Tetrahedron Letters xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 2 April 2013
Revised 22 August 2013
Accepted 24 August 2013
Available online xxxx

Keywords:
Quinazolinone
Cascade reaction
ANRORC-type rearrangement
Regioselective
One-pot reaction

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

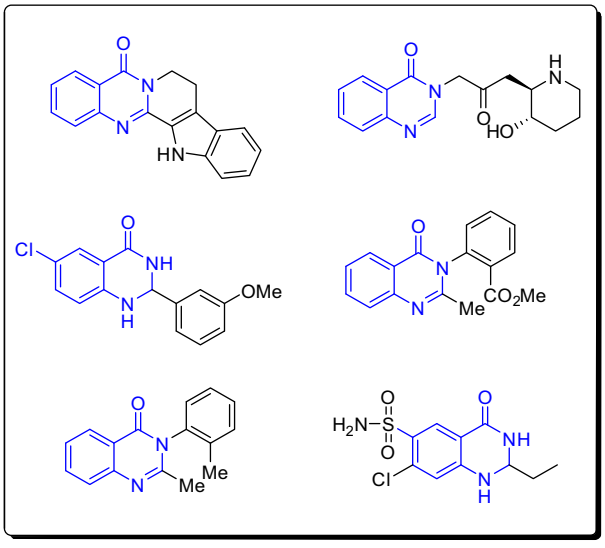

Figure 1. Structures of natural and synthesized bioactive quinazolinones.

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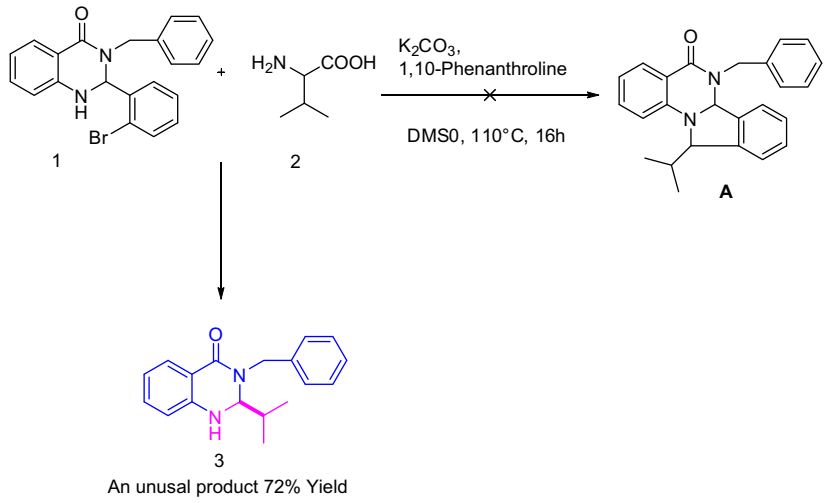
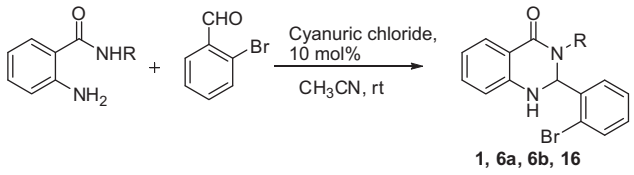
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.08.095



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]

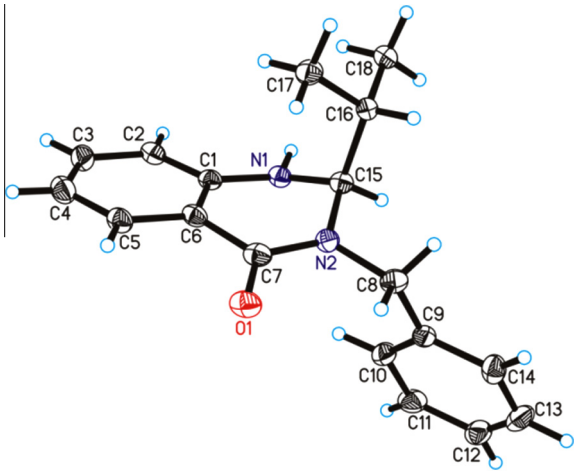


Figure 2. ORTEP drawing of compound **3**.

