted to couple 1,4-naphthoquinone (**5**) with diamine **2a** in the presence of copper(II) acetate at 50 °C, we obtained the coupled product **6a** in 78% isolated yield (Table 3, entry 1). 1,4-Naphthoquinone (**5**) also coupled smoothly with the substituted *ortho*-phenylenediamines **2b** and **2c** to give the corresponding cross-coupled products **6b** and **6c** in excellent yields (entries 2 and 3).

In summary, we have developed a mild and general method for the synthesis of phenazines **3** and benzo[*a*]phen-

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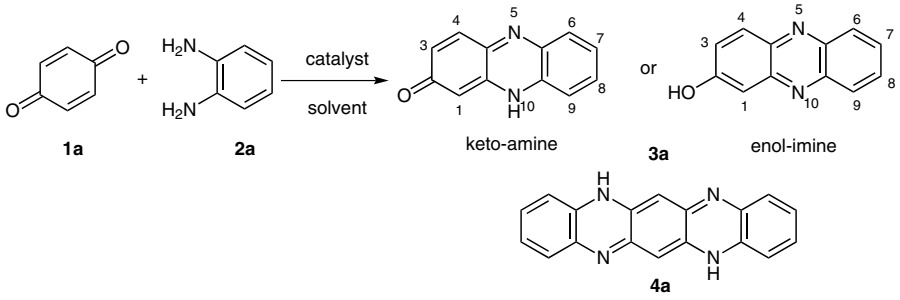
Table 1 Optimization of Reaction Conditions for the Cross-Coupling of 1,4-Benzoquinone (**1a**) and Benzene-1,2-diamine (**2a**)



1a **2a** **3a** **4a**

Entry[a]	Catalyst	Solvent	Temp (°C)	Time (min)	Yield[b]	
					3a	**4a**
1	$Cu(OAc)_2$[c]	AcOH	r.t.	20	20	80
2	–	AcOH	r.t.	20	20	80
3	–	AcOH	0	75	75	20
4	–	AcOH	–10	86	86	10
5[d]	–	AcOH	r.t.	5	5	90
6	–	MeOH	–10	84	84	12
7	–	EtOH	–10	85	85	10
8	–	THF	–10	81	81	13
9	–	CH_2Cl_2	–10	20	20	–
10	–	DMF	–10	50	50	15

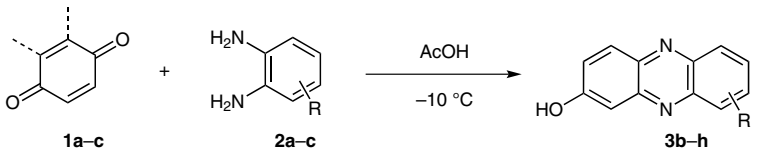
[a] Reaction conditions (unless otherwise stated): 1,4-benzoquinone **1a** (1 mmol), diamine **2a** (1 mmol).
[b] Product composition determined by HPLC.
[c] $Cu(OAc)_2$ (20 mol%).

azines **6** by cross-coupling of the appropriate quinone with an *o*-phenylenediamine. Substituted and unsubstituted quinones reacted smoothly with substituted or unsubstituted *o*-phenylenediamines to give the corresponding cross-coupled products in good to excellent yields.

Phenazines 3; General Procedure

o-Phenylenediamine 2 (1 mmol) was added in a portionwise manner to a solution of benzoquinone 1 (1 mmol) in dry AcOH (5 mL) at –10 °C, and the mixture was stirred continuously for the appropriate time (Table 2). When the reaction was complete (TLC), the mixture was diluted with ice-cold H_2O (50 mL) and neutralized with sat. aq $NaHCO_3$. The product was extracted with CH_2Cl_2 (3 × 30 mL), and the organic extracts were combined, dried (Na_2SO_4), concentrated in vacuo, and filtered. The residue was purified by flash column chromatography (silica gel, *n*-hexane–ethyl acetate, 90:10 to 40:60) to give the coupled product 3. All products were characterized by NMR and mass spectroscopy, and the spectroscopic data for the products agreed with those reported in the literature.

