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Potassium carbonate mediated unusual transformation of 2,3-dihydroquinazolinone via cascade reaction

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ABSTRACT

An unusual potassium carbonate mediated transformation of 2,3-dihydroquinazolinone by a one-pot operation is reported under mild conditions. In addition, it is interesting to report the regioselective transformation of 3-(2-bromophenyl)-2-isopropyl-2,3-dihydroquinazolin-4(1H)-one from compound **16**.

Synthetic strategies that allow the creation of natural product based diverse molecular architectures,[1] present interesting and demanding challenges to the art of organic synthesis.[2] In this context, cascade reactions can be considered green in which more than one reaction occurs consecutively in a one-pot process for the construction of bioactive scaffolds.[3,4] Quinazolinones are considered as privileged core structures due to their wide presence in natural products that include trypanthrine, rutaecarpine, and febrifugine (Fig. 1).[5–9] In addition, many unnatural quinazolinone analogues display various pharmacological[10–12] and biological activities such as histamine H_4 receptor inverse agonists,[13] antitumor, anticonvulsant,[14] antiviral,[15] antihypertensive,[16] antiinflammatory,[17] analgesic,[18] antihyperglycemic,[19] cytotoxicity,[20] antibacterial,[21] and angiotensin II AT1 receptor antagonists.[22] Not surprisingly, numerous efforts have already been made in direct preparation of quinazolinone.[23] In this context, transition metal catalyzed routes to substituted quinazolinone derivatives have appeared in the literature. Recently, the Ma and Fu groups independently developed a copper-catalyzed N-arylation of o-bromobenzoic acid derivatives with amidines and subsequent intramolecular condensation to synthesize the quinazolinone derivatives.[24,25] In addition, Alper et al., reported a palladium catalyzed synthesis of quinazolinone analogues.[26] However these metal catalyzed cascade reactions are expensive and take long reaction time. Among the metal-free transformations, the inexpensive and readily available catalytic system has attracted considerable interest for the construction of pharmacologically active heterocycles.[27] In recent Letters, we

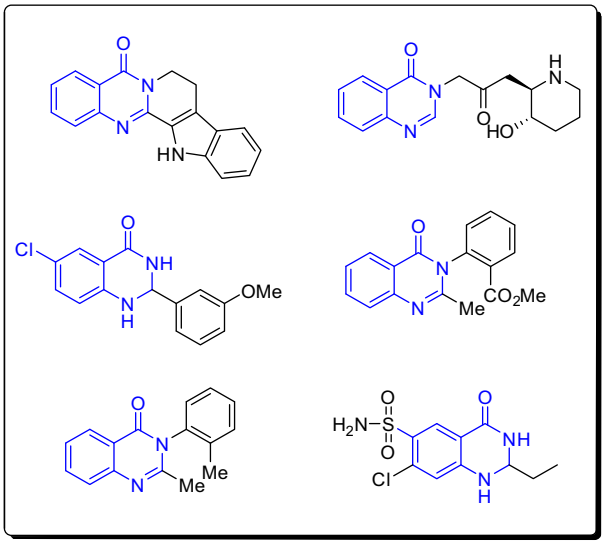

Figure 1. Structures of natural and synthesized bioactive quinazolinones.

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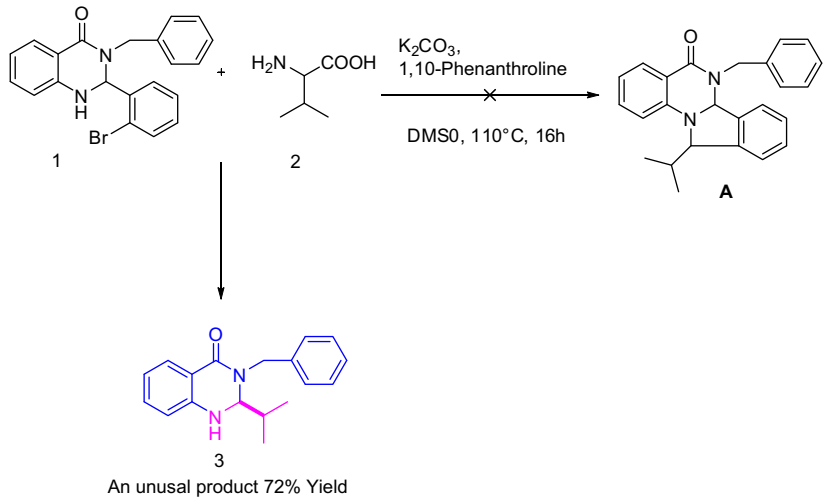
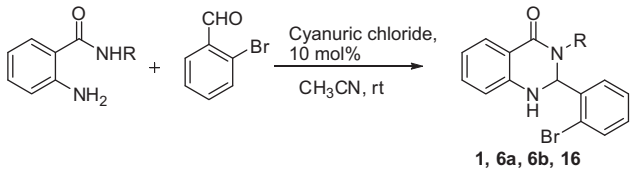


Scheme 2. One possible structure **A** and unexpected transformation of quinazolinone in a one-step sequence.



