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Efficient Synthesis of Thiazolo[4,5-*d*]pyrimidine derivatives without solvent

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Abstract:

4-Amino-5-bromo-2-substituted-aminopyrimidines were successfully reacted with various isothiocyanates in the alkaline alumina under Microwave irradiation to achieve a group of reported 2- aminothiazolo[4,5-*d*]pyrimidine derivatives . These compounds also carried out a multicomponent condensation with carbondisulfid and alkylhalides to furnish a group of reported 2- alkylsulfanylthiazolo[4,5-*d*]pyrimidine derivatives.

Keywords: pyrimidine, thiazolo[4,5-*d*]pyrimidine, 5-Bromo-2,4-dichloro-6-methylpyrimidine, 4-Amino-5-bromo-2-substituted-aminopyrimidines.

Introduction:

The growing pharmaceutical and agrochemical interest for fused pyrimidines has focused the attention of chemists to explore for convenient and general routes to these compounds in synthetically useful yields.

Thiazolo[4,5-*d*] pyrimidines are a group of fused heterocycles which have been described as being antiviral [1-7], antifungal [8], nucleoside analogues [9], agrochemicals [10] and enzyme inhibitors [11] agents. Despite their importance from pharmacological and synthetic point of views, comparatively few routs for

their preparation have been reported. Molina's group described the thermal electrocyclic ring closure of certain carbodiimides and cyclocondensation of iminophosphoranes with carbon disulfide at room temperature as the only useful methods for the preparation of thiazolo[4,5-*d*]pyrimidines [12]. Other methods mainly involve heterocyclization of suitably substituted thiazoles with carbon disulfide [13], acetic anhydride/trimethy orthoformate [14, 15], and guanidine [16]. The syntheses from pyrimidines are limited and mostly reported in patent literature [11, 17].

In a previous communication, an efficient rout was exhibited for the synthesis of this class of heterocyles by starting from 5-bromo-2, 4-dichloro-6-methylpyrimidine [18]. This rout involved 3 steps; a) amination of 5-bromo-2, 4-dichloro-6-methylpyrimidine in ethanolic ammonia, b) replacement of chlorine atom at number 2 position with amines in boiling ethanol, c) condensation with isothiocyanates in DMF in the presence of sodamide shown in ***Figure 1.***

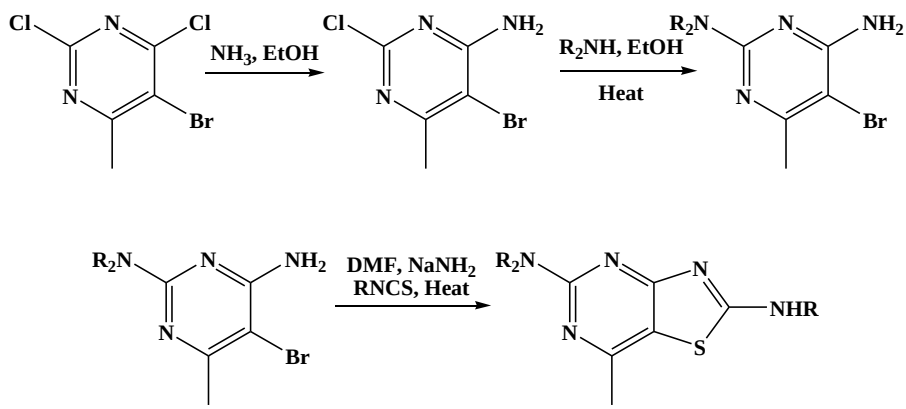


Figure 1

This innovation also pursued by the condensation of 4-amino-5-bromo-2-chloro-pyrimidine with carbondisulfide in DMF in the presence of KOH [19] as shown in ***Figure 2***.

