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An efficient, greener, and solvent-free one-pot multicomponent synthesis of 3-substituted quinazolin-4(3*H*)ones and thienopyrimidin-4(3*H*)ones ☆

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ABSTRACT

Herein, we report an efficient, greener, and solvent-free novel method for the synthesis of 3-substituted quinazolin-4(3*H*)ones and thienopyrimidin-4(3*H*)ones in a one-pot sequence using methyl anthranilate or 2-aminothiophene-3-carboxylate with *N*,*N*′-dimethyl formamide dimethyl acetal and various anilines. The driving force for this reaction is the removal of *N*,*N*′-dimethylamine by various anilines resulting in 3-substituted quinazolin-4(3*H*)ones and thienopyrimidin-4(3*H*)ones.

Lots of efforts have been directed toward the design and applications of multicomponent reactions[1] because MCRs are powerful tools for the construction of organic molecules allowing the formation of several bonds in just a single reaction. In addition to this, carrying out such multicomponent reactions with non hazardous and environment friendly reagents could provide an interesting platform to the scientific community over the conventional approaches. To minimize the use of hazardous reagents, emphasis should be given to the development of greener approaches.

Quinazolin-4(3*H*)one is an important class of heterocycles which possess diverse range of biological properties such as antimalarial,[2] anticonvulsant,[3] antibacterial,[4] antidiabetic,[5] and anticancer activities.[6] Diverse range of the pharmacological activities of quinazolin-4(3*H*)one derivatives have tempted considerable interest for the synthesis of quinazolin-4(3*H*)one using versatile and greener methods. The most common method for the synthesis of 3-substituted quinazolin-4(3*H*)one involves the reaction of anthranilic acid with DMF and $POCl_3$, reported by Perumal et al.[7] Other methods for the synthesis of 3-substituted quinazolin-4(3*H*)ones are from anthranilic acid derivatives.[8–17] Recently, quinazolin-4(3*H*)ones were prepared using silica sulfuric acid,[18] PCl_3,[19] $Zn/HCOONH_4$ under microwave irradiation,[20] $LiNO_3$,[21] and HATU.[22] However, some of these methods are associated with drawbacks such as multistep reactions, costly reagents, harsh reaction conditions, complex and tedious experimental procedures, and low yields.

Considering the above facts, there is still need to develop efficient, greener, and economical methods for the synthesis of quinazolin-4(3*H*)ones. In addition to this, a majority of the condensed pyrimidin-4(3*H*)one heterocyclic compounds have been reported from 2-aminobenzoic acid.[8] Earlier reports on the synthesis of 3-substituted quinazolin-4(3*H*)ones incorporate anthranilic acid as starting material, which has electron rich carboxylate resonance structure thus requires various lewis acid catalysts in order to become electron deficient for the cyclization. In case of methyl anthranilate, the carbonyl group being electrophilic in nature, allows the nucleophilic attack facile for the cyclization without use of any catalysts. To the best of our knowledge, the formation of 3-substituted quinazolin-4(3*H*)ones from methyl anthranilate has not been reported so far.

In continuation to our work on the synthesis of biologically important heterocycles such as quinazolin-4(3*H*)ones,[23] we were interested to investigate the formamidine intermediate resulting from the reaction of methyl anthranilate and *N*,*N*′-dimethyl formamide dimethyl acetal (DMF–DMA) can further converted to quinazolin-4(3*H*)ones with the help of various amines. The synthesis of formamidine using either amines or thioureas with DMF–DMA is well documented in the literatures.[24] This formamidine structure has tempted us to utilize it in the synthesis of quinazolin-4(3*H*)ones by heating it with various amines to elicit the 3-substituted quinazolin-4(3*H*)ones. Herein, we report an efficient, greener, sequential one-pot method for the synthesis of 3-susbstitued quinazolin-4(3*H*)ones from methyl anthranilate, DMF–DMA, and various

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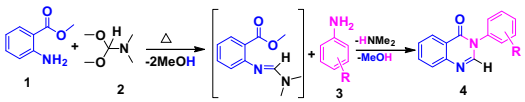


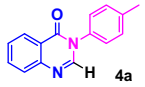
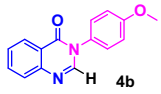
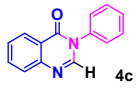
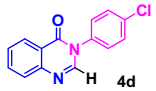
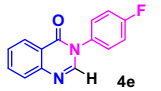
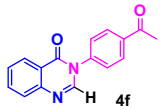
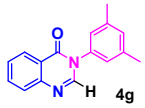
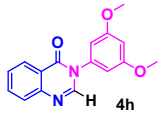
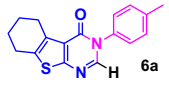
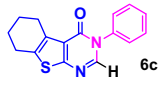
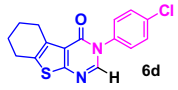
Scheme 1. One pot synthesis of 3-substituted quinazolinones.

amines. This method neither requires any reagent for the cyclization nor the solvents (Scheme 1).