Table 2 Synthesis of Phenazines **3** by Coupling of Benzoquinones **1** with *o*-Phenylenediamines **2**



1a–c **2a–c** **3b–h**

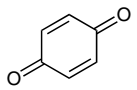
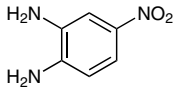
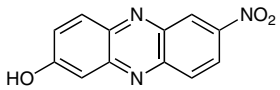
Entry[a]	Benzoquinone	Diamine	Time (min)	Product	Yield (%)[b]
1			90		75
	1a	**2b**		**3b**	

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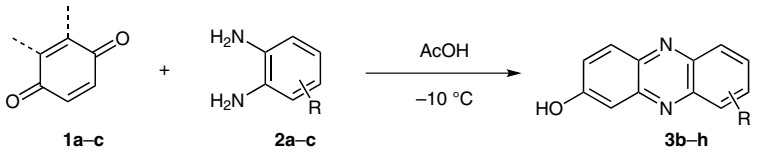
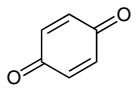
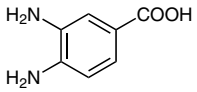
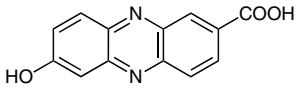
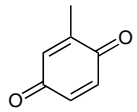
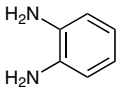
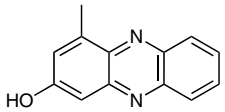
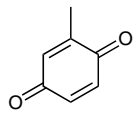
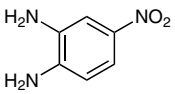
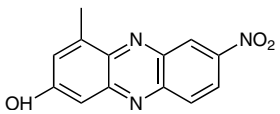
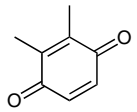
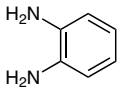
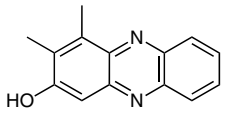
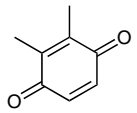
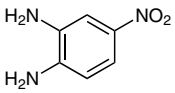
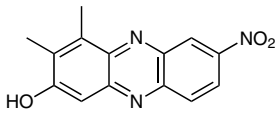
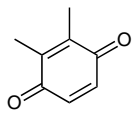
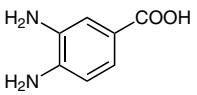
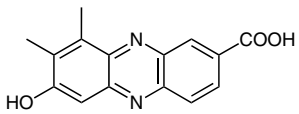
Table 2 Synthesis of Phenazines **3** by Coupling of Benzoquinones **1** with *o*-Phenylenediamines **2** (continued)

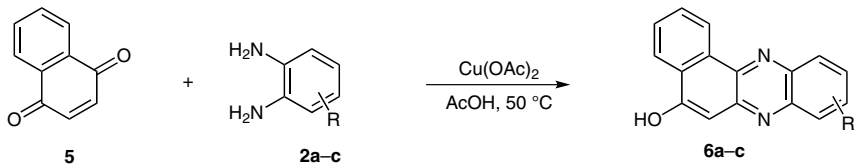


1a–c **2a–c** **3b–h**

Entry[a]	Benzoquinone	Diamine	Time (min)	Product	Yield (%)[b]
2	 **1a**	 **2c**	90	 **3c**	74
3	 **1b**	 **2a**	80	 **3d**	85
4	 **1b**	 **2b**	60	 **3e**	83
5	 **1c**	 **2a**	60	 **3f**	84
6	 **1c**	 **2b**	60	 **3g**	80
7	 **1c**	 **2c**	60	 **3h**	78

[a] Reaction conditions: Benzoquinone **1** (1 mmol), *o*-phenylenediamine **2** (1 mmol), AcOH (5 mL), under O_2.
[b] Isolated yield.

Table 3 Synthesis of Benzo[*a*]phenazines **6** by Coupling of 1,4-Naphthoquinone (**5**) with *o*-Phenylenediamines **2** at 50 °C



5 **2a–c** **6a–c**

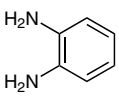
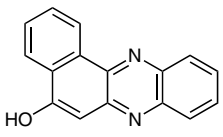
Entry[a]	Diamine	Time (min)	Product	Yield (%)[b]
1	 **2a**	8	 **6a**	78

