

**Aluminum Chloride-Induced  
Heteroarylation of Arenes and  
Heteroarenes. 2. A New Synthesis of  
4-Substituted Phthalazin-1(2H)-ones<sup>†,1</sup>**

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**Abstract:** We herein report the efficient syntheses of 4-(hetero)aryl-substituted 1-chlorophthalazines via heteroarylation of arenes/heteroarenes through  $\text{AlCl}_3$ -induced C–C bond formation reactions. A number of (hetero)arenes were reacted with 1,4-dichlorophthalazine to give aryl/heteroaryl-substituted phthalazines in good to excellent yields. Many of them were converted to the corresponding phthalazin-1(2H)-ones.

4-Substituted 2*H*-phthalazin-1-ones of structure **A** (Figure 1) are of considerable interest due to their antidiabetic<sup>2</sup> and antiallergic activities.<sup>3</sup> They are also useful intermediates for the synthesis of inhibitors of the VEGF (vascular endothelial growth factor)–receptor tyrosine kinases for the treatment of cancer.<sup>4</sup> However, phthalazinone derivatives of structure **B** (Figure 1) have attracted considerable attention in the development of novel antiasthmatic agents with dual activities of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) synthetase inhibition and bronchodilation.<sup>5</sup> Combination of bronchodilatory and anti-inflammatory activities in a single molecule was thought to be more effective in the treatment of bronchial asthma. SAR (structure–activity relationship) studies revealed that the heterocyclic moiety at the C-4 position of the phthalazinone nucleus has a critical role in TXA<sub>2</sub> synthetase inhibitory activity. Therefore, a number of 4-heteroaryl-2*H*-phthalazin-1-ones were synthesized and evaluated for TXA<sub>2</sub> synthetase inhibitory as well as bronchodilatory activities.<sup>6</sup>

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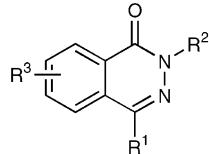
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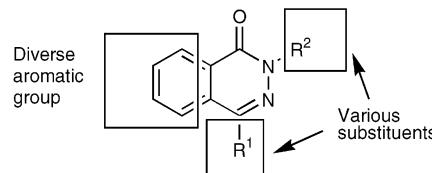


**A:**  $R^1 = -\text{CH}_2\text{-alkyl, } -\text{CH}_2\text{-heteroaryl, } -\text{CH}_2\text{COOH}$

$R^2 = -\text{CH}_2\text{-heteroaryl, } -\text{CH}_2\text{-heterocyclyl; } R^3 = \text{H, OCH}_3, \text{Cl}$

**B:**  $R^1 = \text{heteroaryl, aryl; } R^2 = \text{alkyl; } R^3 = \text{H}$

**FIGURE 1.** Examples of some 4-substituted 2*H*-phthalazinones.

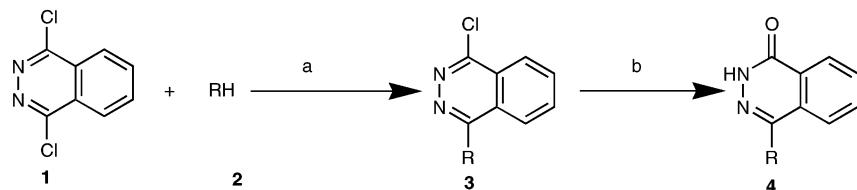


**FIGURE 2.** Diversity-based phthalazinone scaffold.

In pursuance of our research<sup>7</sup> under the new drug discovery program, we became interested in the synthesis of a combinatorial library based on the scaffold of phthalazinone. While the library model, as shown in Figure 2, has three centers for the introduction of diversity into the phthalazinone molecule, we initially focused on the modification of C-4 substituents because of its crucial role in biological activities of such derivatives as reported earlier.<sup>6</sup> Therefore, a straightforward method was required for attaching different R groups to the C-4 position of the phthalazinone ring. Although a number of methods are available for the synthesis of 4-alkyl-substituted phthalazinones,<sup>8</sup> only a few are known for the synthesis of their 4-(hetero)aryl analogues. Among them the most common approach involves the use of 2-acylbenzoic acids, which upon treatment with hydrazine afforded 4-(hetero)arylphthalazinones.<sup>5,6</sup> Synthesis of 2-acylbenzoic acids,<sup>5</sup> however, was accomplished by the reaction of phthalic anhydride with (a) aryl/heteroaryl-lithium (generated from aryl/heteroaryl bromide and *n*-butyllithium), (b) Grignard reagent, or (c) the appropriate arene in the presence of  $\text{AlCl}_3$ . Nevertheless, none of

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SCHEME 1<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a)  $\text{AlCl}_3$ , dichloroethane, 50–80 °C, 3–12 h; (b)  $\text{NaOAc}$ ,  $\text{HOAc}$ , 110–115 °C, 3–5 h.

