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Lithium perchlorate-induced electrophilic activation: one-pot synthesis of 3-aryl-2-thioxotetrahydropyrimidin-4-one derivatives from aryl isothiocyanates

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ABSTRACT

A novel methodology for the synthesis of N-substituted-3-aryl-2-thioxotetrahydropyrimidin-4(1*H*)-one derivatives had been developed by the condensation of aryl isothiocyanates with β-amino esters using lithium perchlorate as a catalyst and triethylamine as a base. This strategy not only overcomes the disadvantages of the reported methods but also provides high yield of the product in short span of time by an easily workable procedure.

1. Introduction

3-Aryl-2-thioxotetrahydropyrimidin-4-one derivatives are an important class of heterocyclic compounds which had found extensive use in pharmaceutical and agrochemical researches. These scaffolds have been used to increase HDL cholesterol concentration and as therapeutic compositions for treating atherosclerotic conditions such as dyslipoproteinemias and coronary heart disease.[1] Moreover these derivatives had shown interesting anticancer properties as well.[2] 3-Aryl dihydrothiouracils are known for their herbicidal and anticonvulsant activities.[3,4] Their homologues, the thiohydantoins are highly promising candidates for androgen-dependent conditions such as prostate cancer which is one of the most frequently diagnosed cancers and the second leading cause of cancer deaths in men after lung cancer.[5]

In our efforts to develop selective androgen receptor modulators, we have focused on 3-aryl-2-thioxotetrahydropyrimidin-4-one derivatives, their homologues the thiohydantoins being well known for their binding affinity with the androgen receptor. The rigid conformation of the thiohydantoin and the aryl substituent at the 3-position with electron-withdrawing group are expected to play an important role in the ligand-binding interactions.[5] Unfortunately there are not many literature reports available on the synthesis of 3-aryl-2-thioxotetrahydropyrimidin-4-one derivatives. The classical method for the synthesis of these compounds involves the condensation of β-amino acids or β-amino nitriles with aryl isothiocyanates to give the corresponding thiourea derivatives which are cyclized in a separate step to afford the desired product under acidic condition.[6–8] But this method suffers from harsh reaction conditions and poor yields. Another method reported for the synthesis of these compounds employs ionic liquid-phase organic synthesis (IoLiPOS) methodology under microwave condition.[9] Although this method affords better yields of the products, it suffers from the disadvantage of involving stoichiometric amount of ionic liquid for the condensation with acryloyl chloride followed by Michael addition of amines to give β-amino esters which were further reacted with isothiocyanates to give the thioureido esters and finally cyclization using diethylamine under microwave irradiation. Thus the multiple steps involved, microwave conditions employed, longer reaction time, and the stoichiometric amount of ionic liquid used have restricted the synthetic applicability of the reaction. To overcome these difficulties it was necessary to develop an alternate method and this prompted us to reinvestigate the condensation reaction between aryl isothiocyanates and β-amino esters so that the desired product could be obtained by a straight-forward procedure in high yields, short reaction time, and with operational simplicity.

2. Results and discussion

The present Letter discusses the synthesis of N-substituted 3-aryl-2-thioxotetrahydropyrimidin-4(1*H*)-one derivatives by direct condensation of aryl isothiocyanates and β-amino esters using lithium perchlorate as the catalyst and triethylamine as the base. The possible retrosynthetic routes for 3-aryl-2-thioxotetrahydropyrimidin-4-one derivatives are depicted in Scheme 1. Out of the two strategies, route B was considered better as route A involves additional step of hydrolysis of cyano group to carboxylic acid and harsh conditions. Route B proceeds by the condensation of aryl isothiocyanates and β-amino esters to afford the 3-aryl-2-thioxotetrahydropyrimidin-4-one derivatives with the intermediacy of the corresponding thioureido ester.

