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REGULAR ARTICLE

A mechanistic insight into the acid catalyzed, one-pot synthesis of isoindole-fused quinazolin 4-ones

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Abstract. One-pot synthesis of isoindole fused quinazolin 4-ones *via* intramolecular 1,3 hydride transfer in the presence of acid catalyst has been described. Substrate scope and mechanistic insights were investigated. Substituents on the amide side have a negligible influence on the key step and therefore the method have wide scope for accessing various bicyclic core structure.

Keywords. Heterocyclic chemistry; 1,3-Hydride transfer; Mechanistic study; Isoindole-fused quinazolinones.

1. Introduction

Quinazolinones are important nitrogenous heterocyclic compounds present in many bioactive natural products, pharmaceuticals.[1] It is present as a building block in many drugs in active use. Because of the rich history of quinazolin 4-ones, it is a privileged pharmacophore to the synthetic chemists. Most common synthesis of the simplest member 2, 3-dihydroquinazolin-4(1*H*)-one involves condensation of aldehyde or ketone with anthranilamide or other 1,5-N-bisnucleophile (**1**). While a considerable number of reports involving reactions of monoaldehyde with anthranilamide are available, the reaction of dialdehyde with anthranilamide is relatively less. Only a few examples where dialdehdye such as furan-3,4-dicarbaldehyde,[2] terephthalaldehyde,[3] glyoxal are coupled to give desired dimeric 2,3-dihydroquinazolin-4(1*H*)-ones. The synthesis of symmetric dimer 2,2'-(1,2-phenylene)bis(2,3-dihydroquinazolin-4(1*H*)-one) from *o*-phthalaldehyde and anthranilamide has been described.[4] Relatively fewer number reports are available describing condensation of *o*-phthalaldehyde with anthranilamide derivatives to give structure **3**.[2] Moreover, the mechanistic study for the formation of structure **3** is not established. As the structure **3** is an important structural motif, it exists in many pharmaceuticals and bioactive molecules[5] and available methods are multistep[6–8] in nature. Further study of the one-pot method (Scheme 1) is necessary. Herein, we wish to report the synthesis of compound **3** with different substituents on the amide side and mechanistic insights for the method presented in Scheme 1.

2. Experimental Methods

2.1 *General information*

Commercially available reagents were used without further purification. All the reactions were carried out at open vessel and monitored by TLC (TLC Silica Gel 60 F254) and it was observed under UV light (254 nm). Yields refer to the isolated product as mentioned in the experimental section. NMRs were recorded in Bruker 400 or 300 MHz spectrometer in DMSO-d_6 solution. Chemical shifts are given in δ relative to TMS, the coupling constants *J* are given in Hz. High-resolution mass spectra were recorded on ESI-TOF mass spectrometry. LCMS taken using ZORBAX EXT (4.6x50 mm, 5μ) column, NH_4OAc (10 mM): CAN::90:10 for liquid chromatogram. X-ray crystallographic data were collected from SMART (Bruker,

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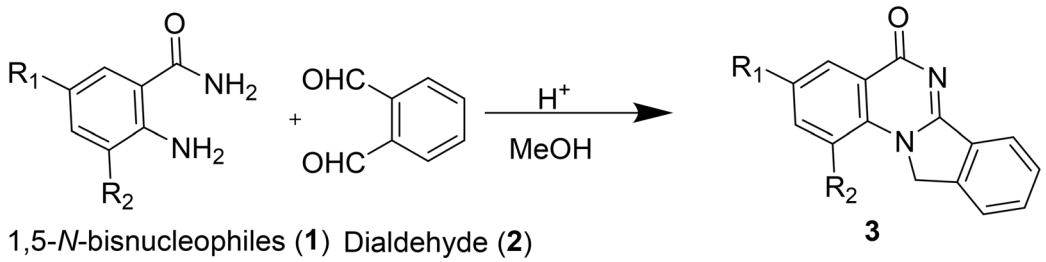


Scheme 1. Synthesis of isoindole-fused quinazolin 4-ones

2000), SHELXL-2018/3, version 2018/3', at 273K, θ range (deg) 2.618 to 27.135, radiation type λ (Mo Kα).