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]

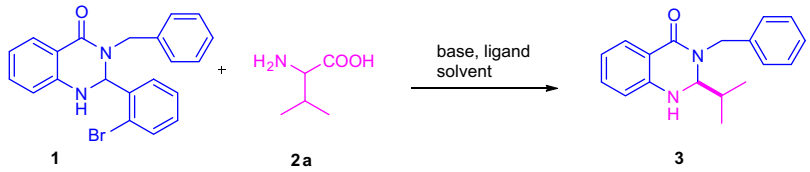
In addition, ring-to-ring interconversions represent an interesting research field for the synthesis of biologically active heterocycles which are difficult to synthesize through the classical methodologies.[30] In this context, ANRORC-like[31] (addition of the nucleophile, ring opening, and ring closure) 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

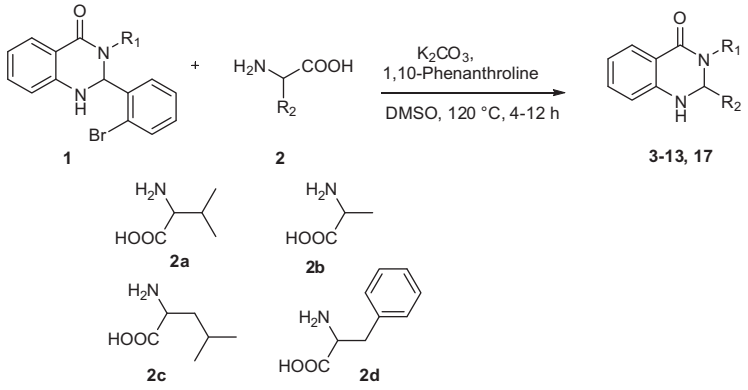
Table 1
Optimization of the reaction conditions



1 2a 3

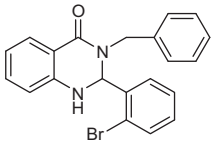
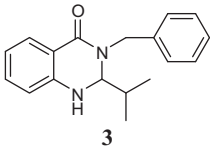
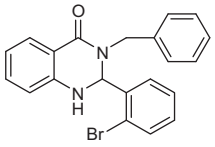
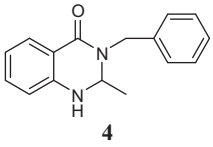
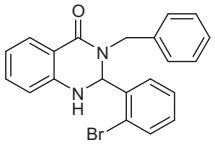
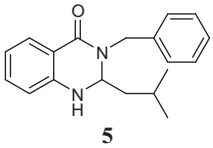
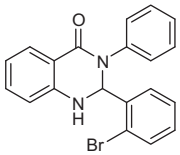
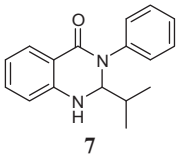
Entry	Base	Ligand	Solvent	Temp	Yield
1	K_2CO_3	1,10-Phenanthroline	DMSO	110	72
2	K_2CO_3	PPh3	DMSO	110	20
3	K_2CO_3	L-Proline	DMSO	110	10
4	K_2CO_3	—	DMSO	110	50
5	K_2CO_3	1,10-Phenanthroline	Dioxane	110	0
6	K_2CO_3	1,10-Phenanthroline	Toluene	110	0
7	K_2CO_3	1,10-Phenanthroline	DMF	110	42
8	K_2CO_3	1,10-Phenanthroline	DMSO + Ethylene glycol	110	60
9	Cs_2CO_3	1,10-Phenanthroline	DMSO	110	30
10	K_3PO_4	1,10-Phenanthroline	DMSO	110	45
11	Na_2CO_3	1,10-Phenanthroline	DMSO	110	15
12	$NaHCO_3$	1,10-Phenanthroline	DMSO	70	0

Table 2
K_2CO_3-promoted cascade synthesis of quinazolinone derivatives via cascade reaction



