A VERSATILE MULTICOMPONENT ONE-POT SYNTHESIS OF THIAZOLE DERIVATIVES UNDER SOLVENT FREE CONDITIONS: DESIGNED BY PASS SHOWED ANTIVIRAL ACTIVITY AS PREDICTED

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ABSTRACT

An efficient and convenient procedure has been developed for the synthesis of thiazole derivatives by one-pot condensation reaction of α-haloketone, thiourea and substituted pyrazolones under environmentally solvent free conditions. Newly synthesized compounds were established on the basis of spectroscopic study. The major advantages of this protocol are high yields, operational simplicity, and short reaction times.

Keywords: Substituted α-haloketones, Thiourea, Substituted pyrazolones, Solvent free conditions.

INTRODUCTION

Thiazole ring system is an important class of compounds in medicinal chemistry. This structure has found applications in drug development for the treatment of cardiotonic[1], fungicidal[2], HIV infection[3], mental retardation in children, age related and neurodegenerative brain damage (Alzheimeris disease, Parkinsonism disease) and other[4-6]. Despite their importance from pharmacological and synthetic point of view, comparatively few methods for their preparation have been reported in the literature. Hantzch thiazoles synthesis in 1887 involves condensation of α-haloketones with thioureas or thioamides in refluxing alcohol under drastic conditions. However, these methods suffer from one or more disadvantages such as long reaction time (24-25 h), harsh reaction conditions. The modified methods of King and Dadson[7], in connection with some other worker[8], have also been reported for the synthesis of thiazole derivatives. However, these methods suffer from one or more disadvantages such as harsh reaction conditions, unsatisfactory yields, cumbersome product isolation procedure and use of volatile organic solvents. Therefore, the development of more economical and environmentally friendly conversion process is highly desirable with the increase in regulatory constraint focused in the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research. Therefore, more and more chemist's synthetic endeavors are developed towards 'green synthesis' which means the reagent, solvent and catalyst are environmentally friendly or solvent free reactions[9].

MATERIALS AND METHODS

Melting points were determined by in open capillary method and are uncorrected. The chemicals and solvents used for laboratory grade and were purified. IR spectra were recorded (in KBr pallets) on SCHIMADZU spectrophotometer. ^{1}H NMR spectra were recorded (in DMSO-d_6) on AVANCE-300 MHz spectrometer using TMS as an internal standard. The mass were recorded on EI-SHIMDZU-GC-MS spectrometer.

Typical experimental procedure for the synthesis of thiazole derivatives (4a-h):

A mixture of substituted pyrazolone **1** (1mmole) and thiourea **2** (1mmole) wetted with 2-4 drops of ethanol, followed by substituted α-haloketone **3** (1mmole) was grinded by pestle in mortar at room temperature for the period as shown in Table-1. The progress of reaction was monitored by thin layer chromatography (TLC). After completion of reaction solid product thus obtained was poured on crushed ice (20 gm). The separated product was filtered washed with ice cold water and recrystalized from 10% aqueous acetic acid to afford to the pure product **4**.

Spectroscopic data of selected compounds:

4a: Yellow crystal; IR (KBr): 3056, 1612 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.82 (s, 2H, CH_2), 7.23 (s, 1H, 5H of thiazole), 7.48-7.80 (m, 8H, Ar-H); EIMS: (m/z): 366 (M^+), 368 (M+2); Anal. Calcd for $C_{19}H_{15}N_4SCl$: C, 62.19; H, 4.12; N, 15.26%. Found: C, 62.11; H, 4.21; N, 15.21%.

4d: Pale Yellow crystal; IR (KBr): 3068, 1616 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.16 (s, 2H, CH_2), 7.21 (s, 1H, 5H of thiazole), 7.36-8.15 (m, 8H, Ar-H); EIMS: (m/z): 380 (M^+), 382 (M+2); Anal. Calcd for $C_{20}H_{17}N_4SCl$: C, 63.08; H, 4.51; N, 14.71%. Found: C, 63.18; H, 4.56; N, 14.65%.

4f: Yellow crystal; IR (KBr): 3052, 1615 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, CH_3), 4.11 (s, 2H, CH_2), 7.26 (s, 1H, 5H of thiazole), 7.31-7.8.11 (m, 8H, Ar-H); EIMS: (m/z): 377 (M^+); Anal. Calcd for $C_{19}H_{15}N_5O2S$: C, 60.47; H, 4.01; N, 18.56%. Found: C, 60.41; H, 4.12; N, 18.51%.

