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A versatile one-pot multicomponent synthesis of novel quinazolinon-2-yl-tetrasubstituted thiophenes

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ABSTRACT

Here, we report a versatile multicomponent synthesis of novel quinazolinon-2-yl-tetrasubstituted thiophenes by a one-pot reaction using different alkyl-3-aminobutenoates, isothiocyanates and 2-halomethyl quinazolinones in good to excellent yields. The reaction probably proceeds by an intramolecular *5-exo-trig* cyclisation.

Multicomponent reactions (MCRs), by virtue of their convergence, productivity, facile execution and generally high yields of products, have attracted much attention from the vantage point of combinatorial chemistry.[1,2] Especially one-pot multicomponent processes have recently gained a considerable and steadily increasing academic, economic and ecological interest because they address very fundamental principles of synthetic efficiency and reaction design.[3] Additionally, the prospect of extending one-pot reactions into combinatorial and solid-phase synthesis[4,5] promises manifold opportunities for developing novel lead structures of pharmaceuticals, catalysts and even novel molecule-based materials.

4(3*H*)-Quinazolinone and related quinazoline scaffolds are a class of fused heterocycles that are of considerable interest because they possess diverse range of biological properties. The quinazolinone moiety is a building block for more than 150 naturally occurring alkaloids[6] such as glycosminine[7], echinozolinone,[8] deoxyvasicinone,[9–11] rutaecarpine[12] and drugs like methaqualone.[13] The natural quinazolinones and their synthetic analogues possess a variety of biological activities, including antimalarial,[14] anticonvulsant,[15,16] antibacterial,[17] antidiabetic[18] and anticancer activities.[19] Examples include the anticancer compound trimetrexate, the sedative methaqualone, the alpha-adrenergic receptor antagonist such as doxazosin and the antihypertensive agent ketanserin. The quinazoline moiety is known to have inhibitory effects on receptor tyrosine kinases, which are promising targets recent days in cancer chemotherapy, which includes approved drugs such as erlotinib, lapatinib and gefitinib (Fig. 1). In addition to this, quinazolines of the type CU-160[20] have also been found to be inhibitors of NF-kB proteins. NF-kB proteins are a class of 'rapid-acting' transcription factors that regulate the expression of more than 400 target genes and play a pivotal role in several important physiological processes including immune and inflammatory responses.[21] Thus, due to the diverse range of the pharmacological activities of quinazolinone derivatives, there has been an enormous interest in the synthesis of quinazolinone using versatile methods. There are numerous methods available for the synthesis of quinazolines.[22]

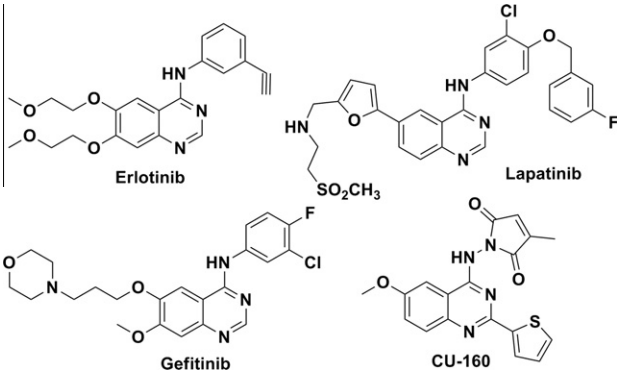

Figure 1. Some biologically important molecules incorporating quinazoline scaffold.

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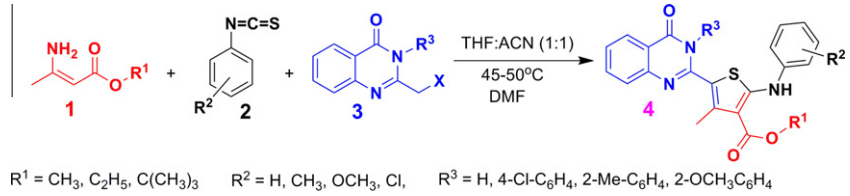


Scheme 1.

Thiophene is an important structural motif in medicinal chemistry and numerous methods for its synthesis have been reported.[23–26] Fascinated by working on fragment tethering approach,[27] we observed that the substitution of different heterocyclic moieties such as thiophene at position 2 of quinazolinone nucleus[28] modulates anti-inflammatory effect and anti-cancer activity by inhibiting the transcription factors[29,30] (Fig. 1). The relevance of compounds composed from two or more heterocyclic rings for drug discovery, regardless of the target, can be best documented by the frequency with which bis-heterocyclic compounds were identified as the most potent ones.[31]

In the context of our ongoing interest for the development of new routes for small heterocyclic compounds bearing especially amino group at the position 2 of the heterocycles, we have been working on the reaction of various alkyl-3-aminobutenoates with different isothiocyanates to produce the alkyl-3-aminobutenoate: isothiocyanate adducts, which can be further explored for the synthesis of heterocyclic compounds. Enaminones are readily available chemical intermediates and their chemistry has received considerable attention in the recent years.[32] As far as the chemical reactivity of alkyl-3-aminobutenoates (here after: enamino esters) is concerned, they can react with both the electrophiles and the neucleophiles as mentioned in the literature.[33–36] We were interested in the use of enamino esters as neucleophiles, in particular their reaction with isothiocyanates.

