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Zeolite Catalysed One Pot Synthesis and Antimicrobial Activity of 1,3,6-Trisubstitutedpyrimidine-2,4-diones.

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ABSTRACT

Zeolite catalyzed rapid synthesis of 1,3,6-trisubstitutedpyrimidine-2,4-diones by condensation of symmetrically disubstituted ureas with betaketoester under solvent-free conditions giving products in 70-88% yield.

Keywords: 1,3,6-Trisubstitutedpyrimidine-2,4-diones, 1,3,6-trisubstituted uracils, methylacetoacetate, ethylbenzoylacatate, solvent-free synthesis, dry media, Zeolite.

INTRODUCTION

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.[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 time which prompted us to develop new and rapid methods for the synthesis of the title compounds, the 1,3,6-tri substituted pyrimidine-2,4-diones.

MATERIALS AND METHODS

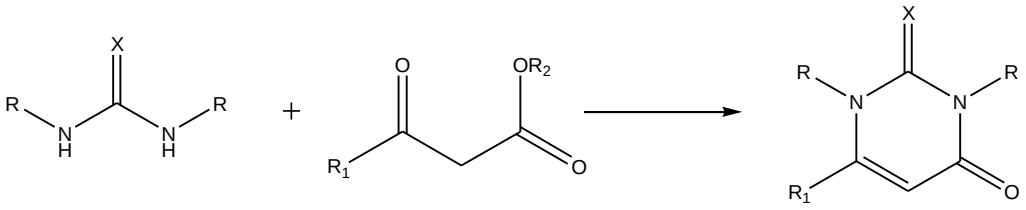
The Proton NMR spectra were recorded at a 400 MHz Bruker NMR spectrometer. The chemical shifts are reported in ppm and were measured in deuterated chloroform and TMS as an internal standard. TLC was used for monitoring the reaction. The substrates were procured from Aldrich and their purity confirmed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

physical and spectroscopic analyses before use. 1,3-Dialkylurea and methylacetoacetate (MAA) or ethylbenzoylacatate (EBA) (1mmol) and Zeolite (100mg) were taken in a 25 mL Pyrex beaker in a Teflon bath and the mixture microwaved and the reaction being monitored by thin Layer Chromatography. The crude product was purified by column chromatography (CCl4/ethyl acetate, 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

Green or clean chemistry is today a very desired subject. That means, we are now-a-days interested in carrying out organic synthesis under solvent- free conditions and using a catalyst if the reaction so demands and employing the 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 aimed at developing the green rapid methods for the synthesis of the title pyrimidine-2,4-diones and we envisioned their rapid synthesis from a betaketoester like methylacetoacetate, ethylbenzoylacatate and a symmetrically disubstituted urea under dry media conditions.

We have already reported the rapid synthesis of 1,3-dialkyl-6-phenylpyrimidine-2,4-diones from the corresponding dialkyl urea and the betaketoester in the absence of a catalyst under closed vessel conditions[13]. The yields of the products obtained were in the range 62-83%. Therefore, there was a need to enhance the yield of the products. In this paper, we report the synthesis of the title compounds by the condensation method from a betaketoester and a dissymmetric urea by using an environmentally friendly catalyst zeolite, which is an inexpensive and environmentally benign substance whose mechanism of action is known to occur via its pores size being suitable to those of the substrates, thereby facilitating the formation of the products.



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

The investigations were initiated by microwaving a mixture of ethylbenzoylacatate (EBA) and 1,3-dimethylurea (DEU) (taken in 1:1 molar ratio) and Zeolite 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 83 % yield after column chromatography compared to 76% yield without the presence of Zeolite catalyst. Similarly, the condensation of diethylurea (DEU) with ethylbenzoylacatate (EBA) gave the 1,3-diethyl-6-phenylpyrimidine-2,4-dione in 78% yield, while the yield of the product in the absence of the Zeolite catalyst was 72% only. The 1,3-dibenzyl-6-phenylpyrimidine-2,4-dione from 1,3-dibenzylurea (DBU) and ethylbenzoylacatate (EBA) was obtained in 86 % 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 betaketoester, 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 Zeolite gave the 1,3,6-trimethylpyrimidine-2,4-dione in 79% yield, whereas the yield of

the product obtained without the use of the Zeolite catalyst was only 71%. Similarly, the yield of the condensation product, 1,3-diethyl-6-methylpyrimidine-2,4-dione from DEU and MAA was 70%, 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 83% 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 Zeolite catalyst

Urea	Betaketoester	No Catalyst	Zeolite
DMU	EBA	76 %	83%
DEU	EBA	72%	78%
DBU	EBA	80%	86%
DMU	MAA	71%	79%
DEU	MAA	62%	70%
DAU	MAA	83%	88%

As can be seen , the yields of the title heterocyclic products, the 1,3,6-trisubstitutedpyrimidine-2,4-diones were better (70-88%) in the presence of the Zeolite catalyst than those obtained in the absence (62-83%) of the Zeolite and the time required for completion of the reactions were also observed to be lower.

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] 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. 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

Zeolite catalyzed the synthesis of 1,3,6-trisubstitutedpyrimidine-2,4-diones. 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%).

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REFERENCES

[1] D. Cole, A.J. Foster, S.W.Freeman, P.E.Murray , I.J.Stanford, , *Anti-Cancer Drug Das*, **1999**, 14,383.

[2] S. Senda, K.J. Hirota, *Med Chem*, **1972**, 15, 471.

[3] A Suzui, S Senda, *CA* **1958**, 52, 11972.
[4] S Senda, A Suzui, *CA* **1959**, 53, 10237.
[5] S Senda, A Suzui, *Chem Pharm Bull*, **1958**, 6,479.
[6] H Egg, I Volgger, *Synthesis*, **1982**, 1071.
[7] S K Dewan, *Indian J Chemistry, Section B*, **2006**, 45, 2337.
[8] S K Dewan, R Singh, A Kumar, *Arkivoc*, **2006**, 2, 41.
[9] S K Dewan, *Synth Commun*, **2004**, 34, 2025.
[10] S K Dewan, R Singh, A Kumar, *Synth Commun*, **2003**, 33, 2, 41.
[11] S K Dewan, Punam, A Kumar, *J Applicable Chemistry*, **2013**, 2, 714.
[12] S K Dewan, Punam, *J Applicable Chemistry*, **2014**, 3, 639.
[13] Punam, A Kumar, SK Dewan, *J Applicable Chemistry*, **2014**, 3, 1495-1498.