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Mukaiyama's reagent promoted mild protocol for one-pot metal-free synthesis of dihydro quinazolinones

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ABSTRACT

We have developed a fast and convenient method to prepare dihydroquinazolin-4(1H)-ones from anthranilamide and different aromatic aldehydes by using the Mukaiyama reagent. The reactions proceeded smoothly with a broad scope of substrates providing the expected products in good to excellent yields under with a low environmental factor and high atom economy. The metal-free condition and the ease of product isolation are the highlighted advantages in solving the issue of trace metal contamination in synthesized pharmaceuticals.

The Mukaiyama reagent (2-chloro-1-methylpyridinium iodide, CMPI) was introduced as a useful reagent for the synthesis of carboxylic esters by Teruaki Mukaiyama in 1975 [1]. CMPI is one of the most valuable reagent for activation of hydroxyl groups of carboxylic acids and alcohols [2]. This important reagent can be easily synthesized from 2-chloropyridine and methyliodide [3,4]. It is widely used for the synthesis of esters [5], lactones [6], amides [7], ketenes [8] lactams [9], from the corresponding carboxylic acids. Furthermore, it is also helpful in conversion of thioureas into carbodiimides [10], and alcohols into the corresponding alkyl thiocyanates [11]. The Mukaiyama reagent also play significant role in peptide synthesis [12]. Inspired with the above results, our group has recently used this reagent for one-pot two-step synthesis of isatoic anhydrides from anthranilic acid and di-*tert*-butyl dicarbonate [13] (Scheme 1). The Mukaiyama reagent also used for C—N bond formation, for synthesis of 3-alkylquinazolin-4-ones [14]. Very recently, a mild and general method for preparation of acyl sulphonamides from carboxylic acids and sulphonamides by using the Mukaiyama reagent was also reported [15].

Furthermore, the importance of heterocyclic compounds has long been recognized in the field of synthetic organic chemistry. Currently, heterocyclic compounds have been extensively studied due to their important properties and applications. It is well known that a number of nitrogen containing heterocyclic compounds exhibited a wide variety of biological activity. The quinazolinone moiety is a building block for many drugs [16] like Quinethazone, Metolazone, Methaqualone and Diuretic (Fig. 1). Among these compounds, quinazolinone derivatives have become especially noteworthy in recent years owing to their broad spectrum of biological activity including anti-inflammatory [17–19] antitumor [20–23,55] antibacterial [24–26] antimalarial [27] antiviral [28–30] anti-fungal [31] anticonvulsant [32] activities.

Thus, due to the diverse range of the pharmacological activities of quinazolinones and their derivatives, there are numerous protocols available for their synthesis and naturally occurring quinazolinone synthesis. Most of the synthetic protocols for quinazolinone [33–42] reported so far suffer from harsh reaction conditions [35], prolonged time period [36], use of hazardous acid catalysts [42], high catalyst loading [38], and expensive methods [40], and yields are oftentimes low due to poor selectivity in such conditions. Several nonacidic transition metal catalyzed [38,41], nanoparticle catalyzed [43], and ionic liquid mediated [44] syntheses of these molecules have also been reported. More recently, efficient, cost-effective and greener process of one-pot metal free conditions also reported [56–58]. Therefore, development of a new catalytic metal free condition route is an active area of research. We herein report an efficient modular one-pot metal free method for the synthesis of 2,3-dihydroquinazolin-4(1H)-one.

Here, we describe an innovative one-pot highly selective synthesis of quinazolinones catalyzed by Mukaiyama reagent. The reaction takes place through a cascade comprising (i) a novel and mild Mukaiyama reagent mediated activation of the carbonyl group of an aldehyde or ketone, which is further attacked by the

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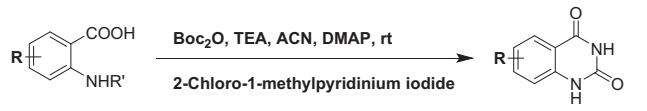
0040-4039/



Mukaiyama reagent promoted one-pot two-step synthesis of isatoic anhydrides[13]

Scheme 1. Mukaiyama reagent promoted one-pot two-step synthesis of isatoic anhydrides [13].