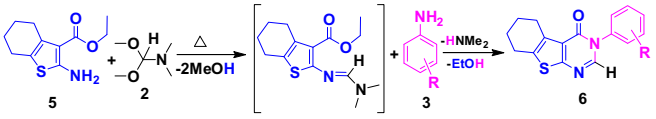
We started our effort by carrying out the reaction of methyl anthranilate **1** and DMF–DMA **2** at warm condition, which resulted in the removal of methanol to give the formamidine intermediate. This formamidine intermediate was then reacted with various amines **3** at elevated temperature to obtain 3-substituted quinazolin-4(3*H*)one **4** which was showing different R_f value as compared to the starting material formamidine on TLC. Further work-up of this reaction gave the off-white crystalline solid. The formation of this product was confirmed by Mass, ^{1}H NMR, and ^{13}C NMR spectrometry. The synthesis of 3-(*p*-tolyl)quinazolin-4(3*H*)one via HATU mediated coupling of 4-hydroxyquinazoline and 4-aminotoluene[22] provided only 41% yield, while the present method provides 79% yield for the same compound suggesting the advantage of the present method over the earlier methods for the synthesis of 3-substituted quinazolin-4(3*H*)ones in many aspects such as percentage overall yield, use of simple and non-hazardous starting materials or reactants, avoiding the use of sophisticated catalysts, solvent-free reaction conditions, all suitable for large scale synthesis.

Thus, in a representative experiment, the sequential reaction of methyl anthranilate **1** and DMF–DMA **2** at 85–90 °C temperature allows the removal of solvent methanol to give the formamidine intermediate. This formamidine intermediate was then reacted

Table 1
3-Substituted quinazolin-4(3*H*)ones and 5,6,7,8-tetrahydrobenzthieno[2,3-*d*]pyrimidin-4(3*H*)ones

Entry	Compounds **4** and **6**	Yield[a] (%)	Reaction time (h)	NMR spectral analysis (400 MHz, DMSO-d_6, chemical shift in δ ppm)	Melting range (°C)
1	 **4a**	79	12	^{1}H = 8.31 (s, 1H), 8.19 (d, 1H), 7.86 (m, 1H), 7.74 (d, 1H), 7.58 (m, 1H), 7.41 (d, 2H), 7.36 (d, 2H), 2.40 (s, 3H, $-CH_3$)	144–146 (144–145)[25]
2	 **4b**	82	11	^{1}H = 8.30 (s, 1H), 8.18 (d, 1H), 7.79 (m, 1H), 7.68 (d, 1H), 7.52 (m, 1H), 7.38 (d, 2H), 7.31 (d, 2H), 3.84 (s, 3H, $-OCH_3$)	191–193 (193–194)[25]
3	 **4c**	72	15	^{1}H = 8.39 (d, 1H), 8.20 (s, 1H), 7.85 (m, 2H), 7.56 (m, 4H), 7.28 (m, 2H)	139–141 (141–142)[25]
4	 **4d**	67	17	^{1}H = 8.32 (d, 1H), 8.24 (s, 1H), 7.80 (m, 2H), 7.55 (m, 3H), 7.36 (d, 2H)	179–181 (180–181)[26]
5	 **4e**	64	18	^{1}H = 8.31 (s, 1H), 8.21 (d, 1H), 7.89 (m, 1H), 7.75 (d, 1H), 7.61 (m, 1H), 7.43 (d, 2H), 7.28 (d, 2H)	204–206 (203–205)[25]
6	 **4f**	61	17	^{1}H = 8.38 (d, 1H), 8.23 (s, 1H), 8.15 (d, 2H), 7.83 (m, 2H), 7.56 (m, 3H), 2.62 (s, 3H, $-CH_3$)	196–198
7	 **4g**	76	16	^{1}H = 8.16 (s, 1H), 8.19 (d, 1H), 7.86 (m, 1H), 7.74 (d, 1H), 7.58 (m, 1H), 7.22 (s, 1H), 7.18 (m, 2H), 2.03 (s, 6H, $-CH_3$)	163–165
8	 **4h**	80	12	^{1}H = 8.12 (s, 1H), 8.24(d, 1H), 7.89 (m, 1H), 7.78 (d, 1H), 7.60 (m, 1H), 6.92 (s, 1H), 6.95 (m, 2H), 3.78 (s, 6H, $-OCH_3$)	225–228
9	 **6a**	64	22	^{1}H = 8.29 (s, 1H), 7.40 (d, 2H), 7.33 (d, 2H), 2.37 (s, 3H, $-CH_3$), 2.70 (m, 2H), 2.63 (m, 2H), 1.75 (m, 4H)	141–143 (140–142)[27]
10	 **6b**	66	20	^{1}H = 8.20 (s, 1H), 7.38 (d, 2H), 7.32 (d, 2H), 3.87 (s, 3H, $-OCH_3$), 2.65 (m, 2H), 2.59 (m, 2H), 1.56 (m, 4H)	134–136 (134–135)[27]
11	 **6c**	63	23	^{1}H = 8.33 (s, 1H), 7.42 (d, 2H), 7.37 (m, 3H), 2.66 (m, 2H), 2.64 (m, 2H), 1.61 (m, 4H)	186–188 (186–189)[27]
12	 **6d**	56	24	^{1}H = 8.37 (s, 1H), 7.44 (d, 2H), 7.38 (d, 2H), 2.69 (m, 2H), 2.67 (m, 2H), 1.63 (m, 4H)	175–177 (176–178)[27]

