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Graphical Abstract

A simple one pot synthesis of novel tricyclic quinazolinones

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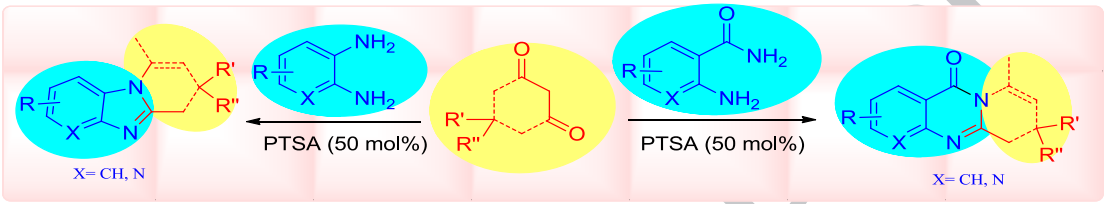

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A simple one pot synthesis of novel tricyclic quinazolinones

Chiranjeevi Bingi,[a] Kaushik Yadav Kola,[a] Ashok Kale,[a] Jagadeesh Babu Nanubolu[b] and Krishnaiah Atmakur*[ac]

[a] *Division of Crop Protection Chemicals, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India.*
[b] *Laboratory of X-ray crystallography, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India.*
[c] *AcSIR- Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India.*

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ABSTRACT

Synthesis of a series of tricyclic quinazolinones have been accomplished starting from anthranilamide and 1,3-cyclic dione promoted by $TsOH.H_2O$. The protocol presented herein based on retro-Dieckmann type reaction, leading to incorporation of dione as an acyclic unit into the product. Simple reaction conditions, broad scope, excellent yields are the advantages of this protocol. Further, this methodology is extended to the synthesis of pyridopyrimidinones and benzimidazopyridines.

Quinazolinones are an important class of compounds among N-heterocycles owing to their diverse range of biological properties such as anticancer,[1] antiinflammation,[2] antihypertensive,[3] antitumor[4] and antibacterial activity.[5] Some of these compounds were also reported as potent chemotherapeutic agents in the treatment of tuberculosis.[6] Well-known indoloquinazoline alkaloid i.e. Rutaecarpine and its 7,8-dehydro analogue[7] is known to exhibit anti-inflammatory activity. Further, 2,3-tetramethylene-4-(3*H*)-quinazolinone (mackinazolinone)[8] isolated from mackinalaya species has been reported for bronchodilatory, anti-inflammatory, antimicrobial and antidepressant activities. Out of these quinazolinone moieties, 4(3H)-quinazolinones are most prevalent either as intermediates or as natural products in many biosynthetic pathways. Based on the importance of these chemical entities, a great deal of effort has been devoted to the synthesis of these compounds and thus a number of protocols have appeared. For example, diverse N-fused heterocycles have been synthesized from pyridine derivatives via transition-metal catalyzed coupling, cycloisomerization, oxidation, and other reactions.[9] Recently, Yu zhou reported the synthesis of pyrido / pyrrolo[2,1-*b*]quinazolin-9(1*H*)-ones through silver mediated intramolecular hydroamination reaction.[10]

Beller, Wu reported the synthesis of fused quinazolinones by palladium-catalyzed carbonylation / nucleophilic aromatic substitution sequence.[11] 11*H*-Pyrido[2,1-*b*]quinazolin-11-one was prepared by the palladium-catalyzed C−H carbonylation of *N*-aryl-2-aminopyridines.[12] In 1983, K. Sumoto and co-workers reported the synthesis of 2-substituted 4-oxo-3,4 dihydroquinazolines and 1-methyl-3,4-dihydropyrido[1,2-*a*] benzimidazoles by fusing enamino-ketones at 250-260 °C.[13] However, they were unsuccessful to convert the dihydroquinazolinones into tricyclic quinazolinones. Similarly, Xiang-Shan Wang[14] reported the iodine-catalyzed reaction of 2-aminobenzamides with 1,3-cyclohexanediones to give quinazolin-4(3*H*)-one and bis quinazolin-4-(3*H*)-one derivatives.