Scheme 1. Synthesis of 2-(2-bromophenyl)-3-aryl-2,3-dihydroquinazolin-4(1H)-one.[28]

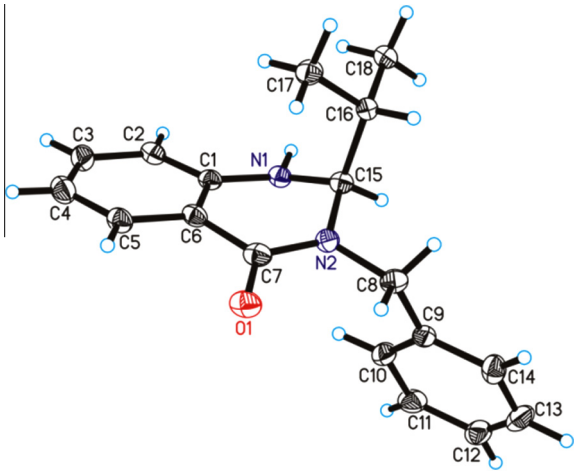


Figure 2. ORTEP drawing of compound **3**.

described a novel and highly efficient protocol of TCT-catalyzed construction of bioactive dihydro/spiro quinazolinones[28] and quinazolinone hybrids as potent antileishmanial agents.[29]

In addition, ring-to-ring interconversions represent an interesting research field for the synthesis of biologically active heterocycles which are difficult to synthesize through the classical methodologies.[30] In this context, ANRORC-like[31] (addition of the nucleophile, ring opening, and ring closure) pattern, is an interesting approach for the ring transformation of heterocyclic systems.[32,33] As part of our ongoing studies to develop new strategies for the synthesis of biologically important heterocycles.[34] Herein, we report an unusual and highly selective potassium carbonate mediated cascade synthesis, which is followed by an ANRORC-type rearrangement for the transformation of bioactive quinazolinone. To our knowledge, no reaction dealing with the direct transformation of quinazolinone has ever been reported in the literature. The proposed transformation is presented in Scheme 2.

We began our investigation with 3-benzyl-2-(2-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (**1**) (Scheme 1) and L-valine (**2a**) as the model substrates to optimize the reaction conditions including optimization of bases, ligands, temperature, and solvents under dry conditions. Instead of the formation of quinazolinone-coupled product **A**, surprisingly an unexpected product (3-benzyl-2-isopropyl-2,3-dihydroquinazolin-4(1H)-one, (**3**) was isolated in 72% yield, which is possibly due to the ANRORC-type rearrangement. ^{1}H NMR, 2-D NMR, ^{13}C NMR, mass spectral data, and crystal data confirmed that the products have the general structure **3**.

Transformation of quinazolinone has little dependence of the reactivity on the structure of substrates. Interestingly, the formed intermediate (2-aminobenzamide, observed on TLC after 7 h, isolated and purified) was completely transformed into product (**3**) after 12 h of reaction. Encouraged by the formation of **3** (Fig. 2), we further optimized the reaction conditions with different substrates (Scheme 4). The representative optimization experiments are summarized in Table 1. K_2CO_3 proved to be the most effective base for this reaction (entries 1 and 9–12). We screened three ligands at 110 °C using 2.0 equiv K_2CO_3 as the base (relative to the amount of quinazolinone) in DMSO (entries 1–3) and 1,10-phenanthroline showed the best activity (entry 1); however, the addition of PPh_3 and L-proline led to a trace amount of product. When the reaction was examined in the absence of ligand (entry 4), the product was formed in low yield (50%). Moreover, when the reaction was performed in the presence of catalyst (palladium acetate), 2-aminobenzamide was formed as the major product. The effect of various solvents was also investigated (Table 1, entries 1, 5–8), reaction was sluggish in DMF and almost no reaction took place when toluene and dioxane were used as solvents. With the optimized conditions in hand (2.0 equiv of K_2CO_3 as base and 15 mol % 1,10-phenanthroline as the ligand), we then investigated the reaction of various substituted quinazolinones with α-amino acids and the results are summarized in Table 2.

It is worthwhile to note that the reaction of 2-(2-bromophenyl)-3-phenyl-2,3-dihydroquinazolin-4(1H)-one (**6**) with L-valine (**2a**) (Scheme 5) gave a minor 2-amino-N-phenylbenzamide (**14**) besides the major quinazolinone (**7**) (Scheme 5). The results of this study are shown in Table 2. Varying the R-substituent from benzyl to phenyl led to faster conversions providing the products **7**–**13** (entries 4–10) and the results are summarized in Table 2. In