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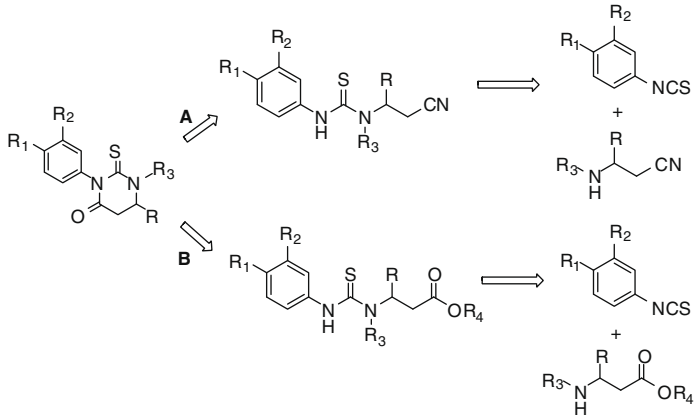


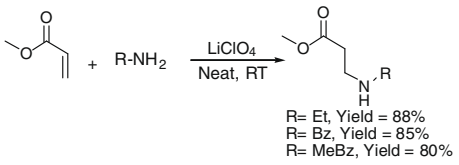
Scheme 1. Retrosynthetic routes for the synthesis of 3-aryl-2-thioxotetrahydropyrimidin-4(1*H*)-one.

Though different methods are available for the synthesis of β-aminoesters, we attempted the Michael addition of different amines to methyl acrylate in the presence of lithium perchlorate under neat condition which afforded the products in excellent yields[10] (Scheme 2).

Aryl isothiocyanates were prepared by the reaction of anilines with thiophosgene in DCM and aqueous sodium bicarbonate. As a model reaction 4-cyano-3-chlorophenyl isothiocyanate was treated with methyl 3-(1-phenylethylamino)propanoate in the presence of triethylamine (TEA) as the base and THF as the solvent under refluxing conditions. Though the reaction led to the formation of methyl 3-(3-aryl-1-(phenylethyl)thioureido)propanoate (A), the intermediate did not further cyclize to form the required product 3-aryl-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one as expected. Similar result was obtained when the reaction was carried out with diisopropylethylamine (DIPEA). This prompted us to explore alternate strategies for the cyclization either by nucleophilic activation using a strong base that can abstract *NH* proton and then condense with ester to give the cyclized product or by electrophilic activation of carbonyl group of ester to induce cyclization employing a mild base. Though reactions were attempted with different bases, the results were disappointing except with DBU which afforded the product in moderate yield. (Table 1, entry 5).

Alternatively resorting to electrophilic activation using Lewis acid facilitated cyclization even with mild bases (Table 1, entries 9–13). Although several Lewis acid catalysts were tried for the reaction in the presence of triethylamine, lithium perchlorate turned out to be the best affording the cyclized product in excellent yield within short time. Similar result was obtained with magnesium perchlorate as well. From the various solvents employed for the reaction it was conspicuous that acetonitrile is the best suited (Table 2).

The high catalytic efficiency of lithium perchlorate and magnesium perchlorate may be due to the better coordination power of the lithium and magnesium which share a diagonal relationship and have high charge/size ratio and hence more covalent character



Scheme 2. Michael addition of amines to methyl acrylate.

Table 1
Influence of different bases in the synthesis of 3-aryl-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one

Entry	Base	Catalyst	Solvent	Temp (°C)	Time (h)	Yield A (%)	Yield B (%)
1	TEA	—	THF	70	12.0	90	—
2	—	—	THF	25	0.2	90	—
3	DIPEA	—	THF	70	12.0	91	—
4	NaH	—	THF	70	2.0	—	—
5	DBU	—	THF	0–25	2.0	—	40
6	DIPEA	—	Toluene	115	4.0	—	25
7	—	$LiClO_4$	THF	70	2.0	90	—
8	—	$LiClO_4$	Toluene	115	2.0	90	—
9	DIPEA	$LiClO_4$	Toluene	115	4.0	—	60
10	DIPEA	$LiClO_4$	DMF	160	4.0	—	58
11	DIPEA	$LiClO_4$	CH_3CN	85	4.0	—	70
12	TEA	$LiClO_4$	DMF	160	1.5	—	59
13	TEA	$LiClO_4$	CH_3CN	85	1.2	—	86

Table 2
Role of solvents and catalysts in the synthesis of 3-aryl-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one

Entry	Base	Catalyst	Solvent	Temp (°C)	Time (h)	Yield A (%)	Yield B (%)
1	TEA	$LiClO_4$	THF	70	2.0	35	53
2	TEA	$LiClO_4$	DCM	40	2.0	30	56
3	TEA	$LiClO_4$	DCE	70	2.0	27	63
4	TEA	$LiClO_4$	EtOH	80	2.0	26	61
5	TEA	$ZrOCl_2{\cdot}8H_2O$	CH_3CN	85	2.0	37	55
6	TEA	$SnCl_2$	CH_3CN	85	2.0	43	44
7	TEA	$ZrCl_4$	CH_3CN	85	2.0	36	54
8	TEA	$MgClO_4$	CH_3CN	85	2.0	—	80
9	TEA	$LiClO_4$	CH_3CN	85	2.0	—	85

leading to better coordination in comparison with the other catalysts.