1 2 3-13, 17

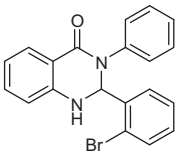
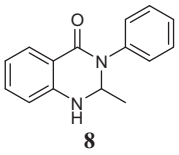
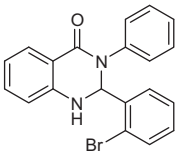
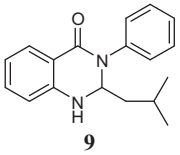
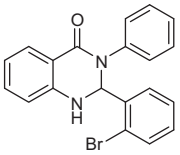
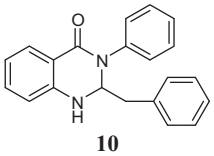
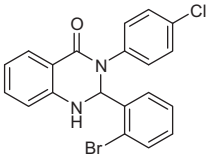
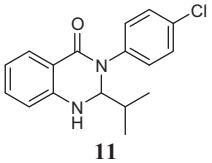
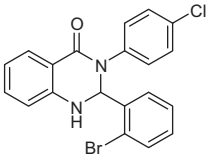
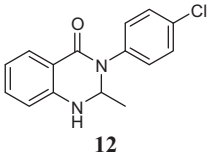
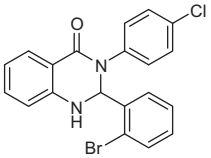
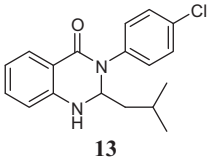
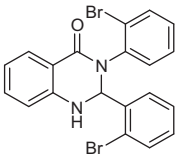
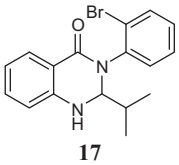
2a 2b 2c 2d

Entry	Starting material	Products	Time (h)	Yield[a] (%)
1		 3	12	72
2		 4	10	62
3		 5	11	66
4		 7	4	70

(*continued on next page*)

Please cite this article in press as: Sharma, M.; et al. *Tetrahedron Lett.* (2013), http://dx.doi.org/10.1016/j.tetlet.2013.08.095

Table 2 (*continued*)

Entry	Starting material	Products	Time (h)	Yield[a] (%)
5		 **8**	3	65
6		 **9**	5	70
7		 **10**	6	48
8		 **11**	4	68
9		 **12**	5	52
10		 **13**	4	60
11		 **17**	8	70

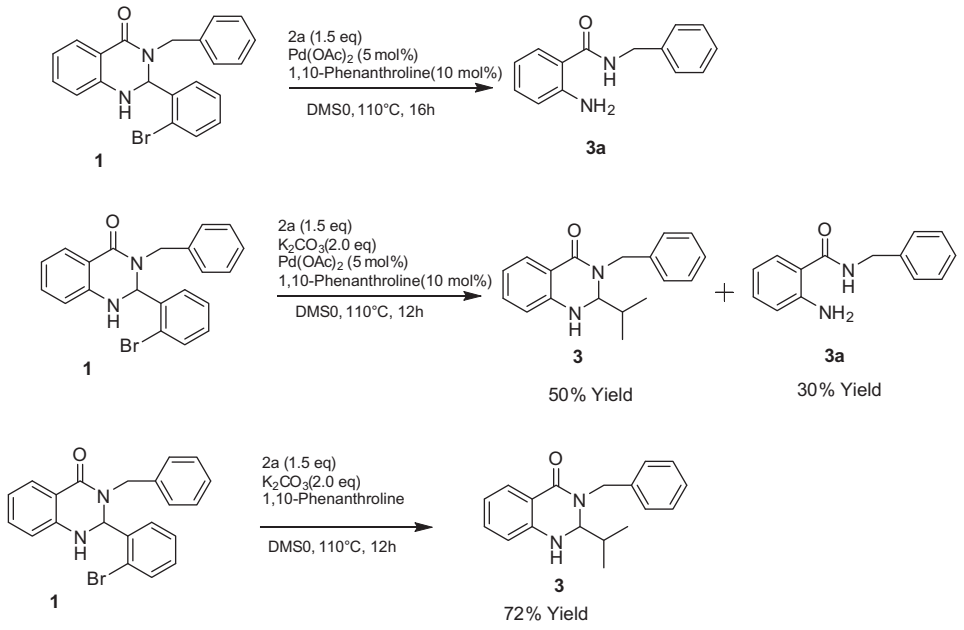
[a] Isolated yields after column chromatography.

general, L-valine, L-alanine, and L-leucine showed higher reactivity and afforded better yield than L-phenylalanine (**10**, 48%).