RESULTS AND DISCUSSION

In continuation of our work[10-11] and in view of the recent emphasis aimed at developing new, selective and environmentally friendly methodologies for the preparations of thiazole derivatives designed by the PASS

showed potent antiviral activity as predicted by the one-pot condensation of substituted α-haloketone, thiourea and substituted pyrazolones under solvent free conditions. The synthetic pathway of the titles compounds are given in the Scheme-1

When attempts were made to carry out the synthesis of thiazole derivatives by classical method in ethanol under reflux temperature, the yield product are poor (60-70%) In general, reactions under solvent free conditions are clean, rapid and afforded higher yields than those obtained by the above conventional mentioned method. The results of the reactions are compared with reflux conditions short reaction times were observed, which is more economy in terms of enhanced reaction rates, improved yielded and high selectivity are the features of obtained in solvent free conditions. The results are presented in Table-1.

Scheme 1: Synthesis of thiazole derivatives under solvent free conditions

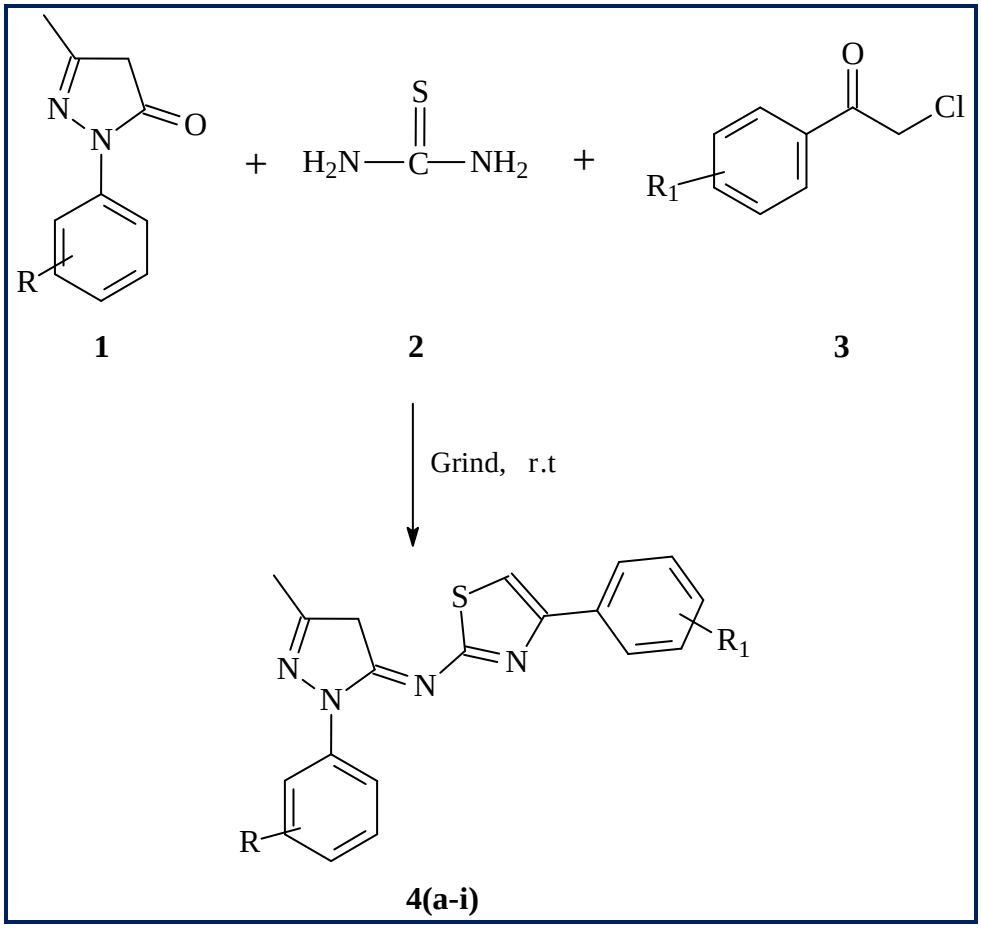

Table 1: Synthesis of Thiazole derivatives under solvent free conditions.

Product	R	R_1	Time(min)	Yield (%)	M. P. (°C)
4a	H	Cl	6	92	148
4b	Cl	F	4	90	164
4c	NO_2	Br	4	91	128
4d	Cl	CH_3	5	88	169
4e	CH_3	H	7	89	122
4f	H	NO_2	5	90	151
4g	NO_2	Cl	4	90	146
4h	Cl	H	8	92	170

CONCLUSION

In summary, we have demonstrated an efficient and one-pot method towards the expeditious synthesis of thiazole derivatives under solvent-free conditions designed by the PASS showed potentially antiviral agents. Present methodology offers very attractive features such as reduced reaction times, higher yields and environmentally benign condition. The simple procedure combined with ease of work-up and entirely solvent-free conditions make this method economic, benign and a waste-free chemical process for the synthesis of thiazole derivatives of

biological importance. Thus, we believe that this green procedure will be worthwhile addition to the present methodologies.

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