2.2 *Experimental procedure and spectral data*

*Synthesis of 5-oxo-11, 12-dihydro-5H-isoindolo[2,1-a]quinazolin-12-ium chloride (**3aHCl**)*: A mixture of anthranilamide (340 mg, 2.50 mmol), and *o*-phthaldehyde (334.9 mg, 2.50 mmol) were taken in 100 mL round bottom flask. Then to this reaction mixture, 30 mL MeOH and 2(*N*) HCl (10 mL) were added. This reaction mixture was stirred at room temperature for 24 h. Then, the precipitate appeared was collected by filtration and washed with water to get **3aHCl** (411 mg, 70%). M.p. 256 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 8Hz, 1H), 8.25(d, J = 8Hz, 1H), 8.06 (dt, J = 8Hz, 1H), 7.87–7.93(m, 3H), 7.77–7.68 (m, 2H), 5.71 (s, 2H); Calculated mass for $C_{15}H_{11}N_2O$ is 235.0871, observed *m/z* = 235.0328.

*Synthesis of isoindolo[2,1-a]quinazolin-5(11H)-one (**3a**)*. The solid mass of **3aHCl** (132 mg) was treated with saturated $NaHCO_3$ solution (5 mL) for 5 min and then the suspension was filtered washed with water, dried to get **3a** (102 mg, 89%) as white solid. M.p. 258 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.14 (s, 1H), 8.12 (d, J = 1.2 Hz,1H), 8.02 (d, J = 8Hz,1H), 7.89–7.85 (dt, J = 8, 15 Hz,1H), 7.82–7.74 (m, 1H), 7.66–7.63 (m, 2H), 7.51 (t, J = 15 Hz, 1H), 5.45 (s, 2H). ESI-TOF MS: Calculated mass for $C_{15}H_{10}N_2NaO$ is 257.0691, observed *m/z* = 257.1372

*Synthesis of 3-nitroisoindolo[2,1-a]quinazolin-5(11H)-one (**3b**)*: Same as described for **3aHCl**. Light yellow solid, yield 86%; M.p. 252 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 2Hz, 1H), 8.64 (d, J = 2Hz, 1H), 8.03 (d, J = 7.2Hz, 1H), 7.83–7.79 (m, 3H), 7.65 (t, J = 7.2Hz, 1H), 5.48 (s, 2H); ^{13}C-NMR (400 MHz, DMSO-d_6+$CDCl_3$) δ 166.8, 148.5, 142.6, 141.4, 139.6, 131.8, 130.1, 127.2, 126.6, 122.2, 122.1, 121.9, 116.6, 115.8, 50.7; ESI-TOF-MS: Calculated mass for $C_{15}H_9N_3NaO_3$ is 302.0542.064, observed *m/z* = 301.948

*Synthesis of 3-bromoisoindolo[2,1-a]quinazolin-5(11H)-one (**3c**):* Same as described for **3aHCl**. White Solid, Yield 88%; M.p. 257 °C; ^{1}H-NMR (400 MHz, DMSO-d_6+$CDCl_3$) δ 8.21 (s, 1H), 8.02 (d, J = 8Hz, 1H), 7.96–7.93 (m, 1H), 7.76–7.69 (m, 2H), 7.62–7.58 (m, 2H), 5.41 (s, 2H); ^{13}C-NMR (DMSO-d_6+$CDCl_3$) δ: 611.4, 149.9, 139.6, 137.5, 133.6, 131.9, 131.6, 131.5, 129.5, 124.5, 123.0, 120.1, 119.6, 116.3, 52.0; ESI-TOF MS: Calculated mass for $C_{15}H_9BrNaN_2O$ is 334.9796, observed *m/z* = 335.002.

