JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of 2-Aryl-1,2-dihydrophthalazines via Reaction of 2-(Bromomethyl)benzaldehydes with Arylhydrazines

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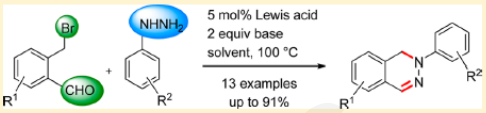
Supporting Information

ABSTRACT: The reaction of 2-(bromomethyl)benzaldehydes with arylhydrazines employing K_2CO_3 as a base and $FeCl_3$ as a catalyst in CH_3CN at 100 °C delivers 2-aryl-1,2-dihydrophthalazines with yields ranging from 60 to 91%. The transformation is considered to proceed as an intermolecular condensation/intramolecular nucleophilic substitution.



INTRODUCTION

Phthalazines and phthalazinones are N-heterocycles with a wide range of biological and pharmacological properties, such as anticonvulsant, antimicrobial, anti-inflammatory, antimycobacterial, antitumor, antihypertensive, antidiabetic, antifungal, and vasorelaxant activity, among others.[1] They also play an important role as intermediates in organic synthesis. This is why numerous methods have been developed for their preparation.[2] Besides fully aromatic phthalazines, partially unsaturated derivatives, such as the 1,2-dihydrophthalazines, are also of considerable interest in medicinal chemistry, as a number of them exhibit significant pharmacological properties. Among the most remarkable compounds are some 1,2-dihydrophthalazines that inhibit dihydrofolate reductase, an essential enzyme in most pathogenic bacteria. The 1,2-dihydrophthalazines have been demonstrated to have potent antibacterial activities against infections that are caused by multiresistant gram-positive pathogens, including staphylococci.[3] Of particular interest is the 1,2-dihydrophthalazine RAB1, which has been identified as a promising inhibitor of antibiotic-resistant *Staphylococcus aureus* and trimethoprim-resistant *Bacillus anthracis*.[4] In addition, it has been found that 1,2-dihydrophthalazines are potent, selective, and noncompetitive inhibitors of the AMPA subtype of glutamate receptors.[5]

In contrast to the synthesis of phthalazines and phthalazinones, the number of methods available for the preparation of 1,2-dihydrophthalazines is only modest. Most of them are based on the reduction of phthalazinium salts, phthalazines, or phthalazinones using reducing reagents, such as $[Fe_3(CO)_{12}]$[6] and $NaBH_4$,[7] or on the addition of organometallic reagents, such as organolithium,[5,8] or Grignard reagents[4b] to phthalazines. Another method is based on the cyclization of phthaldehyde monoarylhydrazones that can be obtained from the condensation of phthalaldehyde with arylhydrazines.[9] In addition, a few 1,2-dihydrophthalazines have been synthesized by reaction between 1,2-bis(halomethyl)benzenes and hydrazines under microwave conditions.[10] Recently, Xu et al. reported on the preparation of 1,2-dihydrophthalazines by the Rh-catalyzed oxidative annulation of sulphonylhydrazones with alkenes using $Cu(OAc)_2$ as the oxidant.[11] Altogether, the number of direct approaches to 1,2-dihydrophthalazines is rather limited. Therefore, the development of new methods for the synthesis of 1,2-dihydrophthalazines is highly desirable.

Recently, we have reported on new approaches to heterocycles that rely on reactions between *o*-disubstituted aromatics or heteroaromatics with disubstituted reagents.[12] As part of this work, we became interested in the reaction between 2-(halomethyl)benzaldehydes and arylhydrazines. In this contribution, we report on a practical synthesis of 2-substituted 1,2-dihydrophthalazines that is based on the reaction between 2-(bromomethyl)benzaldehydes and arylhydrazines under basic conditions and with $FeCl_3$ as the catalyst.

RESULTS AND DISCUSSION

It was envisaged that 1,2-dihydrophthalazines can be synthesized by a domino condensation/intramolecular substitution using a 2-(halomethyl)benzaldehyde **1** and a hydrazine **2** as the substrates. Therefore, in an initial experiment, 2-(bromomethyl)benzaldehyde (**1a**) and phenylhydrazine (**2a**) were reacted with 2 equiv of K_3PO_4 in DMF for 24 h at 110 °C in a sealed vial. After workup and purification, the desired 1,2-dihydrophthalazine **3a** could be isolated in 40% yield (Scheme 1). It is assumed that the reaction starts with the condensation between aldehyde **1a** and hydrazine **2a** to give the hydrazone **4a** as an intermediate. In the second step, **4a** undergoes an intramolecular nucleophilic substitution to yield the 2-substituted 1,2-dihydrophthalazine **3a**.

To facilitate the condensation between the aldehyde function of **1a** and the NH_2 group of the hydrazine **2a**, we decided to run the transformation in the presence of a Lewis acid. When the reaction between **1a** and **2a** with 2 equiv of K_3PO_4 was conducted in the presence of 10 mol % CuI in DMF, the yield of **3a** could be increased to 58% (Table 1, entry 1). The

Received: November 13, 2012
Published: December 20, 2012