



# Copper-catalyzed domino reaction between 1-(2-halophenyl) methanamines and amidines or imidates for the synthesis of 2-substituted quinazolines



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## ABSTRACT

The CuI-catalyzed domino reaction between 1-(2-bromophenyl)methanamines and amidines using  $K_3PO_4$  as the base, pivalic acid as the additive, and aerial oxygen as the oxidant gives access to substituted quinazolines in a single step with yields in the range between 43 and 90%. It is assumed that the reaction proceeds as a Cu(I)-catalyzed intermolecular N-arylation followed by an intramolecular nucleophilic substitution and a Cu(II)-catalyzed oxidation. The amidines can be replaced with imidates and the reaction can also be run with 1-(2-iodophenyl)methanamine.

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## 1. Introduction

There is no doubt that quinazolines and their derivatives are among the most important *N*-heterocyclic structures: the quinazoline moiety is the core structure of numerous natural products<sup>1</sup> and many compounds with a quinazoline core exhibit a wide range of useful biological and pharmacological properties, such as anticancer,<sup>2</sup> antiviral,<sup>3</sup> antibacterial,<sup>4</sup> and antimalarial<sup>5</sup> activities. In addition, a number of compounds with a quinazoline moiety are used as drugs. Among them are prazosin<sup>6</sup> for the treatment of hypertension, erlotinib,<sup>7</sup> gefitinib,<sup>8</sup> and lapatinib<sup>9</sup> for the treatment of different types of tumors, and trimetrexate<sup>10</sup> for the treatment of *Pneumocystis carinii* pneumonia (Fig. 1). This is the reason for the ongoing interest in the development of new methods for the synthesis of quinazolinones and quinazolines.<sup>11</sup> Numerous methods for the synthesis of quinazolines are based on the use of *o*-functionalized nitrobenzenes and anilines.<sup>11,12</sup> During the last decades the interest in the transition metal-catalyzed synthesis of heterocycles has increased considerably.<sup>13</sup> Copper-catalyzed transformations<sup>14</sup> are particularly

attractive, since copper catalysts are cheap and readily available. Another advantage is that copper-catalyzed reactions can often be run in the absence of expensive ligands. It has been demonstrated that quinazolines can be prepared by Pd- as well as Cu-catalyzed reactions between functionalized aromatics and amidines as the substrates.<sup>15–19</sup> As an example, we reported on the Cu<sub>2</sub>O-catalyzed reaction of 2-bromobenzyl bromides with amidines in H<sub>2</sub>O as solvent to yield the corresponding quinazolines in yields up to 85%.<sup>16</sup> In 2008, Fu, Jiang et al. reported on the Cu(I)-catalyzed reaction between 2-bromobenzaldehydes and amidine hydrochlorides to the corresponding quinazolines in good yields.<sup>17</sup> Among others, the reaction between 2-bromobenzaldehyde and benzamidine hydrochloride was performed to yield the corresponding 2-phenylquinazoline in 55% yield. In contrast to their findings, Truong and Morrow reported in 2010 that the CuI-catalyzed reaction between 2-bromobenzaldehyde and benzamidine hydrochloride under similar conditions delivered 2-phenylquinazoline in only 13%.<sup>18</sup>

Similar results have been disclosed by Lobanov et al.<sup>19</sup> When they reacted 2-bromobenzaldehyde and benzamidine hydrochloride under the conditions reported by Fu, Jiang et al. the yield of 2-phenylquinazoline was not satisfactory. In addition to 2-phenylquinazoline, Lobanov et al. observed the formation of a dihydrotriazine, which results from the reaction of two