TABLE 1.  $\text{AlCl}_3$ -Induced Heteroarylation of Arenes and Heteroarenes

Entry	Starting material 2; RH =	Product 3; R =	Temp ( °C)	Time (h)	Yield <sup>a</sup> (%)
1		1-Methyl-1 <i>H</i> -3-azolyl <b>3a</b>	50	12	89
2		2-Methyl-1 <i>H</i> -3-indolyl <b>3b</b>	50	12	93
3		5-Chloro-1 <i>H</i> -3-indolyl <b>3c</b>	55	10	50
4		1-Methyl-1 <i>H</i> -3-indolyl <b>3d</b>	50	12	74
5		1 <i>H</i> -3-Indolyl <b>3e</b>	55	12	93
6		2,4,6-Trimethoxyphenyl <b>3f</b>	75	3.5	99
7		2,4-Dimethoxyphenyl <b>3g</b>	80	4	71
8		4-Hydroxy-3-methylphenyl <b>3h</b>	80	4	50
9		4-Hydroxy-3-chlorophenyl <b>3i</b>	80	4	34
10		2,4-Dihydroxyphenyl <b>3j</b>	75	4	73
11		2-Hydroxynaphthyl <b>3k</b>	80	4	44
12		4-Hydroxy-3-bromophenyl <b>3l</b>	80	4	46

<sup>a</sup> Yield of isolated products.

these multistep methods are general, and they are only useful for the preparation of specific compounds. Moreover, use of pyrophoric organolithium or moisture-sensi-

tive organomagnesium reagents is often inconvenient and requires special precautions for the large-scale preparation of 2-acylbenzoic acids. This prompted us to develop

an alternative and general procedure for the direct attachment of an aryl or heteroaryl moiety to the C-4 position of the phthalazine scaffold. In a recent study we have reported that the  $\text{AlCl}_3$ -induced heteroarylation reaction provides an efficient tool for the introduction of a pyridazine moiety to the pyrrolopyridazine ring in a regioselective manner.<sup>1</sup> To extend the scope of this general procedure to the synthesis of other heterocyclic compounds for the generation of a new lead in our ongoing cardiovascular project,<sup>7f</sup> we investigated the reaction of 1,4-dichlorophthalazine with arenes and heteroarenes. Herein, we describe our recent studies on the  $\text{AlCl}_3$ -induced carbon–carbon bond formation between phthalazine and various (hetero)arenes leading to the new synthesis of 4-(hetero)aryl-2*H*-phthalazin-1-one derivatives of synthetic as well as potential biological interest. Our approach is based on the reversal of the usual synthetic sequences reported in the literature (attachment of the substituent that would appear at the C-4 of the phthalazinone ring followed by the construction of the desired ring), and to the best of our knowledge this demonstration represents the first direct synthesis of these compounds using such a methodology.

The heteroarylation reaction of arenes and heteroarenes was carried out successfully under the Friedel–Crafts reaction conditions shown in Scheme 1 (condition a). When 5.52 equiv of arenes/heteroarenes **2** was reacted with 5.52 equiv of 1,4-dichlorophthalazine (**1**) in the presence of 6.06 equiv of  $\text{AlCl}_3$  using dichloroethane as solvent, 4-(hetero)aryl-substituted 1-chlorophthalazines **3** were formed as exclusive products in good yields. The results are summarized in Table 1.

As can be seen from Table 1, the heteroarylation reaction proceeds well in the presence of various aryl or heteroaryl reactants. A number of nitrogen-containing heteroarenes, e.g., pyrrole (entry 1, Table 1) or indoles (entries 2–5, Table 1), were employed in this  $\text{AlCl}_3$ -induced reaction, and the yields were found to be good to excellent. Arenes were also found to be effective especially where rings were activated by electron-donating groups (entries 6–12, Table 1). An excellent yield of product was observed when a strong electron-donating group such as methoxy occupied the *ortho*- and *para*-positions (entry 6, Table 1). Free phenolic hydroxyl groups were also found to be well tolerated during the reaction (entries 8–12, Table 1), and the heteroarylation occurred at the ring carbon rather than oxygen.<sup>9</sup> Reactions were usually carried out at 50–55 °C for 10–12 h (when RH = heteroarene) or at 75–80 °C for 3–4 h (when RH = arene). The duration of the reaction could be reduced to 6 h in the previous case by increasing the temperature to 80 °C. However, partial decomposition of the product as well as formation of unwanted side products was observed at this higher temperature. Some of the 1-chlorophthalazines **3** thus obtained were converted to the corresponding phthalazinones **4** using sodium acetate in acetic acid under reflux as described in Scheme 1 (condition b). The reaction conditions and yields of the products are listed in Table 2.

