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Rapid Synthesis And Antimicrobial Activity of 1,3,6-Trimethylpyrimidine-2-Thio-4-One Under Green Chemistry Conditions

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ABSTRACT

N,N-Dimethyl thiourea and methylacetoacetate were condensed together in a closed vessel in dry media under microwave irradiation to yield 1,3,6-trimethylpyrimidine-2-thio-4-one in 80% yield.

Keywords: Pyrimidine-2-thione, MW, Dry media, Condensation.

INTRODUCTION

The title compounds are thioanalogues of pyrimidinediones which possess attractive pharmacotherapeutic profiles such as antipyretic, analgesic, anti-inflammatory and hence occupy a significant place in organic synthesis and pharmaceutical sciences [1-2].

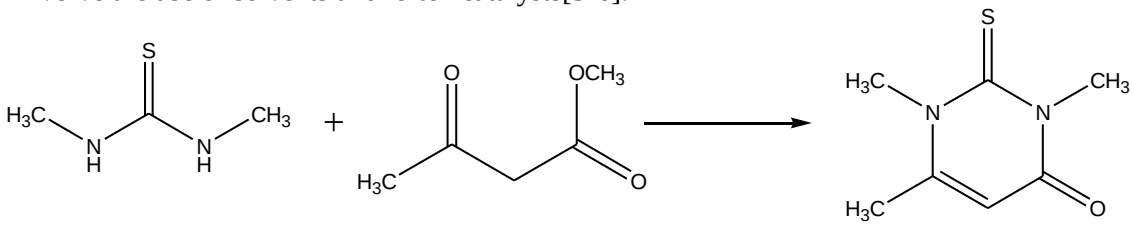
MATERIALS AND METHODS

N,N-Dimethylthiourea and methylacetoacetate were procured from Aldrich. The proton NMR spectra were recorded on a 400MHz NMR Spectrometer. All chemical shifts are expressed in parts per million with respect to trimethylsilane(TMS) and in CDCl3. The IR spectra were obtained on a FT Nicolet instrument.

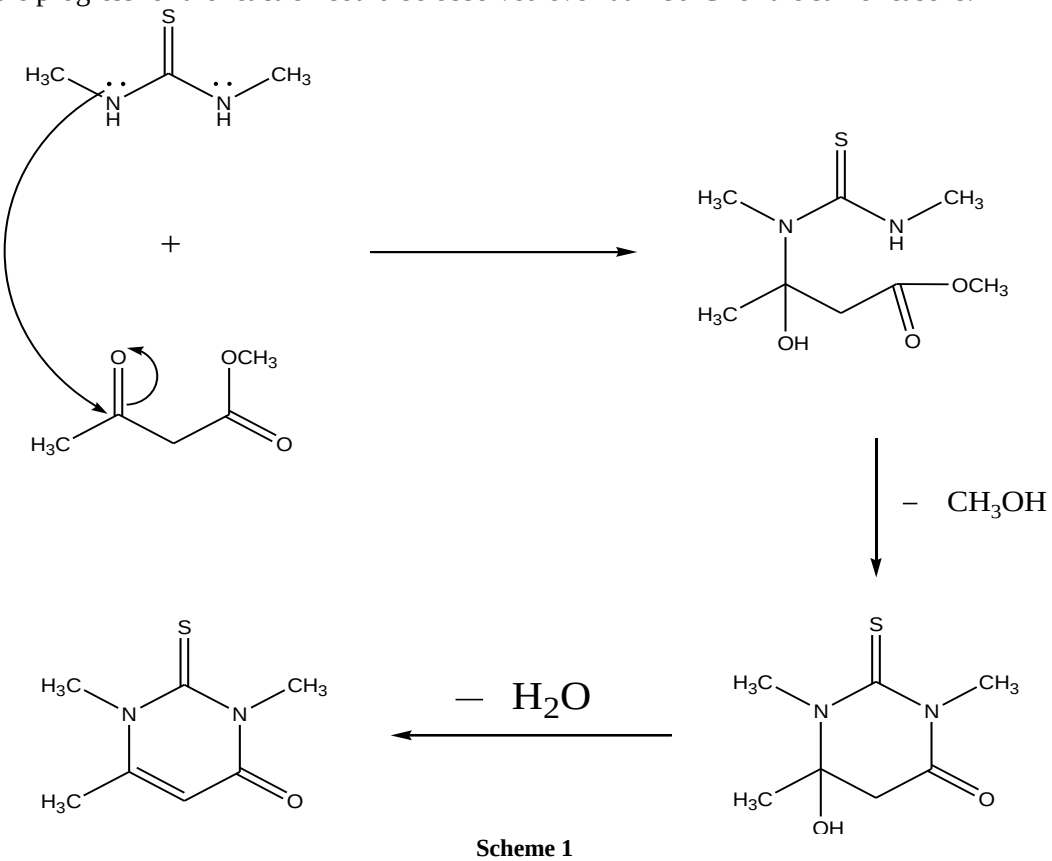
N,N-Dimethylthiourea(DMTU, 1mmol) and methylacetoacatate (MAA, 1mmol) were taken in a 25 mL Pyrex beaker in a Teflon bath which was fitted with a security disk that could resist pressures up to 10 bars. To begin with, the substrates were mixed in 1:1 ratio and the mixture was microwaved at 80^0C for 10 min with the reaction progress being monitored by Thin Layer Chromatography. The crude product was purified by column chromatography with (CCl4/ethylacetate, 94/6) as an eluent over silica gel to afford the desired product in 80% yield. The compound melted at 123^0C(ether).