The catalytic efficiency of lithium perchlorate was examined by employing different mol percentages of the catalyst with equimolar ratios of triethylamine and the reactants (Table 3). From the results obtained it could be inferred that maximum conversion took place at a concentration of 10 mol %.

Further we attempted to study the kinetics of the reaction by measuring the ratio of A and B at time intervals of 15 min for 1.5 h. The ratios of the intermediate A and product B at different intervals were plotted (Fig. 1) which clearly indicates that the intermediate underwent complete conversion to product in 75 min.

The scope of the reaction was generalized by employing different β-amino esters and aryl isothiocyanates[11] (Scheme 4). In all the

Table 3
Effect of catalyst concentration

Entry	$LiClO_4$ (equiv)	TEA (equiv)	Time (min)	Yield A (%)	Yield B (%)
1	0.02(2 mol %)	1.2	75	34	52
2	0.05(5 mol %)	1.2	75	10	80
3	0.10(10 mol %)	1.2	75	—	85
4	0.20(20 mol %)	1.2	75	—	85

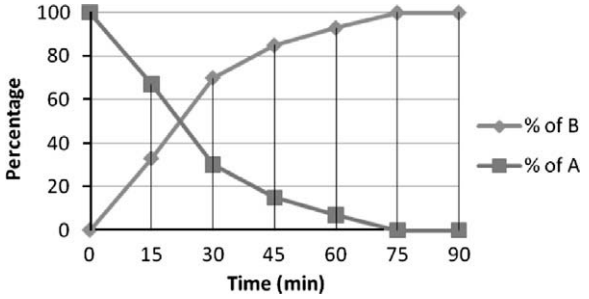
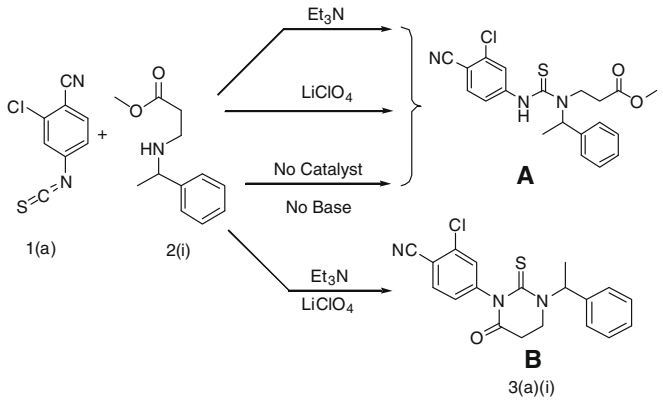


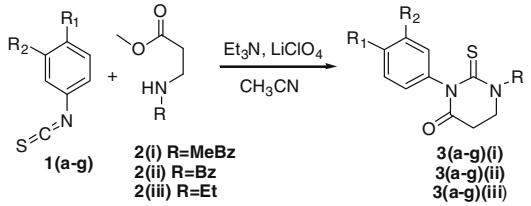
Figure 1. Progress of the reaction at different time intervals.



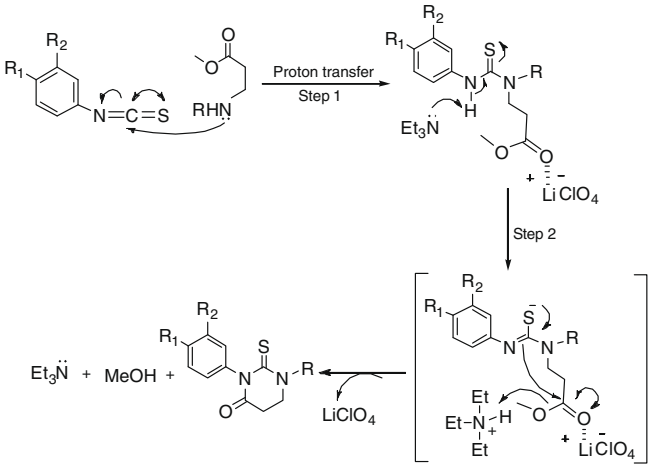
Scheme 3. Optimization of reaction condition for the formation of 3-aryl-2-thioxotetrahydropyrimidin-4(1*H*)-one.