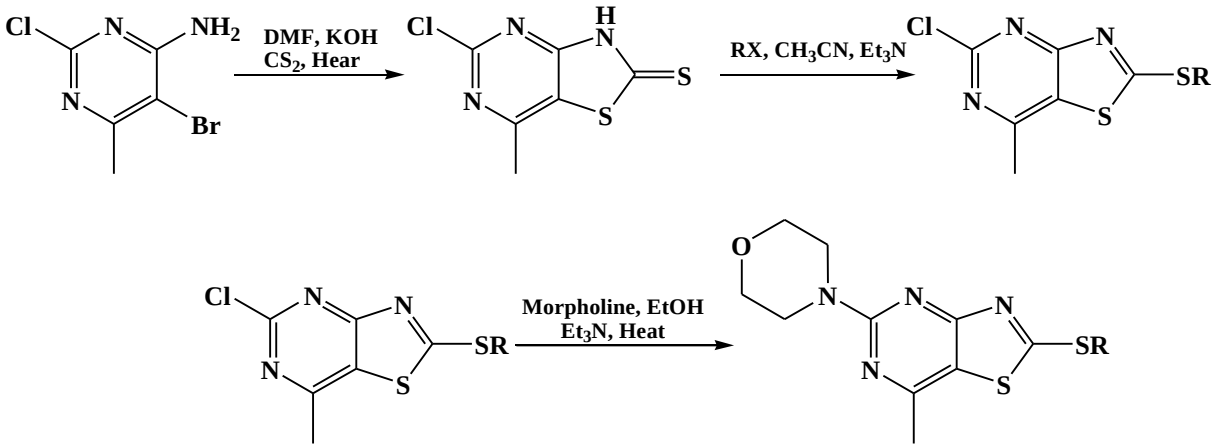
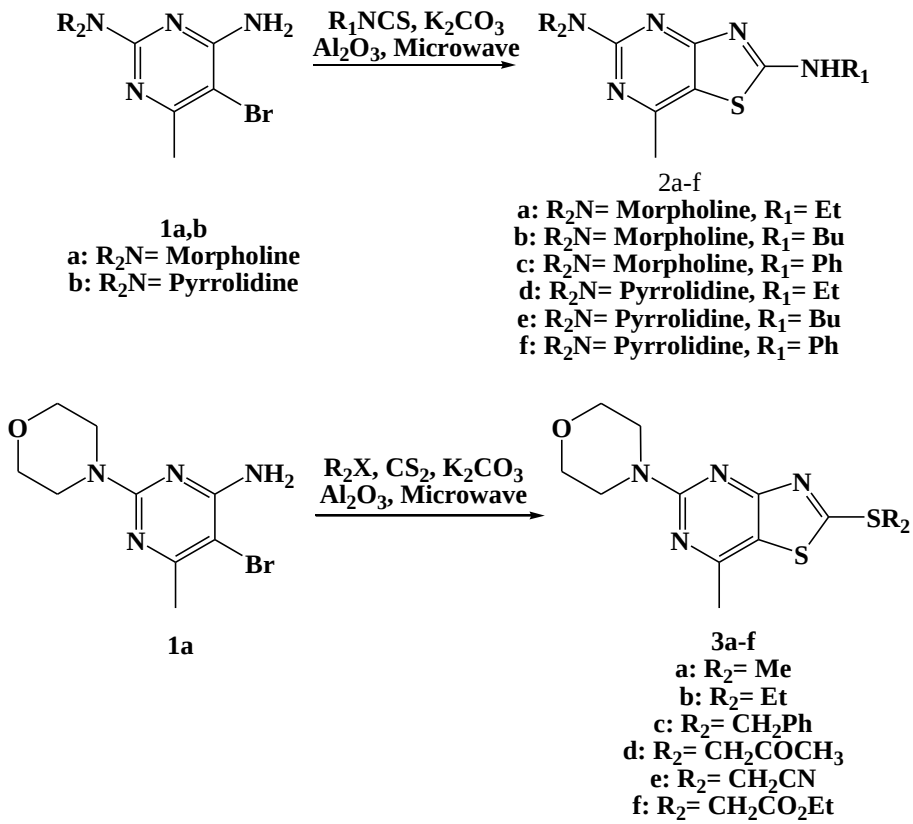


Figure 2

Results and Discussion

In the present study, a new procedure is explored for the preparation of the final products of two last studies [18, 19] without utilization of solvent and by higher yields. We found that 4-amino-5-bromo-2-substituted-aminopyrimidines **1a, b** could easily condense with isothiocyanates to achieve thiazolo[4,5-*d*]pyrimidine derivatives **2a-f** under Microwave irradiation in Alumina solid phase, but using of slight power is essentially avoiding of product decomposition.