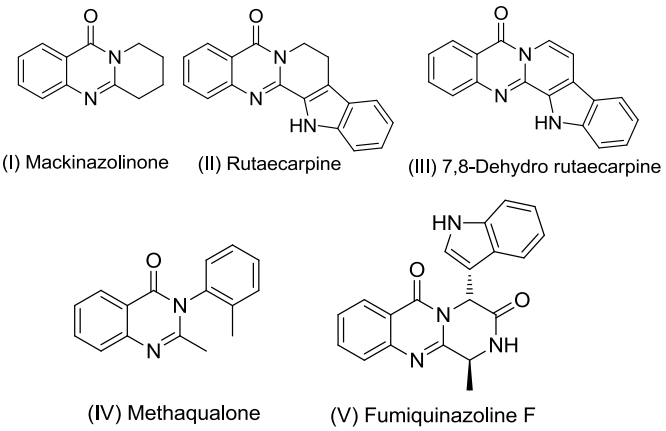


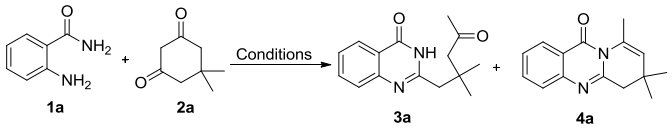
Figure-1: Selected structures of fused quinazolinones.

However, to the best of our knowledge, there are no reports available on the synthesis of tricyclic quinazolinones by incorporating 1,3-dione as an acyclic unit. With this background and also as a part of our ongoing research interest on the synthesis of N-heterocyclic new chemical entities of biological interest,[15] we have come out with a simple, so far unreported

methodology for synthesis of tricyclic quinazolinones in a one pot two component reaction where 1,3-dione incorporates as an acyclic unit into the product.

Initially, we have conducted a reaction with anthranilamide (**1a**) and dimedone (**2a**) by employing $TsOH.H_2O$ at 150 ^oC under neat reaction condition. Interestingly, formation of **3a** and **4a** were observed in poor yields. In order to obtain the compound **4a** exclusively, the same reaction was carried out by employing benzenesulfonic acid, camphorsulfonic acid and $SnCl_2.2H_2O$ independently in toluene medium at 150 ^oC temperature in sealed tube but ended up with the same mixture of **3a** and **4a.** Nevertheless, yield of **4a** improved to around 55% (table-1).

Table 1. Optimization of reaction conditions to obtain tricyclic quinazolone compound (**4a**).[a]



S. No	Solvent	Catalyst	Quantity	Time	Yield (%) 3a	Yield (%) 4a
1	Neat	$TsOH.H_2O$	1eq	10h	40	35
2	Toluene	$TsOH.H_2O$	1eq	8h	20	58
3	Toluene	CSA	1eq	8h	21	55
4	Toluene	BSA	1eq	8h	25	45
5	Toluene	$SnCl_2.2H_2O$	1eq	8h	21	56
6	*m*-Xylene	$TsOH.H_2O$	1eq	8h	-	86
7	*m*-Xylene	CSA	1eq	8h	-	78
8	*m*-Xylene	BSA	1eq	8h	10	68
9	*m*-Xylene	$SnCl_2.2H_2O$	1eq	8h	-	80
10	*m*-Xylene	$FeCl_3$	1eq	8h	10	70
11	*m*-Xylene	CF_3COOH	1eq	8h	-	-
12	*m*-Xylene	H_2SO_4	1eq	8h	-	-
13	AcOH	$TsOH.H_2O$	1eq	8h	40	25
14	Ethanol	$TsOH.H_2O$	1eq	8h	65	-
15	*m*-Xylene	$TsOH.H_2O$	0.5 eq	8h	-	86
16	*m*-Xylene	$TsOH.H_2O$	0.4 eq	8h	-	79
17	*m*-Xylene	I_2	1eq	8h	68	10

[a]Reaction conditions: 2-amino benzamide (**1a**, 3.67 mmol), dimedone (**2a**, 3.67 mmol), additive and solvent (5ml) were stirred in a sealed tube at 150 ^oC temperature for 8h. Yields refer to pure products after column chromatography.