[a] Yields refer to isolated products. Melting points of compounds are uncorrected.



Scheme 2. One pot synthesis of 3-substituted tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4(3*H*)ones.

with *p*-toluidine **3a** at the same temperature to obtain the desired 3-(*p*-tolyl)quinazolin-4(3*H*)one **4a**. Further work up of this reaction gave the off-white crystalline solid.[28] The structure of this compound was confirmed by ^{1}H NMR, ^{13}C NMR, (Table 1) and Mass spectrums. In addition to this, the present protocol is also useful for the construction of 3-substituted 5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)ones from 2-aminothiophene-3-carboxylate, DMF–DMA, and various amines (Scheme 2).

During the course of study, it was observed that the reaction of electron rich anilines furnished very good yield (**4a**, **b**, **g**, **h**), while the electron deficient anilines resulted in comparatively lower yields (**4d**–**f**) as shown in Table 1. It was also observed that anilines substituted with electron releasing groups require less time to form the formamidine intermediate (6–10 h) while electron withdrawing groups present in amines require comparatively more time to furnish the formamidine (12–16 h). Further, it is also observed that the reaction of DMF–DMA with liquid reactants like methyl anthranilate (homogeneous mixture) required less time (10–18 h) for the formation of the quinazolin-4(3*H*)ones, while the solid substrate like 2-aminothiophene-3-carboxylate (due to heterogeneous reaction mixture) required more time (18–24 h) for the thienopyrimidin-4(3*H*)ones with comparatively less yields. According to the Sigma-Hammett equation, if the electron donating group is present at the *para* position of anilines, then the sigma value is negative. In case of anilines with electron donating groups (EDG) there will be an enhancement in the nucleophilic character as compared to the electron withdrawing group (EWG) and thereby the formamidine intermediate will probably be a rate limiting step, therefore, EDGs comparatively result in yield higher than the EWGs (Table 1). The difference between the yield from EDG and EWG groups present in anilines for the quinazolin-4(3*H*)ones synthesis is not significant.

In conclusion, we have demonstrated a novel, efficient, and greener one-pot method for the synthesis of 3-substituted quinazolin-4(3*H*)ones and thienopyrimidin-4(3*H*)ones from simple starting materials like methyl anthranilate or 2-amino-3-carbethoxy thiophenes, *N*,*N*′-dimethylformamide dimethyl acetal, and various anilines to afford products in good to excellent yields. The present method is attractive due to its solvent-free condition, no use of any costly lewis acid catalyst and environment friendly conditions suggesting this protocol could be an alternative to other protocols. The product can be isolated very easily without the use of chromatography in most cases. Furthermore the synthesis of pyrrolopyrmidin-4(3*H*)ones, pyrazolopyrmidin-4(3*H*)ones, and furopyrimidin-4(3*H*)ones using this methodology is under development.

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28. *General experimental procedure for the preparation of 3-substituted-quinazolinones/thienopyrimidinones:* In a hot air dried flask, methyl anthranilate **1** or 2-amino-3-carbethoxy thiophenes **5** (1.0 mmol) and dimethylformamide dimethyl acetal **2** (1.1 mmol) were mixed together and heated to 85–90 °C for 6–18 h. Progress of the reaction was monitored by TLC using ethyl acetate/hexane (2:8). When the TLC shows the consumption of starting material, amine **3** (1.0 mmol) was added with stirring. The reaction was then again maintained at the same conditions for another 10–18 h (in case of thiophene 12–24 h). After completion of the reaction, the reaction mixture was then evaporated to remove the methanol and dimethyl amine from the reaction mass. The reaction mixture was treated with hexane to remove the volatiles and unreacted materials. Then it was poured into cold water, upon stirring precipitates were observed and collected on a Buchner funnel. (If there were no precipitates, particularly in case of thienopyrimidinones, the reaction mixture was extracted in the suitable solvent and purified by column chromatography.). These precipitates were then dissolved in either dichloromethane or ethyl acetate and dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residues were treated with hexane and/or ether to give the pure compounds (**4a**–**h**/**6a**–**d**).