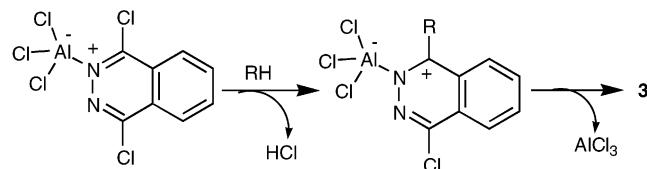
We have described an efficient method for the synthesis of 4-chlorophthalazines via controlled substitution of one

TABLE 2. Synthesis of Phthalazinones **4** from Chlorophthalazines **3**

entry	starting material <b>3</b>	R in product <b>4</b>	temp (°C)	time (h)	yield <sup>a</sup> (%)
1	<b>3d</b>	1-methyl-1 <i>H</i> -3-indolyl ( <b>4d</b> )	110	5	92
2	<b>3e</b>	1 <i>H</i> -3-indolyl ( <b>4e</b> )	110	5	95
3	<b>3f</b>	2,4,6-trimethoxyphenyl ( <b>4f</b> )	115	3	89
4	<b>3g</b>	2,4-dimethoxyphenyl ( <b>4g</b> )	115	4	96
5	<b>3k</b>	2-methoxynaphthyl ( <b>4k</b> ) <sup>b</sup>	110	4	89

<sup>a</sup> Yield of isolated products. <sup>b</sup> Compound **4k** was prepared from **3k** via methylation (using  $\text{MeI}$  and  $\text{K}_2\text{CO}_3$  in DMF) followed by the treatment of  $\text{NaOAc}$  in  $\text{AcOH}$  as shown in Scheme 1 (condition b).

SCHEME 2. Mechanism of the Heteroarylation Reaction



of the chlorines by an aryl or heteroaryl moiety in the presence of  $\text{AlCl}_3$ . The method certainly has tactical advantage over the butyllithium-mediated reaction of 1,4-dichlorophthalazine with 1-methyl-1*H*-imidazole, where uncontrolled substitution of chlorines led to the formation of 1,4-disubstituted phthalazine.<sup>10</sup> Moreover, due to the easy availability of starting arenes and heteroarenes, this method is applicable for the generation of appropriate phthalazin-1-one-based analogues of potential biological interest<sup>6,11</sup> via successive treatment of **4** with  $\alpha,\omega$ -dibromoalkanes and imidazole in the presence of potassium carbonate or with 4-(2-bromoethoxy)benzaldehyde followed by reaction with thiazolidine-2,4-dione. All the 4-substituted phthalazines **3** and the corresponding phthalazinones **4** synthesized were well characterized by their spectroscopic and analytical data.

Mechanistically the heteroarylation reaction proceeds through the complexation of  $\text{AlCl}_3$  with one of the nitrogens of 1,4-dichlorophthalazine followed by nucleophilic attack at the adjacent carbon (Scheme 2). It is evident that the nucleophilicity of the reacting arenes or heteroarenes is crucial in such cases, and therefore, the reaction proceeds smoothly with electron-rich arenes or heteroarenes, leading to the formation of **3**. A further substitution of the chlorine atom of **3** was not observed perhaps due to the increased  $\pi$ -electron density of the phthalazine moiety (imparted by R) that disfavored a second nucleophilic attack on this ring.

All the arenes/heteroarenes are commercially available, whereas **1**, a key substrate for the heteroarylation reaction, was prepared by an established procedure.<sup>12</sup>

In conclusion, the chemistry described above illustrates the usefulness of 1,4-dichlorophthalazine as an efficient

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heteroarylating agent for arenes and heteroarenes and shows a considerable versatility for the syntheses of 4-(hetero)aryl-substituted 1-chlorophthalazines as masked phthalazinones. The method involves the use of readily available starting materials, inexpensive reagents, and mild reaction conditions and therefore has advantages over the syntheses via 2-acylbenzoic acids especially in the large-scale preparation of phthalazinones. The protocol could also be a useful alternative to the Suzuki coupling reactions (when applied to a similar type of C–C bond formation reaction) as preparations of required boronic acids are often cumbersome. We believe that the methodology will certainly broaden the scope for the synthesis and development of phthalazinone-based potential antidiabetic or antiasthmatic agents and therefore

would find wide usage in organic as well as medicinal chemistry.

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**Supporting Information Available:** Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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