Next, the same reaction was further carried out in xylene in presence of $TsOH.H_2O$ (1equivalent) under similar reaction conditions in sealed tube. Interestingly, this time compound **4a** was obtained exclusively in 86%yields (table 1, entry 6). Structure of **4a** was characterized by the spectral data and unambiguously confirmed by the X-ray crystallography studies (Fig-2).[16]

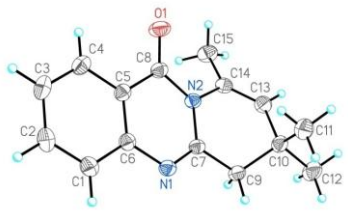
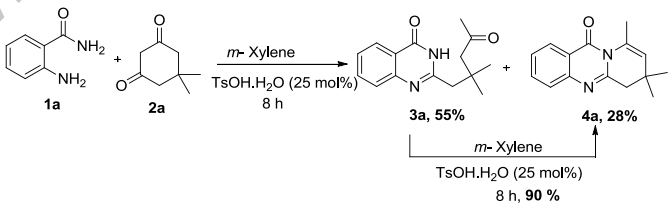


Figure-2: ORTEP diagram of compound **4a**

On the other hand, the same reaction when conducted independently in presence of CSA and $SnCl_2.2H_2O$ in xylene in a sealed tube, gave compound **4a** exclusively (table-1, entries 7&9), whereas in presence of BSA formation of **3a** and **4a** were observed in lower yields. Further, no reaction was observed with trifluoroacetic acid and also with the sulphuric acid. Having obtained the composite results from the aforesaid studies, it was decided to scrutinize the $TsOH.H_2O$ quantity and streamline the reaction parameters to obtain **4a**.

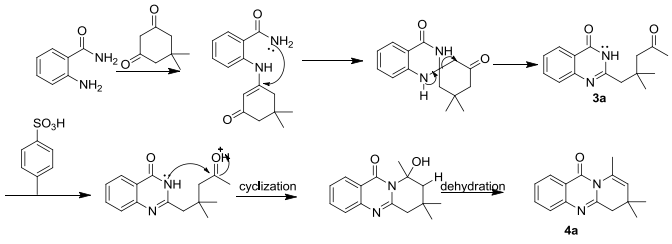
In this instance, a reaction was carried out with **1a** and dimedone by employing 50 mole% $TsOH.H_2O$ in xylene and obtained the product **4a** in 86%yields (table-1, entry-15). However, the same reaction when conducted with 40 mole% $TsOH.H_2O$, decreased in yield i.e., 79% was observed (table-1, entry-16). Further, there was no perceptible improvement in the yields when dosage of $TsOH.H_2O$ increased. Therefore, it was concluded that 50 mole% of $TsOH.H_2O$ in Xylene at 150 ^oC was found to be a suitable parameter to obtain tricyclic quinazolinones (**4**). Dosage of $TsOH.H_2O$ was further substantiated by conducting the controlled experiments with 25 mole% of $TsOH.H_2O$ and obtained **3a** in 55 % and tricyclic quinazolinone compound (**4a**) only in 28 % yields (Scheme-1). Further, compound **3a** was exclusively treated with 25 mole% $TsOH.H_2O$ and was completely converted to **4a**. This is further evident that 50 mole% of $TsOH.H_2O$ is essential and at the same time it is responsible for ring cleavage and as well as for ring closing.

Scheme-1: Control Experiments



Looking at the formation of **3a** and **4a**, we postulated a pathway for the formation of these compounds where **1a** reacts with **2a** leading to enamino ketone followed by the formation of spiro compound. On subsequent ring cleavage of spiro compound in retro-Dieckmann type reaction under acidic condition lead to compound **3a**.[13] Next, lone pair electrons on the amide nitrogen of **3a** are attacking on the carbonyl carbon of acyclic unit leading to the formation of tricyclic ring followed by subsequent dehydration (Scheme-2) is resulting in to the product **4a**.