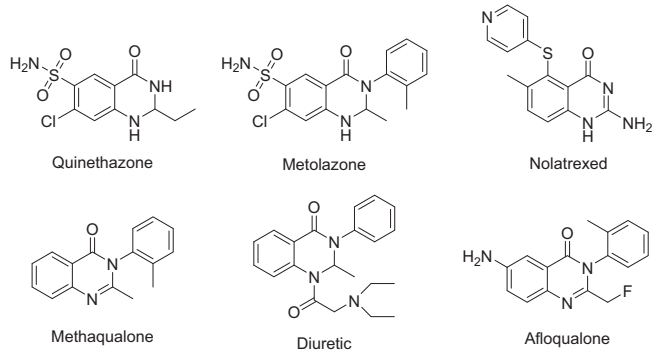


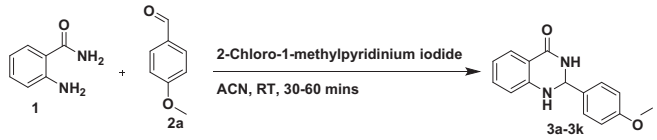
Fig. 1. Structures of biologically important quinazolinones.

amine functionality of anthranilamide to generate the imine and, (ii) intramolecular cyclocondensation of imine to furnish the final quinazolinones. (Scheme 2).

In the current protocol, we have used 2-aminobenzamide (**1**) and 4-methoxy-benzaldehyde (2a) as model substrates for the optimization of the reaction conditions as shown in Scheme 2. The reaction conditions were optimized with respect to the quantity of catalyst (Table 1) and the solvent (Table 2) by studying the condensation of 2-aminobenzamide (**1**) with 4-methoxybenzaldehyde (**2a**).

To determine the catalyst loading, a model reaction of 2-aminobenzamide and 4-methoxybenzaldehyde with different equivalent of CMPI in acetonitrile were carried out. The reaction completed smoothly in the presence of (0.5 eq.) CMPI as a catalyst and Acetonitrile as a solvent at room temperature, affording a single product in 94% yield. Increasing or decreasing the amount of catalyst, more than 0.3 equivalent showed no significant improvement in the yield (Table 1). In absence of CMPI, the reaction in acetonitrile was incomplete even after an extended reaction time.

In order to determine effect of solvent on the reaction conversion using 0.5 eq. of CMPI as catalyst at room temperature, various solvents like THF, 2-Methyltetrahydrofuran, CH_3CH_2OH, 1,4-dioxane, ACN and water was examined. Among these solvents (Table 2, entries 1–6), Acetonitrile (ACN) was selected to be the best reaction media for its higher yielding and shorter reaction time (Table 2, entry 5). Interestingly, in water the reaction proceeds very smoothly but requires a long reaction time, which might be attributed to the poor solubility of the starting substrates in water. The



Effective approach for the one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-one

Scheme 2. Effective approach for the one-pot synthesis 2,3-dihydroquinazolin-4 (1H)-one.

Table 1
Optimization of catalyst loading.

Entry	Amount of CMPI (Eq.)	Yield (%) isolated
1	1.0	93
2	0.3	59
3	0.5	94
4	0.7	94

Table 2
Optimization of solvent.

Entry	Solvents	Time (h)	Yield (%)[a]
1.	THF	8	47
2.	2-Methyltetrahydrofuran	10	39
3.	CH_3CH_2OH	12	48
4.	1,4-Dioxane	10	50
5.	ACN	0.5	94
6.	H_2O	16	74

0.5 eq of CMPI, rt.
[a] Purified yield.

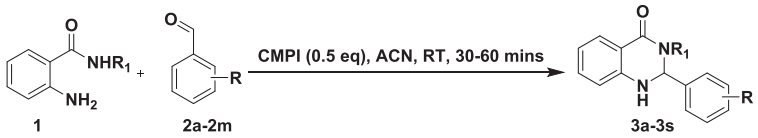
results of the solvents optimization experiments are summarized in Table 2.

