Montmorrilonite KSF Catalysed One Pot Synthesis and biological Activity of 1,3,6-Trisubstitutedpyrimidine-2,4-dione Uracils.

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ABSTRACT : Montmorrilonite KSF catalyzes the rapid synthesis of 1,3,6-Trisubstituted pyrimidine-2,4-diones by condensation of symmetrically disubstituted ureas with betaketoesters under solvent-free conditions.

KEYWORDS : solvent-free synthesis, dry media, 1,3,6-Trisubstitutedpyrimidine-2,4-diones, 1,3,6-trisubstituted uracils, methylacetoacetate, ethylbenzoylacatate, rapid synthesis, closed Teflon vessel, Montmorrilonite KSF .

INTRODUCTION

Hetyerocycles related to the title compounds are associated with attractive pharmacotherapeutic profiles such as analgesic, anti-inflammatory, and anti-pyretic biological profiles.[1-2] The title compounds, 1,3,6-trisubstitutedpyrimidine-2,4-diones, have been synthesized by methods such as by the condensation between the monosubstituted ureas and the diketene, 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 gives moderate yields and includes a series of tedious extractions work-up.[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, the 1,3,6-risubstitutedpyrimidine-2,4-diones .

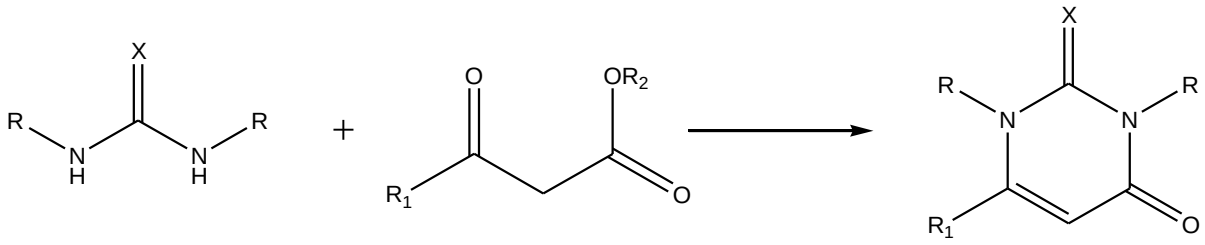
METHODS AND MATERIALS

A 400 MHz Bruker NMR spectrometer was used to record the NMR spectra. 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. The substrates were procured from Aldrich and their purity confirmed by physical and spectroscopic analyses before use. 1,3--Dialkylurea and methylacetoacatate (MAA) or ethylbenzoylacetate (EBA) (1mmol) and the catalyst (100mg) 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. The crude product was purified by column chromatography (CCl4/ethylacetate, 94/6) as eluant over silica gel to afford the desired product. The structures of all the products were unambiguously confirmed by spectroscopic and physical data as reported earlier.

RESULTS AND DISCUSSION

Organic synthesis is enormously being carried out under solvent- free conditions now. And a catalyst is also used if the reaction so demands and that is being done in conjunction with the green technique of heating by microwaves i.e. under green chemistry conditions rather than under the classical reaction conditions that involves the use of solvents.[7-11] Therefore, we became interested in developing the green rapid methods for the synthesis of the title pyrimidine-2,4-diones. We envisioned their rapid synthesis from a betaketoester like methylacetoacetate, ethylbenzoylacetate and a symmetrically disubstituted urea under the dry conditions of dry media.

Recently, we reported a rapid synthesis of 1,3-dialkyl-6-phenylpyrimidine-2,4-diones from the dialkyl urea and the betaketoester in the absence as well as in the presence of the zeolite, sodium chloride, silica gel, Mont K-10 catalysts under closed vessel conditions[13]. In this paper, we report the synthesis of the title compounds by the condensation method from a betaketoester and a dissymmetric urea by using Mont KSF, an inexpensive, non-corrosive, non-toxic and environmentally benign substance containing both Lewis and Bronsted acidities which are likely to catalyse the condensation reaction better than MontK-10 having a lower Bronsted acidity character.



R= Me, Et, Allyl, benzyl X= O R_1= Ph, Me R_2 = Me, Et

We initiated investigations by microwaving a mixture of ethylbenzoyl acetate (EBA) and 1,3-dimethylurea (DEU) (in 1:1 molar ratio) and Mont KSF (100mg) 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 from 1:1 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-dimethyl-6-phenylpyrimidine-2,4-dione was formed in 87 % yield after column chromatography compared to 76% yield without the presence of catalyst. Similarly, the condensation of diethylurea (DEU) with ethylbenzoyl acetate (EBA) gave the 1,3-diethyl-6-phenylpyrimidine-2,4-dione in 80% yield, while the yield of the product in the absence of the catalyst was 72% only. The 1,3-dibenzyl-6-phenylpyrimidine-2,4-dione from 1,3-dibenzylurea (DBU) and ethylbenzoyl acetate (EBA) was obtained in 91 % isolated yield compared to 80% in the absence of the catalyst. Encouraged by these results and 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 , we decided to attempt the condensation of another readily available beta-ketoester, methylacetoacetate (MAA) with ureas such as DMU, DEU and DAU to obtain the corresponding heterocyclic products. Thus, the condensation of DMU with MAA in the presence of the catalyst gave the 1,3,6-trimethylpyrimidine-2,4-dione in 82% yield, whereas the yield of the product obtained without the use of the catalyst was only 71%. Similarly, the yield of the condensation product, 1,3-diethyl-6-methylpyrimidine-2,4-dione from DEU and MAA was 74%, while the yield in the absence of the catalyst was only 62%. The condensation of 1,3-diallylurea (DAU) and methylacetoacetate (MAA) gave the desired product, 1,3-diallyl-6-methylpyrimidine-2,4-dione in 90% isolated yield, while the yield obtained in the absence of the catalyst was 83%. The yield of the products obtained in the presence and absence of the catalyst are collected in Table 1

Table 1: YIELDS OF THE PRODUCTS IN THE ABSENCE AND PRESENCE OF THE Mont- KSF

Urea	Betaketoester	No Catalyst	Mont-KSF
DMU	EBA	76 %	87%
DEU	EBA	72%	80%
DBU	EBA	80%	91%
DMU	MAA	71%	82%
DEU	MAA	62%	74%
DAU	MAA	83%	90%

As can be seen , the yields of the title heterocyclic products, the 1,3,6-trisubstitutedpyrimidine-2,4-diones were as anticipated better (74-90%) in the presence of the catalyst than those obtained in the absence (62-83%) of the catalyst and the time required for completion of the reactions were also observed to be lower as anticipated..

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] The antimicrobial activity of these synthesized compounds was also assayed 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 hours 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. Some of the synthesized compounds have exhibited moderate antimicrobial activity. The other of the synthesized compounds are being explored and will be reported in future along with the pharmacotherapeutic activities of some related compounds .

CONCLUSION

We have developed a new green rapid one-pot method for the synthesis of 1,3,6-trisubstitutedpyrimidine-2,4-diones from the condensation between a 1,3-dialkyl urea and a betaketoester in high yields (70-88%) in the presence of the Mont-KSF catalyst.

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