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An efficient one-pot protocol for the solvent-free synthesis of novel quinoline-3-thiocarboxamide and 2,3-dihydroquinazolin-4(1*H*)-one derivatives

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ABSTRACT

An efficient and straightforward synthesis of a series of novel poly-substituted quinoline-3-thiocarboxamides **3** and 2-(2-oxo-2-arylethylidene)-2,3-dihydroquinazolin-4(1*H*)-ones **4** from 3-oxo-*N*,3-diarylpropanethioamide **1** and the respective 2-aminoarylketone/2-aminoarylcarboxylic acid ester **2** by a two-component solvent-free reaction protocol was described.

1. Introduction

Several natural[1] and synthetic compounds possessing the ubiquitous quinoline and quinazoline moieties as part of their molecular scaffolds were blessed with anticancer,[2] antimicrobial,[3] anti-inflammatory,[4] antituberculosis,[5] antimalarial,[6] antibacterial,[7] antihypertensive,[8] antiviral,[9] and tyrosine kinase inhibiting properties.[10] A few quinazoline derivatives were also used as chemotherapeutic agents[11–13] and potent inhibitors of epidermal growth factor receptor.[14] Similarly, some quinoline-3-carboxamide derivatives have been reported as cholesteryl ester transfer protein inhibitors[15] and anti-angiogenic agents against metastatic prostate cancer.[16] A few biologically active natural compounds containing quinoline and quinazoline rings were shown in Fig. 1. Some of the synthetic methodologies adopted so far for obtaining these molecules were depicted in Fig. 2. Ito Hiroyuki and co-workers[17] have reported the fungicidal activity of several quinoline-3-carboxamide and quinoline-3-thiocarboxamide derivatives. Subhas Bose and co-workers[18] have synthesized N3-(4-methylphenyl)-6-chloro-2-methyl-4-phenyl-3-quinolinecarbothioamide by thionation of the corresponding carboxamide using Lawesson's reagent. Kiyoshi Tsuji's group[19] has obtained N1-methyl-4-hydroxyquinoline-2-one-3-carbothio amide derivatives in multiple steps involving several reagents and complex reaction conditions. Mei-Xiang Wang[20] has reported the synthesis of substituted quinazolinones in multiple steps starting from benzoylketene dithioacetal, methyl *o*-aminobenzoate. Wolfe and co-workers[21] have synthesized substituted quinazolinones by converting 2,3-dimethyl-4(3*H*)-quinazolinone. Sundeep Rayat[22] has also prepared substituted quinazolinones in a series of tedious reactions. These protocols involve multi-step reactions, high temperature or prolonged reaction time leading to lower yield. In view of their biological importance, a straight forward synthetic protocol was desirable for generating decent libraries of these compounds.

In our laboratory, we have focused on development of new, simple, ecofriendly and efficient synthetic protocols for complex heterocyclic molecules starting from *N*-aryl-α-mercapto-enaminoketone.[23,24] The presence of diverse and multiple reactive sights within the 3-oxo-propanethioamide molecule **1**, makes it a good synthon for the preparation of nitrogen and sulfur containing

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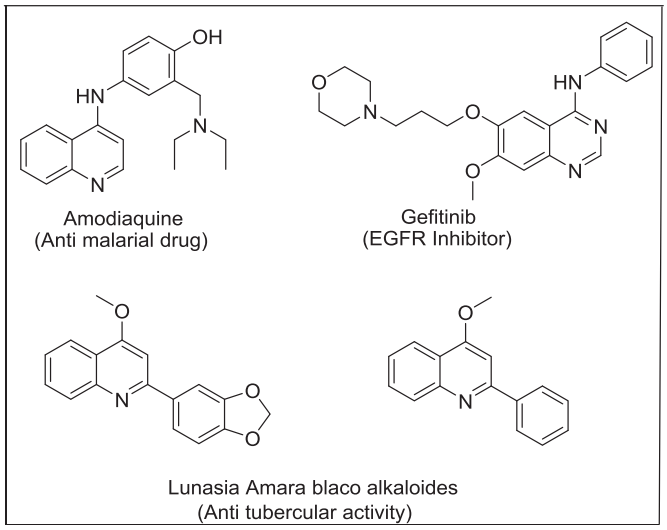


Fig. 1. Few biologically active natural compounds containing quinoline and quinazoline rings.

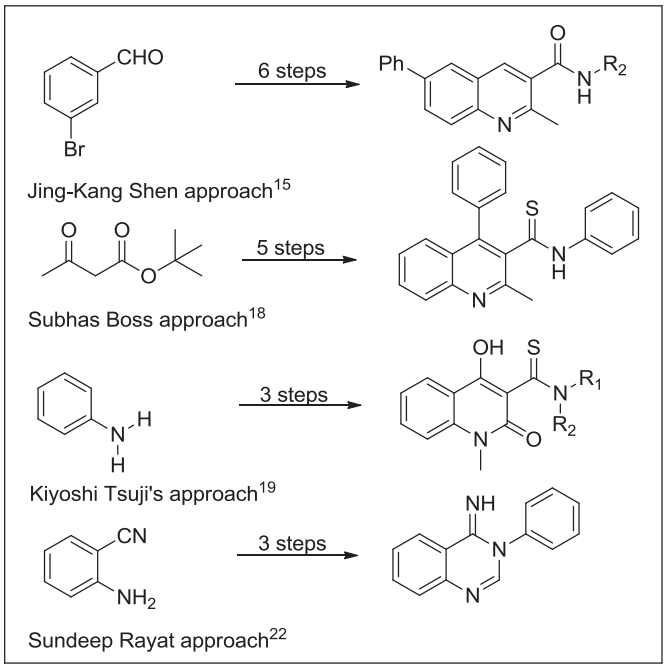
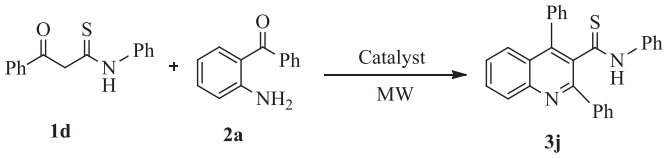