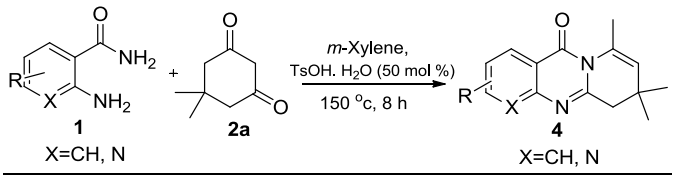
Scheme-2: Plausible mechanism for formation of **4a**

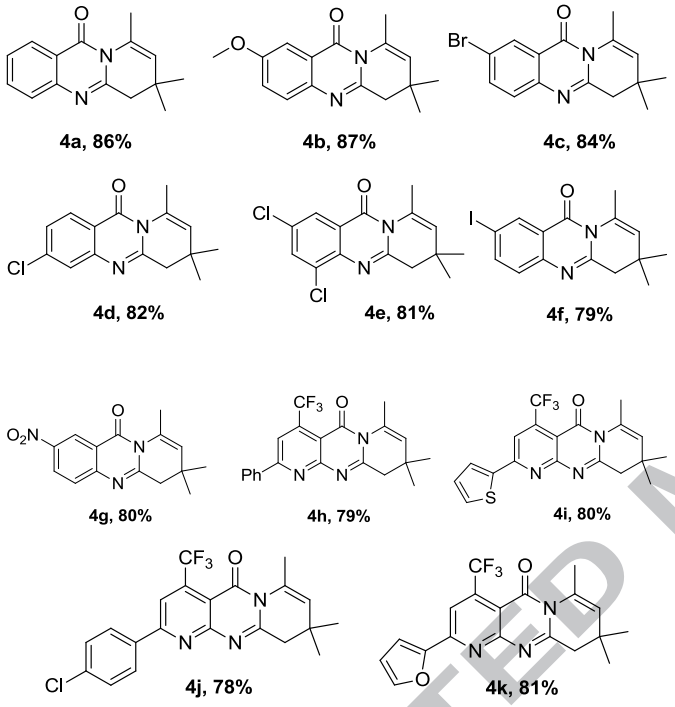


With the set reaction conditions on hand, the scope of this protocol was generalized by extending to various anthranilamides bearing electronic donating and electron withdrawing groups and also varying 1,3-diones leading to **4a-k**. To our satisfaction this method is highly compatible and no electronic effect was observed. However, the yields were varied. Compounds with electronic donating groups gave the better yields when compared to the electron withdrawing groups (scheme-3). Encouraged by the synthesis of tricyclic

quinqzolinones (**4a-g**) exclusively in excellent yields, this protocol is extended to prepare trifluoro methyl substituted tricyclic quinqzolinones compounds (**4h-k)** in good yields.

Scheme-3: Preparation of tricyclic quinazolinones (**4**) from anthranilamide and dimedone.[a]

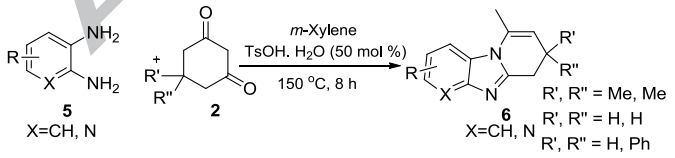


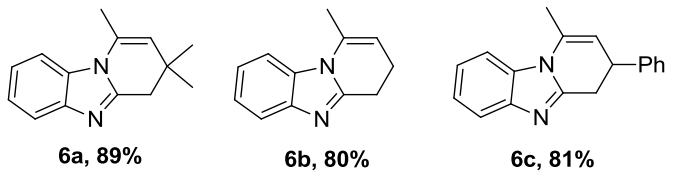


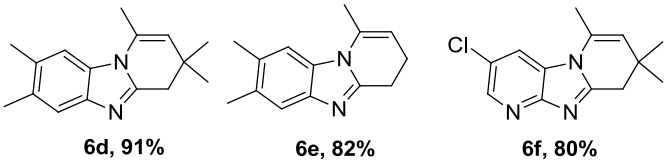
[a]Reaction conditions: 2-amino benzamide (**1**, 3.67 mmol), cyclic 1,3-dione (**2**, 3.67 mmol), $TsOH.H_2O$ (1.83 mmol) and *m*-xylene (5ml) were stirred in a sealed tube at 150 °C temperature for 8h. Yields refer to pure products after column chromatography.

