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A facile One Pot Synthesis and Antimicrobial activity of 1,3,6-Trisubstitutedpyrimidine-2,4-diones and 1,3,6-Trisubstitutedpyrimidine-2-thio-4-ones

Punam[1], Deepika[2], Anil Kumar[3] and Sharwan K Dewan[4*]

1. Department of Chemistry, Mahavira Swami Institute of Technology, Jagdishpur, Sonepat, Haryana, **INDIA**
2. College of Pharmacy, Pt B d Sharma University of Health Sciences, Rohtak, Haryana-124 001, **INDIA**
3. Department of Chemistry, AIJHM PG College, Rohtak, Haryana-124001, **INDIA**
4. Department of chemistry, M D University, Rohtak, Haryana-124 001, **INDIA**

Email: sharwankumardewan@yahoo.com

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ABSTRACT

1,3,6-Trisubstituted pyrimidine-2,4-diones and their thioanalogues, 1,3,6-Trisubstitutedpyrimidine-2-thio-4-ones have been rapidly synthesized in high yields by condensing symmetrically disubstituted ureas and thioureas with betaketoesters in dry media .

Keywords: 1,3,6-Trisubstitutedpyrimidine-2,4-diones, 1,3,6-Trisubstitutedpyrimidine-2-thio-4-ones, solvent-free synthesis, dry media, rapid synthesis.

INTRODUCTION

Immense interest has gone into derivatizing uracils from the point of view of research into nucleic acids as well as from pharmacotherapeutic considerations since the discovery of uracils from RNA [1]. Compounds related to the title heterocycles have been found to be associated with attractive pharmacotherapeutic profiles such as analgesic, anti-inflammatory, and anti-pyretic biological profiles.[2]

The 1,3,6-Trisubstitutedpyrimidine-2,4-diones, the title compounds have been synthesized by methods such as by the condensation between the monosubstituted ureas and the diketone, by condensing the monosubstituted ureas and ethylacetoacetate in the presence of conc. H_2SO_4.[2-5] These methods yield 1 or 3-substituted-6-methyl uracils which are subsequently alkylated to give the 1,3-disubstituted-6-methyluracil. A recent method for the synthesis of these compounds involves the condensation of a disubstituted urea with an excess of acetic anhydride in presence of 4-methylpyridine solution but the method includes a series of tedious extractions work-up and also gives moderate yields.[6]

In general, the reported methods suffer from drawbacks like many steps, low yields and long reaction times which prompted us to develop new and rapid methods for the synthesis of the title compounds.

MATERIALS AND METHODS

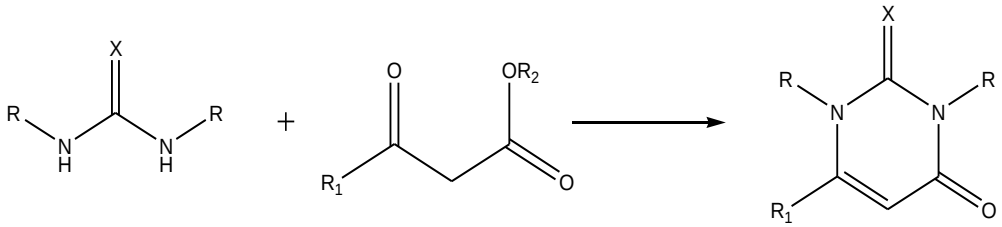
The substrates were procured from Aldrich and their purity confirmed by physical and spectroscopic analyses before use. The Proton NMR spectra were recorded at a 400 MHz Bruker NMR spectrometer. The chemical shifts are reported in ppm and were measured in deuterated chloroform and TMS as an internal standard. TLC was used for monitoring the reaction.

N,N-Dialkylurea or N,N-Dimethylthiourea DMTU(1mmol) and methylacetoacatate (MAA) or ethyl benzoylacetate (EBA) (1mmol) were taken in a 25 mL Pyrex beaker in a Teflon bath and the mixture microwaved, with the reaction being monitored by thin Layer Chromatography using CCl4: ethylacetate (3:1). The crude product was purified by column chromatography (CCl4/ethylacetate, 94/6) as eluent over silica gel to afford the desired product. The structures of all the products were unambiguously confirmed by spectroscopic and physical analyses.

RESULTS AND DISCUSSION

Now a days, the academic and industrial chemists are interested in carrying out organic synthesis under solvent- free conditions, avoiding the use of a catalyst, if possible and employing the technique of heating by microwaves i.e. under green chemistry conditions rather than under the classical reaction conditions which involve the use of solvents and often, catalysts.[7-11] Therefore, we aimed at developing the green rapid methods for the synthesis of the title pyrimidine-2,4-diones from a betaketoester like methylacetoacetate, ethylbenzoylacetate and a symmetrically disubstituted urea in dry media conditions without the use of a catalyst.

We have already reported the preliminary results of the synthesis of 1,3-dimethyl-6-phenylpyrimidine-2,4-dione, and 1,3-diethyl-6-methylpyrimidine-2,4-dione from the corresponding dialkyl urea and the betaketoester. In this paper, we report the synthesis of 1,3-diethyl-6-phenylpyrimidine-2,4-dione, 1,3-dibenzyl-6-phenylpyrimidine-2,4-dione and 1,3-diallyl-6-phenyl-pyrimidine-2,4-dione and 1,3,6-trimethylpyrimidine-2-thio-4-one by condensation method from a betaketoester and the corresponding dissymmetric urea.