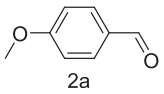
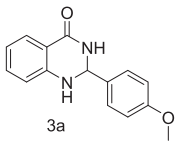
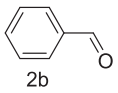
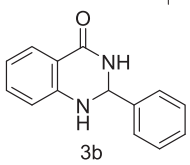
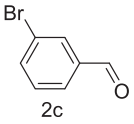
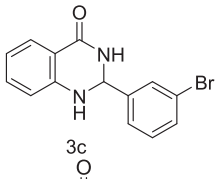
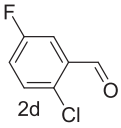
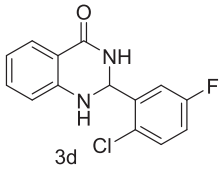
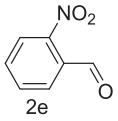
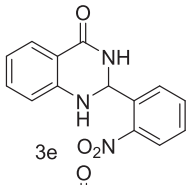
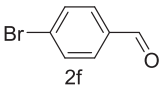
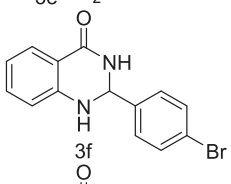
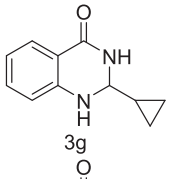
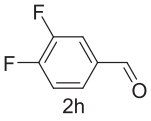
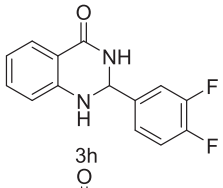
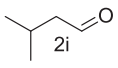
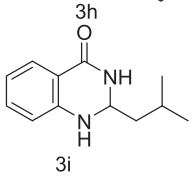
With the optimized parameters in hand we have also performed [59] wide substrate study with different aromatic aldehydes having electron-donating and electron withdrawing substituents to form a series of dihydroquinazolin-4(1H)-ones derivatives **(3a-k)**. The electronic effects have no significant impact on reaction rate; nevertheless, in *ortho*-substituted aldehydes the reaction time was long, which directly reflects its steric property. Substituted (naphthalen-1-yl/2-yl)benzaldehyde was also readily introduced into the quinazolinone skeleton at the 2-position, and desired products **(3j and 3k)** were formed in good yield. To demonstrate the utility of this method, 2,3-disubstituted quinazolinones **(3l-3s)** were also synthesized with aliphatic and aromatic amines. The reaction of anilines with isatoic anhydride led to the synthesis of *N*-substituted benzamide **(3t)**, which have poor nucleophilicity toward the cyclocondensation reaction in the synthesis of 3-substituted quinazolinones. We screened CMPI as catalyst in such cyclocondensation reactions, and the results obtained are good (**3i-3s**, Table 3). These 3-substituted quinazolinones are also important molecules in pharmacological aspects. As only few methods are available for the synthesis of these 3-substituted quinazolinones, our methodology can serve as a useful tool in synthesis of these pharmacologically active scaffolds, with good to excellent yield of desired products.

A plausible mechanism for the formation of these quinazolinones is proposed in Scheme 3. Being an electron deficient system, CMPI (0.5 eq) might activate the carbonyl group of aldehyde, which is simultaneously attacked by anthranilamide to form the intermediate with 0.5 equivalent amount of HCl. The so produced HCl might further catalyse the reaction to form the Schiff base after the elimination of the bulky 1-methylpyridin-2-one group, and finally intramolecular cyclization affords the desired product in quantitative yield. The isolation of the intermediates in the given course of reaction is not possible as the CMPI-aldehyde adduct may be unstable or short-lived, and in next step the elimination of 1-methylpyridin-2-one group might be very fast.

In conclusion, we have successfully developed a practical and operationally simple method for the synthesis of 2,3-dihydroquinazolin-4(1H)-one by using CMPI from 2-aminobenzamide and benzaldehyde in Acetonitrile medium at room temperature. This mild transformation would provide a simple, compatible, and potentially powerful method for the modular construction of quinazolinones. Furthermore, the moderate reaction conditions,