*Synthesis of 1,3-dibromoisoindolo[2,1-a]quinazolin-5(11H)-one (**3d**)*: Same as described for **3aHCl**. White Solid, Yield 91%; M.p. 259 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 2Hz, 1H), 8.27 (d, J = 2Hz, 1H), 8.03 (d, J = 8Hz, 1H), 7.84–7.78 (m, 2H), 7.65 (d, J = 8Hz, 1H), 5.98 (s, 2H); ESI-TOF MS: Calculated mass for $C_{15}H_8$ Br_2N_2NaO is 414.8881, observed *m/z* = 414.753.

*Synthesis of 7,8,9,10-tetrahydrobenzo[4',5']thieno[3',2':5,6]pyrimido[2,1-a]isoindol-6(13H)-one (**3e**):* Same as described for **3aHCl**. White Solid, Yield 92%; M.p. 254 °C; ^{1}H-NMR (400MHz, DMSO-d_6 + $CDCl_3$) δ 7.96 (d, J = 8Hz, 1H), 7.70–7.62 (m, 2H), 7.56 (t, J = 8Hz, 1H), 5.24 (s, 1H), 2.94 (m, 2H), 2.73 (m, 2H), 1.84–1.76 (m, 4H); ESI-TOF-MS Calculated mass for $C_{17}H_{14}N_2NaOS$ is 317.0725, observed *m/z* = 317.0002

Synthesis of 11H-benzo[5,6][1,2,4]thiadiazino[3,4-a]isoindole 5,5-dioxide (**3f**): Same as described for **3aHCl**. White Solid, Yield 83%; M.p. 295 °C; ^{1}H NMR (400MHz, DMSO-d_6) δ 7.92 (dt, J = 8Hz, J = 12 Hz, 2H), 7.81–7.77 (m, 3H), 7.63 (m,1H), 7.53(m, 2H), 5.38 (s,2H); ESI-TOF-MS calculated mass for $C_{14}H_{10}N_2NaOS$ is 293.0361, observed *m/z* = 293.1225

2.3 *Experimental procedure for **3aDCl***

A mixture of anthranilamide (50 mg) and *o*-phthaldehyde (49 mg) were taken in a 50 mL round bottom flask. Then 3 mL methanol-d_4, 0.5 mL D_2O and 0.5 mL DCl (20%) were added into this reaction

mixture under argon atmosphere. The reaction mixture was stirred for 24 h to get white precipitation. The mixture was then diluted with 2 mL D_2O, filtered to collect white solid mass (61 mg, 71%). It was dried to get spectroscopic data. ^{1}H-NMR in DMSO-d_6 is essentially same with **3aHCl** except the position of residual H_2O present in the DMSO-d_6 solvent. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.43 (d, J = 8Hz, 1H), 8.26 (d, J = 8Hz, 1H), 8.07 (t, J = 8Hz, 1H), 7.94–7.88 (m, 3H), 7.78–7.69 (m, 2H), 5.71 (s, 2H); ESI-TOF-MS calculated mass for $C_{15}H_{10}DN_2O^+$ is 336.0929, observed m/z = 236.0995.

Compound **3aDCl** was treated with saturated bicarbonate and the white solid obtained after base treatment was subjected to ^{1}H-NMR. It was exactly same as observed for **3a**.