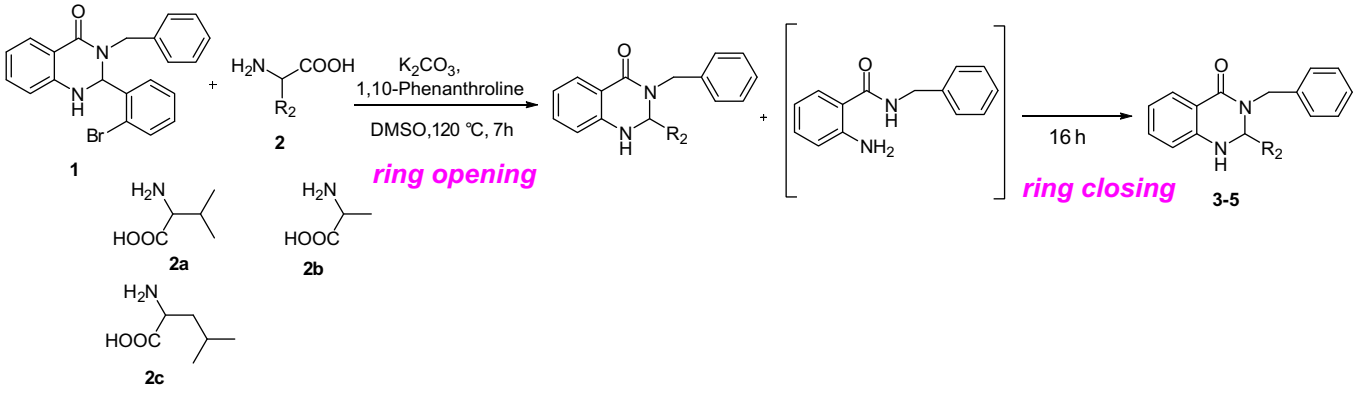
To extend the substrate scope, we also attempted cascade reactions of 2-(2-bromophenyl)-3-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one with amino acids to synthesize various quinazolinone derivatives under our standard conditions (Scheme 5). As shown in Table 2, all the examined substrates gave the corresponding quinazolinones with comparable yields (compare Table 2, entries 8–10). In general, no significant difference of reactivity was observed for substituted quinazolinone with various amino acids. The results indicated that electronic variations on the benzene ring have a minor impact on the yields.

Further to validate our assumption, we optimized the same reaction with 2,3-bis(2-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (**16**) and L-valine (**2a**) (Scheme 6) and interestingly, it was observed that reaction was regioselectively transformed into the corresponding target product (**17**) in 70% yield under our standard conditions (Table 2, entry 11).