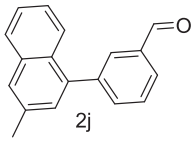
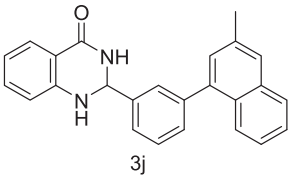
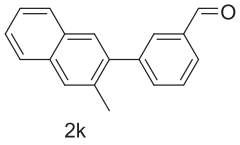
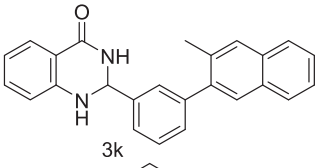
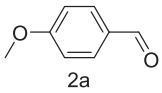
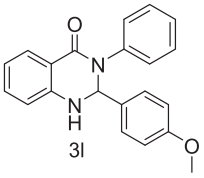
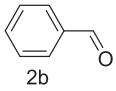
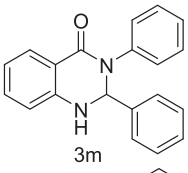
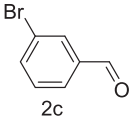
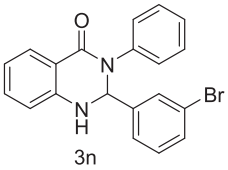
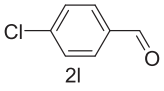
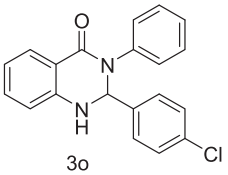
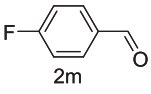
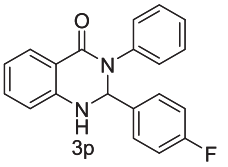
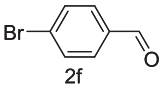
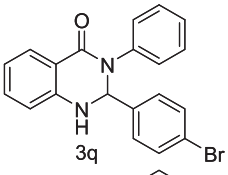
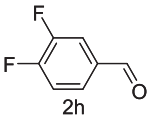
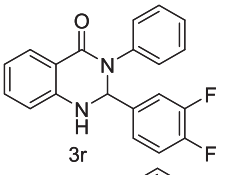
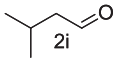
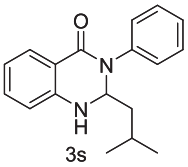
Table 3
Scope of the reaction with different aromatic and aliphatic aldehydes.



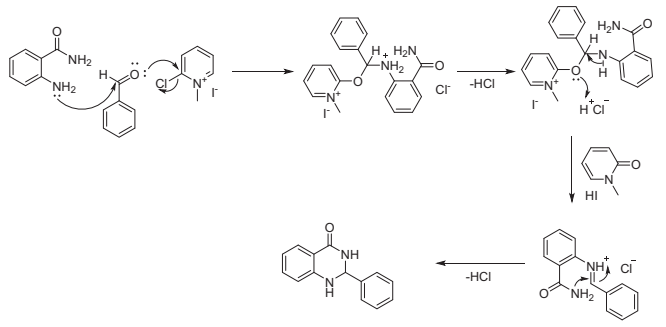
Entry	aldehyde	R_1	Dihydroquinazolinones	Yield %[a]	Melting point °C (reported)
3a		H		94%	186–188 (187–189) [45]
3b		H		95%	221–222 (218–220) [41]
3c		H		88%	185–189 (188–189) [46]
3d		H		99%	170–172
3e		H		84%	192–193 (190–193) [47]
3f		H		89%	203–205 (202–204) [48]
3g		H		99%	150–152
3h		H		92%	205–208
3i		H		65%	172–174 (171–172) [49]

(*continued on next page*)

Table 3 (*continued*)

Entry	aldehyde	R_1	Dihydroquinazolinones	Yield %[a]	Melting point °C (reported)
3j	 2j	H	 3j	86%	>250
3k	 2k	H	 3k	72%	198–200
3l	 2a	Ph	 3l	65%	204–207 (202–205) [50]
3m	 2b	Ph	 3m	78%	210–213 (212–214) [51]
3n	 2c	Ph	 3n	68%	191–193 (188–190) [43]
3o	 2l	Ph	 3o	87%	220–223 (222–224) [52]
3p	 2m	Ph	 3p	62%	239–241 (236–238) [53]
3q	 2f	Ph	 3q	72%	218–220 (222–224) [53]
3r	 2h	Ph	 3r	73%	194–196
3s	 2i	Ph	 3s	57%	163–166 (165–167) [54]

[a] Isolated yield.



Scheme 3. Plausible reaction mechanism for the formation of dihydroquinazolinone.

absence of metal, any cocatalyst, and no production of non-volatile make this an environmentally friendly methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152791.

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[59] General procedure: To a solution of 2-aminobenzamide (1.0 eq.) and aromatic \aliphatic aldehyde (1.0 eq) in Acetonitrile (10 time w\v) was added CMPI (0.5 eq) under nitrogen atmosphere. The reaction mass was allowing to stirred for 30-60 min at room temperature. The reaction is monitored by thin layer chromatography (TLC) (ethyl acetate/hexane 1:1). After the reaction completion, the reaction mixture was diluted with diethyl ether and the reaction mixture was filtered, washed with diethyl ether, dried under vacuum to give desired product. All the compounds (3a-3s) synthesized according to the general method. The compounds were confirmed by 1H NMR, 13C NMR and Mass analysis.