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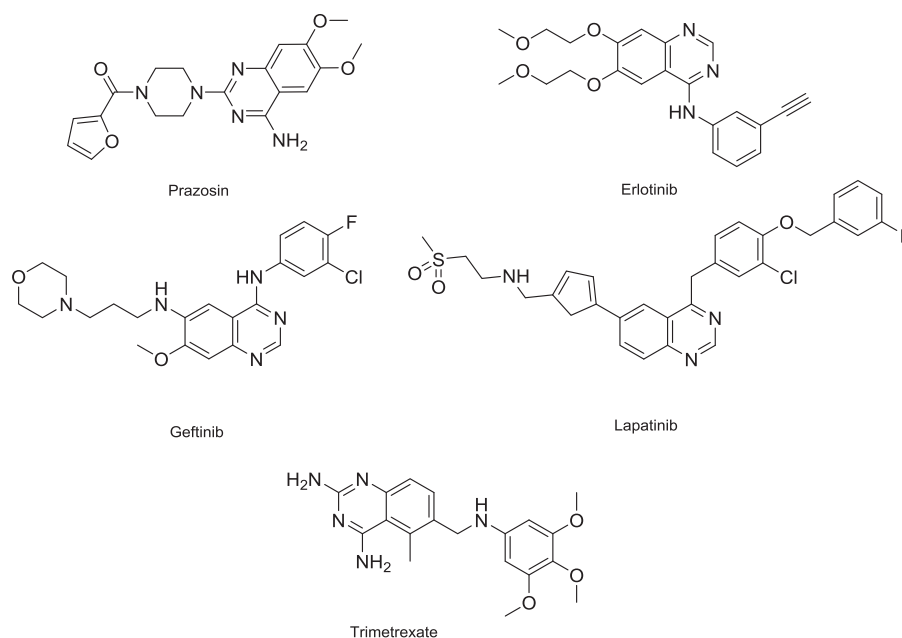
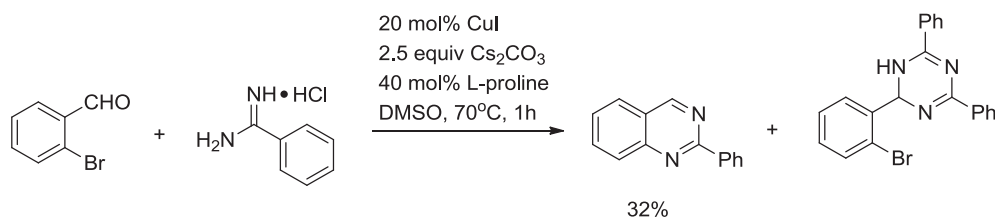


Fig. 1. Selected drugs with a quinazoline moiety.

molecules benzamidine and one molecule benzaldehyde (Scheme 1). Both, the groups of Truong and Lobanov reported that the Cu(I)-catalyzed formation of quinazolines is only satisfactory when instead of 2-bromobenzaldehydes the more expensive 2-iodobenzaldehydes are employed as substrates. When we repeated the reaction between 2-bromobenzaldehyde and benzamidine hydrochloride under the conditions of Fu, Jiang et al., the yield of 2-phenylquinazoline did not exceed 25%. Inspired by these observations, we became interested to reveal whether the copper-catalyzed reaction between 1-(2-bromophenyl)methanamines and amidines or imidates is an alternative to the transformations with 2-bromobenzaldehydes as the substrates to allow for the preparation of 2-substituted quinazolines in useful yields. So far, the synthesis of quinazolines by reaction between 1-(2-halophenyl)methanamines and amidines or imidates has not been reported.<sup>20</sup> It should be mentioned, however that Fu et al. have been able to prepare quinazolines by the copper-catalyzed reaction between 1-(2-bromophenyl)methanamines and aromatic carboxamides.<sup>20f</sup>

10 mol % CuI as a catalyst and 2.2 equiv  $K_2CO_3$  as a base, but in the absence of any further additive, in DMF at 110 °C for 24 h under argon, 2-phenylquinazoline (**3a**) was formed as the only product. However, the yield amounted to only 20% (Table 1, entry 1). This prompted us to perform the reaction in the presence of different additives. When the transformation was run in the presence of L-proline or DMEDA; i.e., ligands that are well-known to increase the yields of Ullmann couplings,<sup>14</sup> the results were disappointing (Table 1, entries 2 and 3). This is why we switched to acidic additives that have proven successful in a number of copper-catalyzed transformations.<sup>21</sup> When the reaction was run with 40 mol % picolinic acid in DMF under argon, the yield of **3a** could be almost doubled (Table 1, entry 4). A slightly better result was observed with 40 mol % pivalic acid in DMF (Table 1, entry 5). The yield could be increased by 10% to 54% when DMF was replaced by 1,2-dichlorobenzene (1,2-DCB) as a solvent (Table 1, entry 6). Interestingly, a similar result was obtained when the transformation was run under air (Table 1, entry 7). Unfortunately, a decrease of the amount of pivalic acid from 40 mol % to 30 mol % was not successful, since the yield dropped to 41% (Table 1, entry 8). The for-



Scheme 1. Cu(I)-catalyzed reaction of 2-bromobenzaldehyde with benzamidine hydrochloride according to Lobanov et al.<sup>19</sup>

## 2. Results and discussion

The reaction between 1-(2-bromophenyl)methanamine (**1a**) and benzamidine hydrochloride (**2a**) was chosen as the model reaction. When equimolar amounts of **1a** and **2a** were reacted with

matation of **3a** could also be achieved with propionic acid and isovaleric acid; however, the yields did not exceed the yield obtained with pivalic acid (Table 1, entries 9 and 10).

All further reactions were performed with 40 mol % pivalic acid as an additive. Next, the influence of the base on the

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