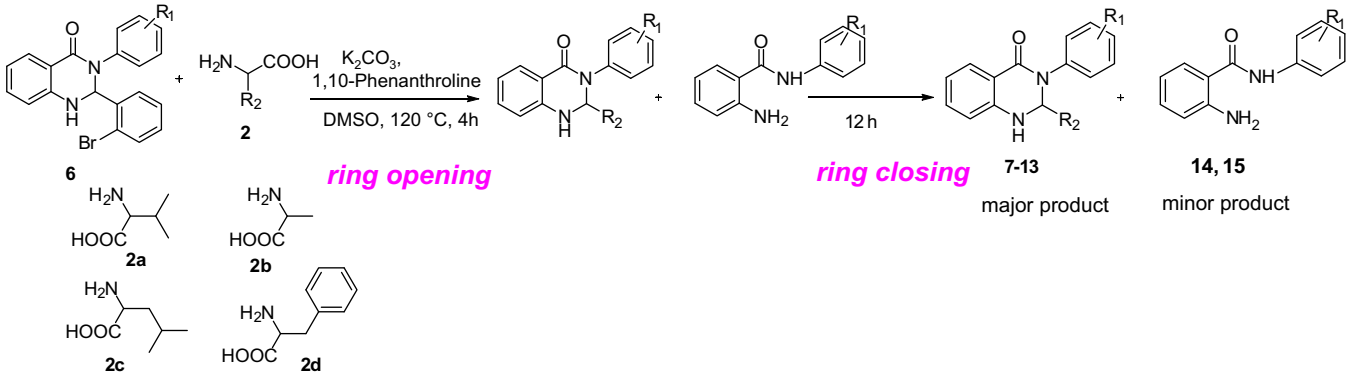
The complete ^{1}H and ^{13}C NMR signal assignments and connectivity were determined from a combination of ^{13}C, DEPT 135, DEPT 90, COSY, TOCSY, HSQC, and HMBC data and spatial correlations are established by NOESY, COSY, and TOCSY correlations which established the spin systems, which were N-H, H-2 to the isopropyl group; H-5, H-6, H-7, H-8 in ring-B and H-2′,6′, H-3′,5′ and H-4′ in ring-C. H-2 of ring A is giving HMBC correlation with C-9 and C-4 and HMBC correlations of H-6 and H-8 to C-10 and H-5 and H-7 to C-9 showed ring A and B are connected to each other. H-2′ and H-6′ are giving HMBC correlations to benzylic-carbon and protons of benzylic-CH_2 are giving HMBC correlations to C-2′,6′ and C-4. N-H is giving HMBC correlation with C-2 and H-2 is giving HMBC correlation to benzylic-CH_2 and benzylic protons are giving HMBC correlation to C-2 which showed that both benzylic-CH_2 and C-2 are connected through N-3 atom. NOE correlation indicated that the isopropyl group protons and benzylic-CH_2 protons are close in space which established the linkage of benzyl and isopropyl groups through N-3 and C-2 atom of A ring, respectively. An impor-



Scheme 3. Reactions of **1** in the presence of $Pd(OAc)_2$.



Scheme 4. Synthesis of 2-alkyl-3-benzyl-2,3-dihydroquinazolin-4(1H)-ones.



Scheme 5. Synthesis of 2-alkyl-3-aryl-2,3-dihydroquinazolin-4(1H)-one.

Scheme 6. Regioselective transformation of quinazolinone.

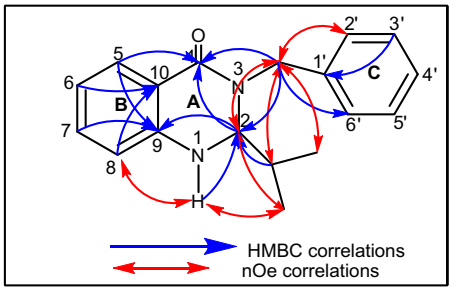


Figure 3. The important HMBC and NOE correlations in synthesized compound **3**.

