Tetrahedron Letters 58 (2017) 1071–1074

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A simple one pot synthesis of novel tricyclic quinazolinones

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ARTICLE INFO

Article history:
Received 2 January 2017
Revised 28 January 2017
Accepted 31 January 2017
Available online 3 February 2017

Keywords:
2-amino benzamides
1,3-diketones
Quinazolinones
Pyridopyrimidinones
Benzimidazopyridines

ABSTRACT

Synthesis of a series of tricyclic quinazolinones have been accomplished starting from anthranilamide and 1,3-cyclic dione promoted by $TsOH{\cdot}H_2O$ 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 (see Fig. 1). 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.

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 $TsOH{\cdot}H_2O$ at 150 °C 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 $SnCl_2{\cdot}2H_2O$ independently in toluene medium at 150 °C 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).

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http://dx.doi.org/10.1016/j.tetlet.2017.01.106
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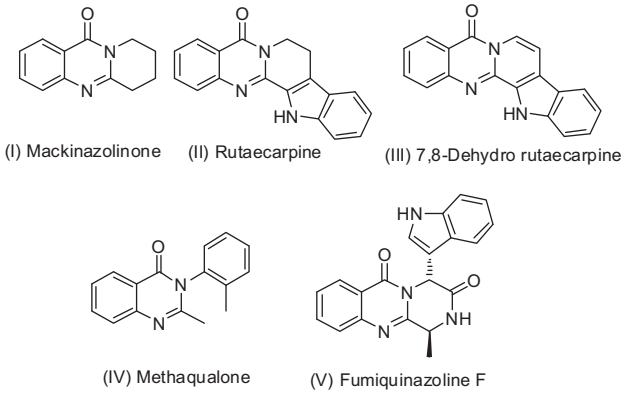


Fig. 1. Selected structures of fused quinazolinones.

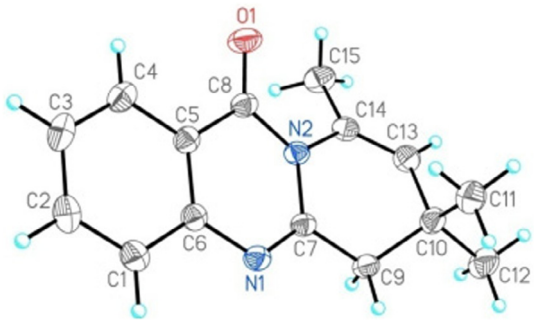


Fig. 2. ORTEP diagram of compound **4a**.

Next, the same reaction was further carried out in xylene in presence of $TsOH{\cdot}H_2O$ (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]

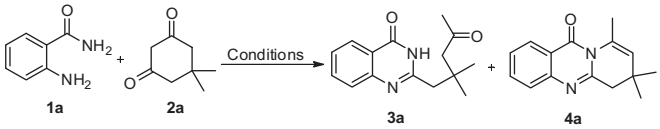
On the other hand, the same reaction when conducted independently in presence of CSA and $SnCl_2{\cdot}2H_2O$ in xylene in a sealed tube, gave compound **4a** exclusively (Table 1, entries 7&9), whereas in presence of BSA formation of **3a** and **4a** were observed in lower yields. Further, no reaction 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 $TsOH{\cdot}H_2O$ quantity and streamline the reaction parameters to obtain **4a**.

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

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 into the product **4a**.

With the set reaction conditions on hand, the scope of this protocol was generalized by extending to various anthranilamides

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	$TsOH{\cdot}H_2O$	1 eq	10 h	40	35
2	Toluene	$TsOH{\cdot}H_2O$	1 eq	8 h	20	58
3	Toluene	CSA	1 eq	8 h	21	55
4	Toluene	BSA	1 eq	8 h	25	45
5	Toluene	$SnCl_2{\cdot}2H_2O$	1 eq	8 h	21	56
6	*m*-Xylene	$TsOH{\cdot}H_2O$	1 eq	8 h	–	86
7	*m*-Xylene	CSA	1 eq	8 h	–	78
8	*m*-Xylene	BSA	1 eq	8 h	10	68
9	*m*-Xylene	$SnCl_2{\cdot}2H_2O$	1 eq	8 h	–	80
10	*m*-Xylene	$FeCl_3$	1 eq	8 h	10	70
11	*m*-Xylene	CF_3COOH	1 eq	8 h	–	–
12	*m*-Xylene	H_2SO_4	1 eq	8 h	–	–
13	AcOH	$TsOH{\cdot}H_2O$	1 eq	8 h	40	25
14	Ethanol	$TsOH{\cdot}H_2O$	1 eq	8 h	65	–
15	*m*-Xylene	$TsOH{\cdot}H_2O$	0.5 eq	8 h	–	86
16	*m*-Xylene	$TsOH{\cdot}H_2O$	0.4 eq	8 h	–	79
17	*m*-Xylene	I_2	1 eq	8 h	68	10

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