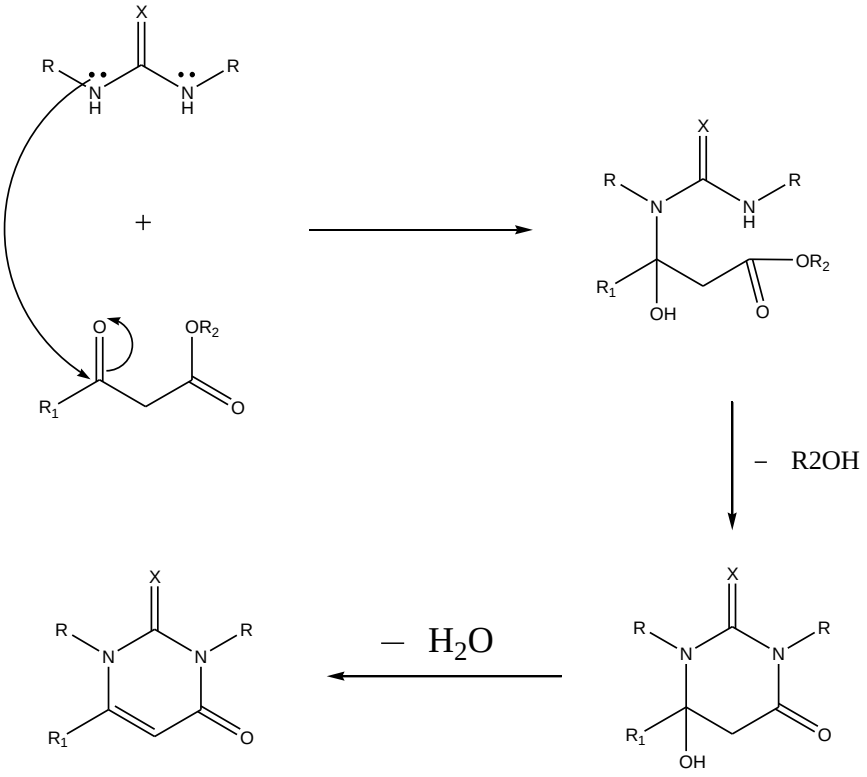


R= Me, Et, Allyl , R_1= Ph, Me , $R_{2=}$ Me, Et , X=O, S

The investigations were initiated by microwaving a mixture of ethylbenzoyl acetate (EBA) and 1,3-diethylurea (DEU) taken in 1:1 ratio in an open vessel at various temperatures. Monitoring of the reaction by thin layer chromatography (TLC) showed that the reaction did not occur to any appreciable extent under these conditions. Adjusting the substrate ratio from1:1 to 1:2 or 1:3 also did not prove successful. However, when the reaction was carried out in a Teflon bath that was fitted with a security disk that could resist pressures up to 10 bars, the desired product, 1,3-diethyl-6-phenylpyrimidine-2,4-dione was formed in 72 % yield after column chromatography. Similarly, the 1,3-dibenzyl-6-phenylpyrimidine-2,4-dione from 1,3-dibenzylurea (DBU) and ethylbenzoyl acetate (EBA) was obtained in 80 % isolated yield. Encouraged by these results, we now decided to attempt the condensation of another readily available beta-ketoester, methylacetoacetate (MAA) with ureas such as DAU to yield the corresponding product. Thus, the condensation of 1,3-diallylurea (DAU) and methylacetoacetate (MAA) gave the desired product, 1,3-diallyl-6-methylpyrimidine-2,4-dione in 83% isolated yield.

In order to extend the versatility of the above method and to introduce diversity in the target uracils accessible from the above developed novel one pot method and to expand the scope of the condensation reaction , we became interested in synthesizing the corresponding thio-analogues of the title heterocycles. Thus, we replaced DMU with 1,3-dimethylthiourea (DMTU) in its condensation with ethyl benzoylacetate (EBA) . The desired product, 1,3-dimethyl-6-phenyl-pyrimidine-2-thio-4-one was obtained in a good isolated yield of 83 % isolated yield. Next, we condensed DMTU with another betaketoester, methylacetoacetate and obtained the corresponding uracil,1,3,6-trimethylpyrimidine2-thio-4-one in an isolated yield of 81 %. These results show that the thio-analogues of 1,3,6-Trisubstitutedpyrimidine-2,4-diones were also accessible by our newly developed method. A suitable mechanism for their formation is shown in Scheme.

We have also assayed the antimicrobial activity of these synthesized compounds by agar well diffusion method as recommended by CLSI. The four representative bacterial and one antifungal isolates used were: S.aureus ATCC 27853, E.coli ATCC 25922, P. aeruginosa ATCC 27853, B. subtilis ATCC 6633 and Candida albicans ATCC 90028. The three antimicrobial agents, cefepime, amikacin and linezolid were used as internal standards. DMSO was used as a control. The plates were incubated for 24 h at 37^0C and zones of inhibition were measured with the help of Vernier calipers. The preliminary results of the activity indicated that the title compound displayed a moderate activity against the bacterial strains examined. We are also examining some other pharmacotherapeutic properties of these compounds and all these will be reported together in future.



Scheme

APPLICATIONS

Compounds related to the title heterocycles have been found to be associated with attractive pharmacotherapeutic profiles such as analgesic, anti-inflammatory, and anti-pyretic biological profiles.[2,13] Some of the synthesized compounds have exhibited moderate antimicrobial activity. The

other pharmacotherapeutic activities of the synthesized compounds are being explored and will be reported in future.

CONCLUSIONS

We have developed a new green rapid one-pot method for the synthesis of 1,3,6-Tri substituted pyrimidine-2,4-diones and thei thio-analogues 1,3,6-Trisubstitutedpyrimidine-2-thio-4-ones from the condensation between 1,3-dialkyl urea or 1,3-dialkylthiourea and a betaketoester in high yields.

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