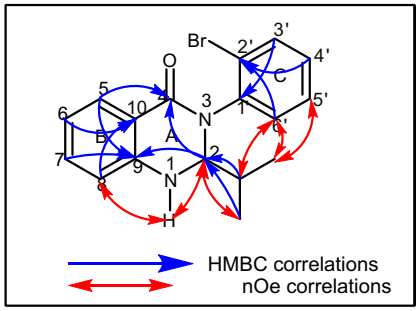


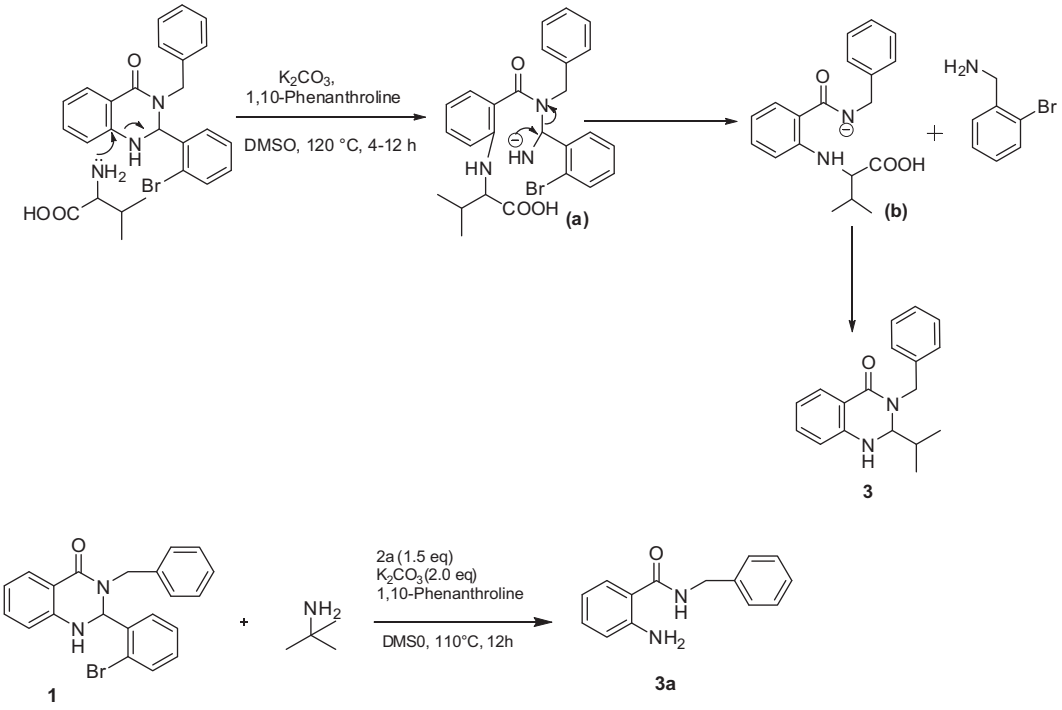
Figure 4. The important NOE and HMBC correlations in synthesized compound **17**.

tant NOE correlation between N–H and H-8 fixed the position of N–H in A ring (Fig. 3).

The product is regioselective which is established by NMR, COSY, and TOCSY correlations showing that a spin system is established from H-2 to the isopropyl group which showed that the isopropyl group is attached to C-2 atom which established the regioselectivity of desired product. HMBC correlation of the isopropyl group with C-2 also strengthened the regioselectivity of the product (Fig. 4).

The exact mechanism of this reaction is not clear; however, the reaction may proceed by an unusual base-mediated cascade synthesis followed by ANRORC-type rearrangement (ring opening; mechanistic rationale is supported by the formation of 2-aminobenzamide). In order to explore the reaction mechanism and effect of transition metal catalyst for the synthesis of quinazolinone derivatives, the following control experiments were performed as shown in Schemes 3 and 7. Initially, amine as a nucleophile might attack the C9 of the quinazolinone ring which leads to the ring opening. The formed intermediate **b** after decarboxylation and ring cyclization afforded the target compound **3**.

In summary, we have developed an unusual and highly selective potassium carbonate mediated cascade strategy which provides a new route for assembling biologically important quinazolinones. The protocol uses cheap and readily available K_2CO_3 as the base, substituted quinazolinone and α-amino acids as the starting materials to assemble the corresponding quinazoli-



Scheme 7. Plausible reaction mechanism for the formation of 2,3-dihydroquinazolinone.

nones in a one-pot manner. The reaction goes through a K_2CO_3-mediated ANRORC-type rearrangement without the addition of any catalyst. We expect our findings will promote the transformation of other heterocyclic skeletons as useful synthetic building blocks for the creation of highly decorated derivatives of the medicinally privileged scaffolds.

Acknowledgments

The author is grateful to Indian Council of Medical Research (MS) and University Grant Commission (RM) for the financial support in the form of a fellowship. The authors also acknowledge SAIF-CDRI for providing spectral and analytical data. CDRI Communication number 8535.

Supplementary data

Supplementary data (copies of ^1H, ^{13}C NMR spectra of the compounds and crystallographic data for compound **3**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.095.

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