RESULTS AND DISCUSSION

Today, the academicians as well as 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 the classical reaction conditions which involve the use of solvents and often catalysts[3-6].



N,N-dimethylthiourea (DMTU) and methylacetolacetate (MAA) were taken in 1:1 ratio and the reaction mixture was irradiated at different temperatures . First of all, the mixture was microwaved at 40^0C. The progress of the reaction was monitored by Thin Layer Chromatography that showed that the reaction occurred very slowly and did not occur to an appreciable extent even after 45 min of irradiation. When the temperature was increased to 50^0C, no appreciable progress could still be noted. This was followed by an increase in the temperature to 60^0C but again no appreciable progress could be observed. Subsequently, when the temperature was adjusted to 100^0C, 150^0C, 180^0C, again no noticeable changes in the reaction progress occurred. On the basis of very careful monitoring by TLC, we were led to the conclusion that MAA underwent evaporation to a considerable extent under the open vessel conditions. Therefore, we decided to enhance the quantity of the MAA to twice the molar ratio of the thiourea taken. However, no appreciable progress of the reaction could be observed even at 180^0C for the same reasons.



Scheme 1

In view of the above results, we decided to attempt the reaction under closed vessel conditions. The condensation was now carried out in a Teflon bath which was fitted with a security disk that could resist pressures up to 10 bars. To begin with, the substrates were mixed in 1:1 ratio and the mixture microwaved at various temperatures ranging from 40 to 60^0C but the reaction occurred slowly and did not progress well even after 45 min as observed under the open vessel conditions. However, when carried out at 80^0C, the reaction underwent completion within 8 min giving the desired product in 80% isolated yield after column chromatography. The proton NMR of the product exhibited three 3H singlets at 2.34 and 3.73 and 3.84ppm respectively owing to C-methyl, and two N-methyl protons. The olefinic proton at C-5 appeared at 5.89ppm corresponding to the structure of the desired product. The ir, elemental and mass spectral analyses agreed well with the desired structure. The mechanism of the formation of the products is shown in scheme 1.

APPLICATIONS

The title compound has shown moderate antimicrobial activity. The antimicrobial activity of the title compound was assayed by agar well diffusion method as recommended by CLSI. The four representative bacterial and one antifungal isolates were namely S.aureus ATCC 27853, E.coli ATCC 25922, P. aeruginosa ATCC 27853, B. subtilis ATCC 6633 and Candida albicans ATCC 90028. Three antimicrobial agents (cefepime, amikacin and linezolid) were used as internal standards and 100% DMSO was used as a control. The plates were incubated for 24 hours at 37^0C. The zones of inhibition were measured employing the Vernier calipers. The preliminary results of the activity indicated that the title compound displayed a weak activity against bacterial strains. Therefore, we think that analogues of the title compound need to be synthesized for examining their antimicrobial activity. The other biological activities of the title compound are in progress.

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