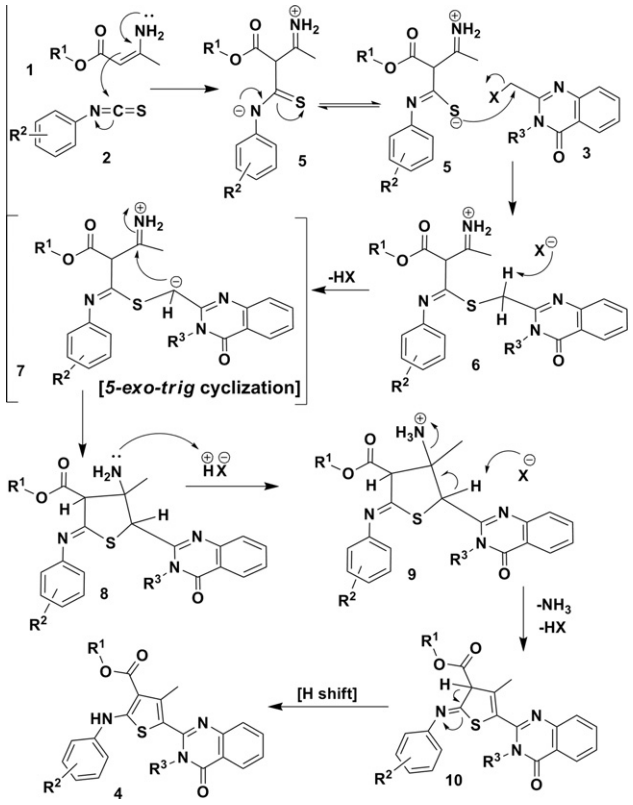
The existing methods for the synthesis of quinazolinone-thiophene heterocycles connected through C–C bond involve the N-acylation of 2-amino benzoic acids or 2-amino benzamides with substituted or unsubstituted thiophene-2-carboxylic acid chloride, followed by ring closure with or without the aid of various amines to furnish the 2-thienyl quinazolinones.[37] Synthesis of such building blocks involves number of steps. We have recently reported a multistep process to prepare substituted thiophenes attached to quinazolinone rings, and their use as potential anti-inflammatory and anticancer agents.[38] In order to simplify the process and to obtain new derivatives, we have developed a one-pot, multicomponent process which proceeds in good to high yields, and which is reported herein.

We report here, a multicomponent reaction leading to quinazolinon-2-yl-tetrasubstituted thiophenes **4**, by reacting different enamino esters **1**, isothiocyanates **2** and 2-halomethyl quinazolinones **3** in one pot to furnish **4** in good to excellent yields[42] (Scheme 1).

A plausible reaction mechanism (Scheme 2) involves the reaction of isothiocyanate **2** and enamino ester **1** to give intermediate **5**. The resulting sulfide is a strong neucleophile and reacts with 2-halomethyl quinazolinone to afford the intermediate **6**. In the next step, an acidic proton of the methylene group is (formally) abstracted by a halide ion, resulting in carbanion formation. This carbanion then attacks the electrophilic imine carbon, producing an intramolecular *5-exo-trig* cyclisation followed by protonation at the amine and undergoes NH_3 and HBr eliminations, respectively. Final step is the aromatisation of the ring by H-shift in order to form a stable thiophene compound.