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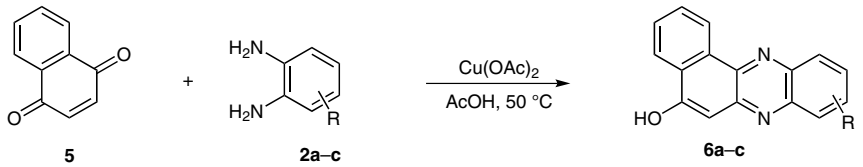
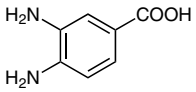
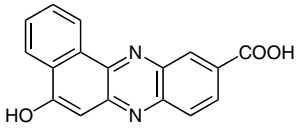
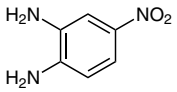
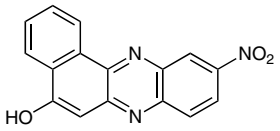
Table 3 Synthesis of Benzo[*a*]phenazines **6** by Coupling of 1,4-Naphthoquinone (**5**) with *o*-Phenylenediamines **2** at 50 °C (continued)



Entry[a]	Diamine	Time (min)	Product	Yield (%)[b]
2	 **2b**	10	 **6b**	75
3	 **2c**	10	 **6c**	70

[a] Reaction conditions: 1,4-naphthoquinone **5** (1 mmol), *o*-phenylenediamine **2** (1 mmol), $Cu(OAc)_2$ (20 mol%), AcOH (5 ml), 50 °C, under O_2.
[b] Isolated yield.

7-Nitrophenazin-2-ol (3b)
Yellow-brown solid; yield: 180 mg (75%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.85 (s, 1 H), 7.40 (d, *J* = 2.5 Hz, 1 H), 7.71–7.75 (dd, *J* = 2.6 and 9.4 Hz, 1 H), 8.20 (d, *J* = 9.4 Hz, 1 H), 8.41 (d, *J* = 9.4 Hz, 1 H), 8.45–8.49 (dd, *J* = 2.4 and 9.4 Hz, 1 H), 8.97 (d, *J* = 2.3 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.9, 149.6, 147.9, 146.0, 142.3, 141.1, 131.5, 131.1, 129.1, 125.0, 121.4, 115.6. HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{12}H_8N_3O_3$: 242.0566; found: 242.05639.

Benzo[*a*]phenazines 6; General Procedure
1,4-Naphthoquinone (**5**; 1 mmol) and *o*-phenylenediamine **2** (1 mmol) were dissolved in anhyd AcOH (5 mL), and $Cu(OAc)_2$ (0.20 mmol) was added under O_2 at r.t. The mixture was then heated at 50 °C for the appropriate time (Table 3). When the reaction was complete (TLC), the mixture was diluted with ice-cold H_2O (20 mL) and neutralized with sat. aq $NaHCO_3$. The product was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layers were combined, dried (Na_2SO_4), concentrated in vacuo, and filtered. The residue was purified by flash column chromatography (silica gel, *n*-hexane–ethyl acetate, 90:10 to 40:60) to give the benzo[*a*]phenazine product **6**. The products were characterized by NMR and mass spectroscopy, and the spectroscopic data of the compounds agreed with those reported in the literature (Figure 1).

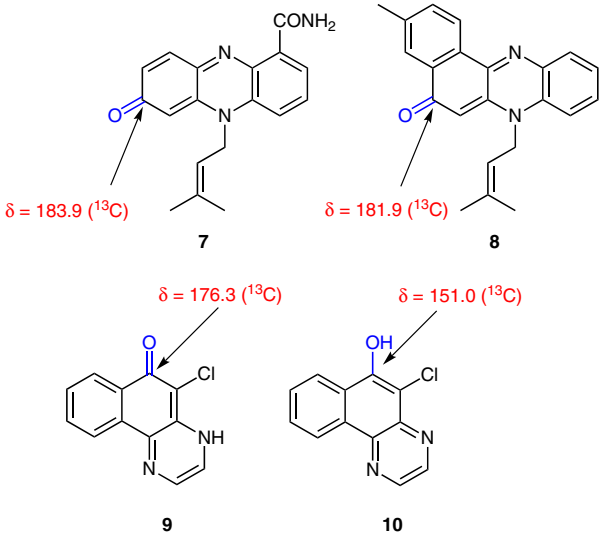


Figure 1 Structures of known phenazines with ^{13}C NMR chemical shifts (ppm)

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