Further, this protocol also extended to 1,2-diaminobenzene (**5**) to result in corresponding tricyclic benzo imidazo pyridine compounds (**6**) in high yields (Scheme-4).

Scheme-4: Preparation of 3,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridines (**6**) from 1,2-diamino benzene and 1,3-diketone.[a]



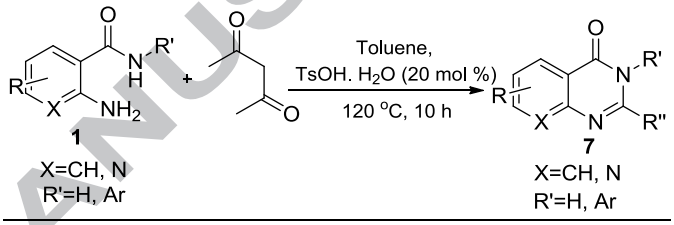


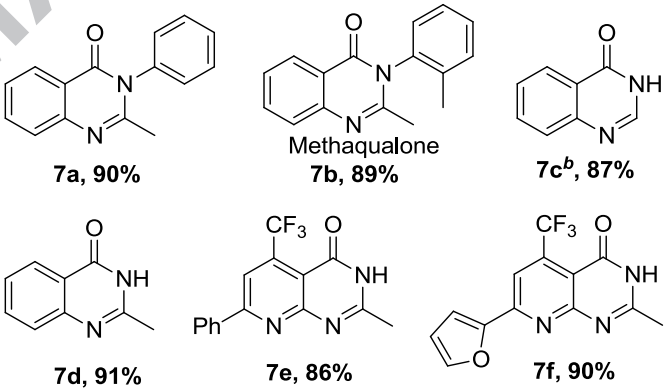


[a] Reaction conditions: 1,2-diamino benzene (**5**, 4.62 mmol), cyclic 1,3-dione (**2**, 4.57 mmol), $TsOH.H_2O$ (2.31 mmol) and *m*-xylene (5ml) were stirred in a sealed tube at 150 °C temperature for 8h. Yields refer to pure products after column chromatography.

Furthermore, this protocol is also extended to acyclic ketones, where 2-amino benzamides, 2-amino nicotinamides are successfully reacted with acyclic 1,3-diones leading to quinazolones[17] and pyridopyrimidinones (**7**). It is notable to mention that products **7** were obtained in good yields with 20 mole% of $TsOH.H_2O$ (Scheme-5) in toluene medium.

Scheme-5: Preparation of quinazolin-4(3*H*)-one (**7**) from 2-amino benzamides and 1,3-diketone.[a]





[a]Reaction conditions: 2-amino benzamide (**1**, 3.67 mmol), acetyl acetone (4.04 mmol), $TsOH.H_2O$ (0.73 mmol) and toluene (5ml) [b]2-amino benzamide (**1**, 3.67 mmol), $TsOH.H_2O$ (0.73 mmol) in 5 ml of DMF were stirred in a sealed tube at 120 °C temperature for 10h. Yields refer to pure products after column chromatography.

In conclusion we have developed a novel method for the synthesis of tricyclic quinazolinones by incorporating dimedone as a C_6-acyclic unit which was derived from retro-Dieckmann type ring cleavage. To the best of our knowledge this is for the first time that the dione moiety is incorporated as an C_6-acyclic unit to get the tricyclic quinazolinones. Further, this method has wide applicability, high compatibility and may useful in synthesizing more N-containing heterocycles.

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16. CCDC **1448259** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html[or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: www.ccdc.cam.ac.uk/data_request/cif.
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Highlights

A simple one pot synthesis of novel tricyclic quinazolinones

- $TsOH.H_2O$ induced synthesis of tricyclic quinazolinones from anthranilamide and diones
- Protocol based on retro-Dieckmann type reaction
- Incorporation of dione as an acyclic unit into the product stream for the first time
- Methodology extended to pyridopyrimidinones and benzimidazopyridines
- Simple reaction conditions, broad scope and excellent yields.