Scheme 1

This strategy also extended for multicomponent condensation of 5-bromo-6-methyl-2-morpholin-4-ylpyrimidin-4-amine **1a** with carbondisulfide and alkylhalides to produce thiazolo[4,5-*d*]pyrimidine derivatives **3a-f** as shown in **Scheme 1**. This is worthy of noting that these compounds were prepared in three steps earlier [19].

Experimental and physical data of all prepared compounds are exhibited in **Table 1**. As shown in **Table 1**; products were prepared in slight Microwave power, low reaction time, high yields and no significant difference observed between the physical data with the original reported values [18, 19].

Table 1. Experimental and Physical data of thiazolo[4,5-*d*]pyrimidine derivatives **2a-f** & **3a-f**

Entry	R_2N	R_1	R_2	Power (Watt)	Reaction Time (Second)	Yield %	mp (Obtained) °C	mp (Reported(Ref)) °C
2a	Morpholine	Et	-	120	240	75	170-172	170-171 (18)
2b	Morpholine	Bu	-	120	240	80	139-140	138-140 (18)
2c	Morpholine	Ph	-	120	240	90	167-169	166-169 (18)
2d	Pyrrolidine	Et	-	120	240	80	159- 161	159- 160 (18)
2e	Pyrrolidine	Bu	-	120	240	90	151-153	151-154 (18)
2f	Pyrrolidine	Ph	-	120	240	90	150-153	150-153 (18)
3a	Morpholine	-	Me	100	200	85	204-206	204-205 (19)
3b	Morpholine	-	Et	100	200	80	130-132	129-131 (19)
3c	Morpholine	-	CH_2Ph	100	200	70	143-144	143-145 (19)
3d	Morpholine	-	CH_2COCH_3	100	180	75	187-189	185-189 (19)
3e	Morpholine	-	CH_2CN	100	180	70	186-188	185-189 (19)
3f	Morpholine	-	CH_2CO_2Et	100	180	85	175-179	173-180 (19)

Experimental:

Warning:

Appended procedures could be could be operate on an industrial Microwave devices and utilization of domestic devices is too dangerous to be accepted. Application of larger scales is not recommended because precursors are flammable and inflammatorily compounds.

Compounds **1a, b** were prepared according to an earlier report [18].

General procedure for the preparation of thiazolo[4,5-*d*]pyrimidine derivatives 2a-f:

A mixture of 4-amino-5-bromo-2-substituted-aminopyrimidines **1a** or **1b** (0.002 mol), appropriate isothiocyanate (0.0024 mol) and alumina (10 gr) were finely grinded and transferred to a polyethylene cell and then irradiated by Microwave under suitable power. Reaction progress determined by Thin Layer Chromatography TLC technique over silica gel with ethyl acetate eluent.

General procedure for the preparation of thiazolo[4,5-*d*]pyrimidine derivatives 3a-f:

A mixture of 5-bromo-6-methyl-2-morpholin-4-ylpyrimidin-4-amine **1a** (0.002 mol), appropriate alkylhalide (0.0024 mol), carondisulfide (0.3 ml), potassium carbonate (1 gr) and alumina (10 gr) were finely grinded and transferred to a polyethylene cell and then irradiated by Microwave under suitable power. Reaction progress determined by Thin Layer Chromatography TLC technique over silica gel with ethyl acetate eluent.

Conclusion:

In conclusion, 4-Amino-5-bromo-2-substituted-aminopyrimidines could easily condense with is othiocyanates or (carbondisulfide + alkylhalides) over Alumina under Microwave irradiation.

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