Table 4
Reactions of β-amino esters with aryl isothiocyanates

Entry	R_1	R_2	R	Time (h)	Yield (%)	Product
1	CN	Cl	α-MeBz	1.2	86	3(a)(i)
2	H	NO_2	α-MeBz	2.5	70	3(b)(i)
3	Cl	CF_3	α-MeBz	2.5	80	3(c)(i)
4	Cl	H	α-MeBz	1.5	85	3(d)(i)
5	CN	CF_3	α-MeBz	3.0	90	3(e)(i)
6	NO_2	CF_3	α-MeBz	3.0	88	3(f)(i)
7	F	Cl	α-MeBz	2.5	75	3(g)(i)
8	CN	Cl	Bz	2.5	90	3(a)(ii)
9	H	NO_2	Bz	2.5	84	3(b)(ii)
10	Cl	CF_3	Bz	2.5	84	3(c)(ii)
11	Cl	H	Bz	2.0	81	3(d)(ii)
12	CN	CF_3	Bz	3.0	85	3(e)(ii)
13	NO_2	CF_3	Bz	3.0	92	3(f)(ii)
14	F	Cl	Bz	2.5	85	3(g)(ii)
15	CN	Cl	Et	3.0	89	3(a)(iii)
16	H	NO_2	Et	3.5	85	3(b)(iii)
17	Cl	CF_3	Et	3.5	90	3(c)(iii)
18	Cl	H	Et	3.0	87	3(d)(iii)
19	CN	CF_3	Et	3.0	88	3(e)(iii)
20	NO_2	CF_3	Et	3.0	88	3(f)(iii)
21	F	Cl	Et	2.5	86	3(g)(iii)



Scheme 4. Reactions of β-amino esters with aryl isothiocyanates.



Scheme 5. Mechanism for the formation of 1-alkyl-3-aryl-2-thioxotetrahydropyrimidin-4(1*H*)-ones.

cases, desired products were obtained in reasonably high yields over a short period of time (Table 4).

The course of the reaction was further examined to obtain a better perspective of the reaction mechanism. 4-Cyano-3-chlorophenyl isothiocyanate when condensed with methyl 3-(1-phenylethylamino)propanoate in the presence of triethyl amine in refluxing acetonitrile afforded only the intermediate A and did not undergo the subsequent cyclization. Similar result was obtained when $LiClO_4$ was employed in the absence of triethylamine. Moreover it was also observed that intermediate A was formed even by mixing the aryl isothiocyanate and β-aminoester without employing any base or catalyst (Scheme 3) which clearly suggests that neither the Lewis acid nor the base has any significant role in the formation of the intermediate A (Scheme 5, Step 1) but exert their influence in the cyclization of the intermediate A to the product B (Step 2). Hence it is evident that the cyclization proceeds through the coordination of lithium perchlorate to the oxygen of the ester carbonyl which in fact increases the electrophilicity at the carbonyl carbon of the intermediate A facilitating the base-mediated attack of *NH* to form the cyclized product.

3. Conclusion

A simple one-pot strategy for the synthesis of *N*-aryl-2-thioxotetrahydropyrimidin-4-ones by using lithium perchlorate from aryl isothiocyanates and β-aminoesters with triethylamine in acetonitrile medium was developed. The reaction afforded the desired product in excellent yield and short reaction time with easy purification as no side products were formed, thereby overcoming the disadvantages of the known methods.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.043.

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11. *General procedure for the synthesis of N-aryl-2-thioxotetrahydropyrimidin-4-one derivatives*: Aryl isothiocyanate (2.57 mmol) in acetonitrile (20 mL) was taken in a RB flask to which β-amino ester (2.57 mmol) was added followed by triethylamine (3.08 mmol) and $LiClO_4$ (10 mol %, 0.26 mmol). The reaction mixture under reflux was periodically monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure; the residue was diluted with DCM, washed with water (2×25 ml), then with brine (1×25 ml), and dried over Na_2SO_4. It was further concentrated and purified by column chromatography on silica gel using a mixture of ethyl acetate–hexane (15:85) to obtain the pure product, which was recrystallized from MeOH.