3. Results and Discussion

At the onset of the work, we have started synthesis of the compound **3a** by using the condition mentioned by Reinhard *et. al.* [2] Equimolar mixture of 2-aminobenzamide *o*-phthalaldehyde smoothly converted into compound **3a** in methanol and 2(*N*) HCl (aqueous) in 3:1 ratio at room temperature, from which white solid mass of hydrochloride salt (**3aHCl**) separated out. The solid mass was collected by filtration and washed with 3:1 methanol water provided analytically pure compound **3aHCl**. Crystallization of **3aHCl** was carried out in aq. methanol and the structure were solved by single-crystal *X*-ray diffraction study which is available as Supplementary Information. Crystal data and structure (Figure 1) shows that the tetracyclic skeleton is in planer geometry. The hydrogen bonding of the amide hydrogen through a water molecule forms a network in the solid. It is interesting to note that the position of the heteroatom in the structure of **3aHCl** (crystal structure) in solid-state is different from that in solution-state as there is absent of amide proton in the ^{1}H-NMR in DMSO-d_6 solvent. Compound **3aHCl** was converted to **3a** by washing with aqueous $NaHCO_3$ solution and ^{1}H-NMR was according to the structure and exactly matched with the reported data[6, 7] Use of other mild Lewis acid resulted in low yield. Aprotic solvent DMF can be used; however methanol or ethanol medium benefits product isolation without column purification. We used methanol for synthesizing the compounds mentioned here.

Using the above-mentioned condition, substrate scope was investigated with different substituted amide. We have synthesized varieties of the substituted tetracyclic skeleton (**3b-d**). Notably, for the substituted antranilamides (Table 1, entry 2–6), compound **3b-c** (Figure 2) were isolated directly from the reaction mixture by simple filtration in the salt-free form. This is presumably because of electron-withdrawing group present in the amide part (entry 2–6, Table 1), making the tertiary amine center less basic. Compound **3b-d** are not reported in the literature. We have confirmed the structures by NMR and HRMS. Compound **3e**, synthesized under the acid-catalyzed condition in 91% isolated yield from the compound **4** and *o*-phthalaldehyde with improved isolated yield and reaction condition.[9] Compound **3f** was isolated as a white solid from the equimolar mixture of 2-aminobenzenesulfonamide and *o*-phthalaldehyde under the reaction condition mentioned in Table 1. Synthesis of compound **3f** is reported in a multistep procedure without sufficient spectroscopic data.[8] Because of poor solubility in common organic solvents, we were unable to collect ^{13}C-NMR data of **3d**. Investigation of substrate scope revealed that the electronic nature of the substituent present on the amide moiety does not affect significantly on yield.

Mainly two types of mechanistic pathways; namely, intramolecular hydride transfer (Path-A)[9] and tautomerism (Path-B)[10] have been proposed for the reaction of *o*-phalaldehyde and structurally similar 1,5-*N*-bisnucleophiles. Path-A involves intramolecular 1,3-hydride transfer (as proposed by Abdel-Latif *et al.* [9]) without the participation of solvent proton in the key step. Whereas, in the Path-B (Scheme 2) multiple tautomeric sequences by which hydrogen atom transferring with the participation of solvent proton may lead to the compound **3aHCl** (as proposed by Ukhin *et al.* [10]). To confirm the mechanistic pathway for the formation of **3aHCl**, we have carried out the reaction of *o*-phthalaldehyde with 2-aminobenzamide in DCl/CD_3OD at RT. We observed the exclusive formation of compound **3aDCl**, but not **3aD_2Cl**. For further confirmation of

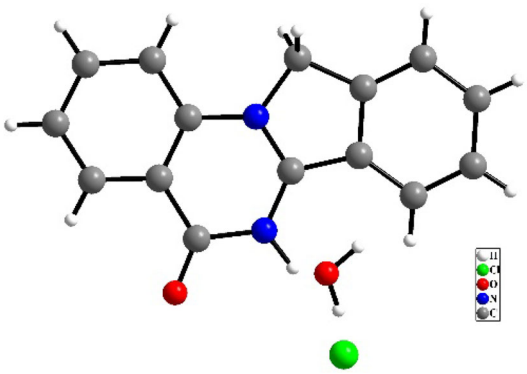
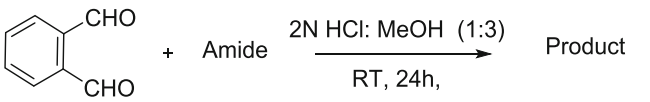