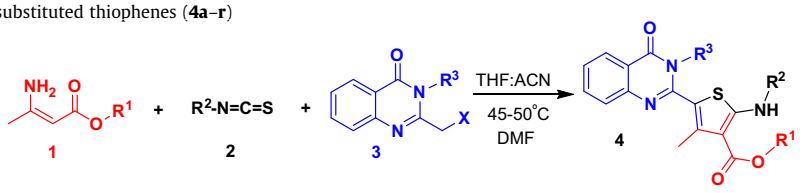
During the course of our study, it was observed that the reaction of enamino ester of tertiary butyl acetoacetate gave better yields as compared to enamino esters of methyl or ethyl acetoacetate. We have checked the reaction of electron-releasing ($-CH_3$ and $-OCH_3$) groups as well as electron-withdrawing (–Cl) groups present in the phenyl ring of isothiocyanates. Electron-releasing groups present in phenyl ring of isothiocyanates gave better yields as compared to their counterpart electron-withdrawing groups. Even the reaction of 2-bromomethyl quinazolinone **3a** with enamino ester and isothiocyanates was very fast and completed within 3–4 h. Furthermore we checked the generality of this reaction using 2-chloromethyl 3-substituted quinazolinones (**3b–d**) with the enamino esters and isothiocyanates to produce thiophene compounds (entries **4n–r**) but the reactions were slower in comparison with 2-bromomethyl quinazolinones. In order to hasten the reaction rate for the synthesis of **4n–r**, a pinch of KI (Finkelstein reaction) was added in the reactions of 2-chloromethyl 3-substituted quinazolinones (Table 1). Other examples of this reaction involve the use of 3,5-dichloro isothiocyanate and benzyl isothiocyanate with enamino ester and quinazolinones to give (entry **4l and m**).

In conclusion, we have reported a novel one-pot multicomponent transformation involving three components such as enamino esters, isothiocyanates and 2-halomethyl quinazolinones to yield functionally diverse quinazolinon-2-yl-tetrasubstituted thiophenes through the C–C bond formation via an intramolecular *5-exo trig* cyclisation in good to excellent yields. The advantage of this method is its facile



Scheme 2. A plausible reaction mechanism for quinazolinon-2-yl-tetrasubstituted thiophene formation.

Table 1
Synthesis of quinazolinon-2-yl-tetrasubstituted thiophenes (**4a–r**)



Entry	R^1	R^2	R^3	Product	Yield[a] (%)
1	CH_3	C_6H_5	H	**4a**	80
2	CH_3	4-OCH_3–C_6H_4	H	**4b**	82
3	CH_3	4-CH_3–C_6H_4	H	**4c**	76
4	CH_3	4-Cl–C_6H_4	H	**4d**	65
5	CH_2CH_3	C_6H_5	H	**4e**	60
6	CH_2CH_3	4-OCH_3–C_6H_4	H	**4f**	62
7	CH_2CH_3	4-CH_3–C_6H_4	H	**4g**	58
8	$C(CH_3)_3$	C_6H_5	H	**4h**	90
9	$C(CH_3)_3$	4-OCH_3–C_6H_4	H	**4i**	93
10	$C(CH_3)_3$	4-CH_3–C_6H_4	H	**4j**	81
11	$C(CH_3)_3$	4-Cl–C_6H_4	H	**4k**	76
12	CH_3	3-Cl, 5-Cl–C_6H_3	H	**4l**	62
13	CH_3	CH_2–C_6H_4	H	**4m**	79
14	CH_3	4-Cl–C_6H_4	4-Cl–C_6H_4	**4n**	65
15	CH_3	4-OCH_3–C_6H_4	4-Cl–C_6H_4	**4o**	59
16	CH_3	C_6H_5	2-CH_3–C_6H_4	**4p**	56
17	CH_3	C_6H_5	2-OCH_3–C_6H_4	**4q**	61
18	CH_3	4-OCH_3–C_6H_4	2-OCH_3–C_6H_4	**4r**	64

[a] Isolated yield without chromatography, X = Br for entries 1–13 and Cl for entries 14–18.

conditions and the product can be isolated very easily with excellent purity and that too without the use of column chromatography. The simplicity of the present process makes it an interesting alternative to other approaches. Furthermore the presence of an amino group ortho to the ester function in thiophenes makes them biologically important synthetic intermediates for the synthesis of other heterocyclic compounds like thienopyrimidinones.[39–41]

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Supplementary data

Supplementary data (general experimental procedures and spectral data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.046.

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42. *General experimental procedure for the preparation of quinazolinon-2-yl-tetrasubstituted thiophenes*: A stirred solution of isothiocyanate **1** (1 mmol) and enamino ester **2** (1 mmol) in a mixture of solvent tetrahydrofuran and acetonitrile (1:1) was heated to 45–50 °C and maintained for 5–6 h. To this mixture, a solution of 2-halomethyl quinazolinones **3** in DMF was added and allowed to stir for another 3–4 h at room temperature. In case of 2-chloromethyl 3-substituted quinazolinone, a pinch of potassium iodide was added. Completion of the reaction was monitored by TLC. The reaction mixture was subjected to evaporation to remove low boiling solvents followed by addition to the cold water to produce the precipitates. These precipitates were filtered and dissolved in organic solvents such as ethyl acetate, dichloromethane in which they are soluble, followed by drying over sodium sulfate. The organic layer was then concentrated to give the crude compounds which were further treated with diethyl ether and/or hexane to produce the pure solid compounds (**4a**–**r**). The structures of compounds were assigned with the help of NMR and mass spectra.