Fig. 2. Some of the synthetic methodologies adopted so far for obtaining these molecules were depicted.

heterocyclic compounds. We have reported here a new, simple, versatile and solvent-free protocol using $InCl_3$ as catalyst under microwave irradiation conditions to obtain a series of novel *N*-aryl-2,4-disubstituted-quinoline-3-thiocarboxamides (**3**) and 6-substituted-3-aryl-2-(2-oxo-2-arylethylidene)-2,3-dihydroquinazolin-4(1*H*)-ones (**4**) in high yield.

Initially, we have investigated the reaction of 3-oxo-*N*,3-diphenylpropanethioamide **1d** and 2-aminobenzophenone **2a** using different catalysts and reaction conditions to obtain *N*,2,4-triphenylquinoline-3-carbothioamide **3j** (Scheme 1). Refluxing **1d** and **2a** in presence of 10 mol% of $InCl_3$ in protic solvents like ethanol or methanol and aprotic media like dichloromethane, tetrahydrofuran or DMF under microwave irradiation for 10 min did not result



Scheme 1. Preparation of compound **3j.**

in any product (Table 1, entries 1 to 5). However, the neat reaction of **1d** and **2a** under microwave irradiation conditions at 80 °C using 10 mol% of $InCl_3$ as catalyst under solvent free conditions for 10 min has resulted in the formation of **3j** in excellent yield of 89% (Table 1, entry 6). The effect of variation in the reaction parameters such as microwave irradiation time, temperature and concentration of catalyst has been studied (Table 1, entries 7 to 12). Further screening of other catalysts like indium(III) bromide, indium(III) triflate, indium(III) fluoride, zinc(II) chloride, boron trifluoride etherate, iron(III) chloride, aluminium(III) chloride, mineral acids such as H_2SO_4 or HCl, and bases like DMAP, triethylamine, piperidine, pyrrolidine and pyridine in the reaction was carried-out and the results were summarized in Table 1 (Table 1, entries 13 to 27). From this study, it was evident that the desirable reaction parameters for obtaining higher yield of **3j** in the reaction of **1d** and **2a** involve use of 10 mol% of Indium (III) chloride as catalyst under microwave irradiation in neat phase for 10 min (Table 1, entry 6). The same reaction when carried-out under conventional heating has resulted in lower yield of the desired product, even after prolonged reaction period. (Table 1, entry 15).

The optimized reaction protocol has been extended for the microwave induced neat cyclization-condensation reaction of 3-oxo-*N*,3-diarylpropanethioamides **1a-h** with the respective 2-aminobenzophenones (**2a**, **2c**) and 2-aminoacetophenone (**2b**) using 10 mol% $InCl_3$ as catalyst under microwave conditions at 80 °C

Table 1
Optimization of reaction parameters in the preparation of **3j** from **1d** and **2a**.

Entry	Catalyst (10 mol %)	Solvent	Temp. (°C)	Time (min)	%Yield[a]
1	$InCl_3$	EtOH	reflux	10	–
2	$InCl_3$	MeOH	reflux	10	–
3	$InCl_3$	CH_2Cl_2	reflux	10	–
4	$InCl_3$	THF	reflux	10	–
5	$InCl_3$	DMF	80	10	–
6	$InCl_3$	–	80	10	89
7	$InCl_3$	–	100	10	88
8	$InCl_3$	–	60	10	80
9	$InCl_3$	–	80	7	80
10	$InCl_3$	–	80	20	86
11	$InCl_3$[b]	–	80	10	70
12	$InCl_3$[c]	–	80	10	85
13	$InBr_3$	–	80	10	50
14	$In(OTf)_3$	–	80	10	30
15	$InCl_3$[d]	–	80	40	78
16	InF_3	–	80	10	–
17	$ZnCl_2$	–	80	10	–
18	$BF_3 \cdot OEt_2$	–	80	10	–
19	$FeCl_3$	–	80	10	–
20	$AlCl_3$	–	80	10	–
21	DMAP	–	80	10	–
22	NEt_3	–	80	10	–
23	Piperdine	–	80	10	–
24	Pyrrolidine	–	80	10	–
25	Pyridine	–	80	10	–
26	H_2SO_4	–	80	10	–
27	HCl	–	80	10	–

[a] Isolated yield.
[b] 5 Mol% catalyst was used.
[c] 20 Mol% catalyst was used.
[d] Reaction was carried out under conventional heating.