Figure 1. Crystal structure of **3aHCl**

Table 1. Synthesis of isoindole fused quinazolin 4-ones



Entry	Amide	Product
1	2-Aminobenzamide	**3aHCl**
2	2-amino-5-nitrobenzamide	**3b**
3	2-amino-5-bromobenzamide	**3c**
4	2-amino-3,5-dibromobenzamide	**3d**
5	Compound **4**	**3e**
6	2-aminobenzenesulfonamide	**3f**

Reaction conditions: aldehyde (2.50 mmol), amide (2.50 mmol), in 30 mL MeOH and 10 mL HCl (2*N*) at RT for 24 h

structure **3aDCl**, it was treated with aqueous $NaHCO_3$ and observed the formation of **3a**. The NMR and HRMS spectra of **3a** obtained from the above mentioned deuterated experiment shows no deuterium incorporation in the structure **3a**. Formation of **3aDCl** and **3a** under deuterated solvent clearly shows that the rearrangement of initial intermediate **6** into **3a** is intramolecular hydride transfer as shown in Path-A in Scheme 2. The 1,3-hydride transfer is being facilitated by the electron-rich amide nitrogen donor center. Acid-catalyzed intramolecular hydride transfer from *sp3* carbon adjacent of nitrogen center to closely spaced electrophilic center is well-known and an established phenomenon.[11]

Based on the deuterated solvent experiment, the proposed mechanism for the formation of **3a** is assumed to be essentially same as proposed by Abdel-Latif *et al.*[9] (Path-A, Scheme 2. The method involves initial formation of monomeric compound **5**, followed by iminium ion (**6**) formation. The subsequent intramolecular 1,3-hydride transfer gave compound **3aDCl**. After the treatment of **3aDCl** with aqueous $NaHCO_3$ the resultant outcome was **3a**.

4. Conclusions

In summary, one-pot synthesis of isoindole fused quinazolin-4 ones was carried out in the presence of an acid catalyst. Electronic nature of substituents on amide side have a negligible effect on the key step intramolecular hydride transfer. The mechanistic study under deuterated solvent revealed that the reaction proceeds through intramolecular 1,3-hydride transfer reaction. Further study needed to understand the stereo chemical aspect of the hydride transfer reaction. The method could be applicable with differently substituted *o*-phthaladehyde derivatives.

Supplementary Information (SI)

Crystallographic data for the structures 3aHCl in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1907967. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk) Supplementary information containing crystal structure and refinement parameters and spectra are available at https://www.ias.ac.in/chemsci.

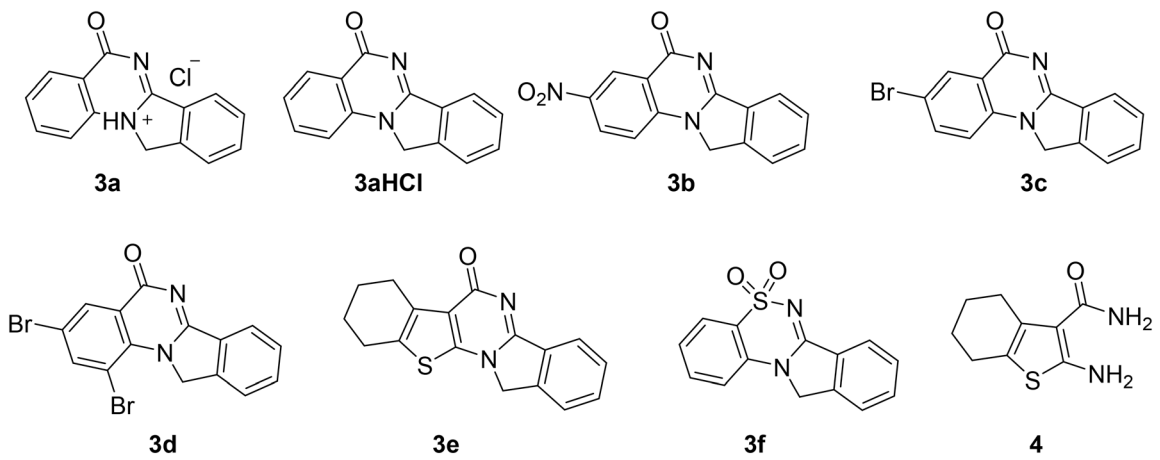
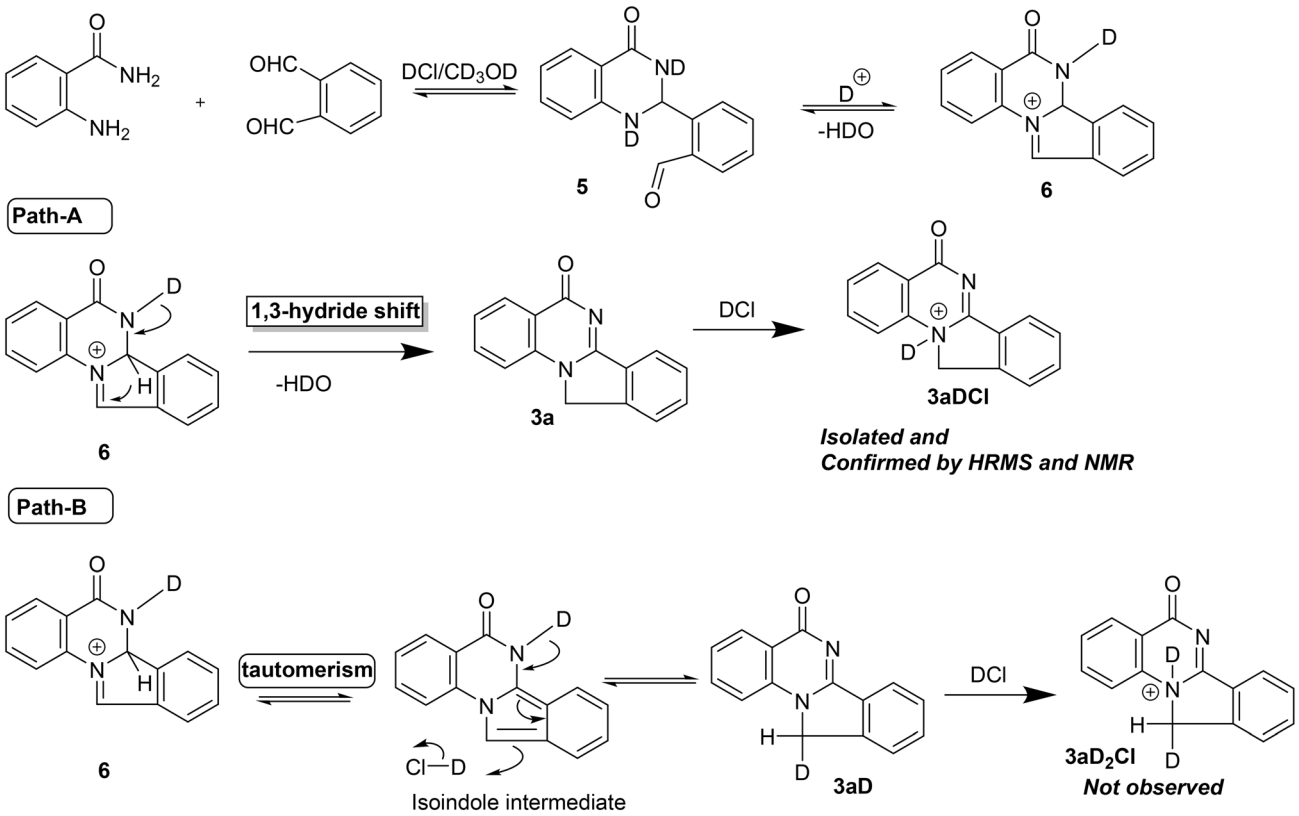


Figure 2. Structure of the synthesized isoindole fused quinazolin 4-ones



Scheme 2. Possible mechanism

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