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# One Pot Synthesis and Antimicrobial Activity of 1, 3, 6-Trisubstituted Pyrimidine-2, 4-diones Catalyzed by TsOH

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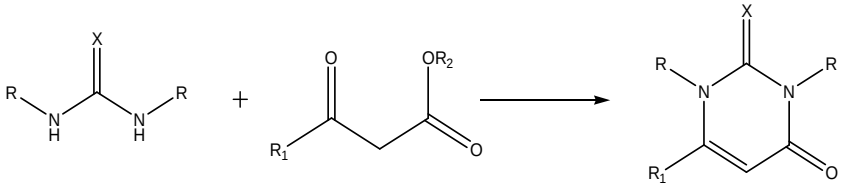
## ABSTRACT

*TsOH catalyzes the rapid synthesis of1,3,6-Trisubstituted pyrimidine-2,4-dione uracils by condensation of symmetrically disubstituted urea's with betaketoestersin dry media.*

**Graphical abstract**




**Keywords:** TsOH, 1,3,6-Trisubstitutedpyrimidine-2,4-diones, 1,3,6-trisubstituted uracils, Methyl Acetoacetate, Ethylbenzoylacetate, Solvent-free synthesis, Dry media, Rapid synthesis, Closed Teflon vessel.

## INTRODUCTION

Heterocyclic 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 urea's 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 gives moderate yields and includes a series of

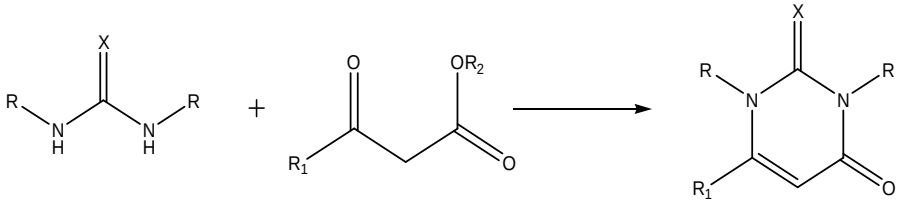
tedious extractions work-up[6]. In general, the reported methods suffer from drawbacks like many steps, low yields and long reaction times which prompted us to develop new and rapid methods for the synthesis of the title compounds, the 1, 3, 6-risubstitutedpyrimidine-2, 4-diones.

## MATERIALS AND METHODS

The NMR spectra were recorded at 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 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 ($CCl_4$/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

We are these 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 involve 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, ethylbenzoylacetate and a symmetrically disubstituted urea under dry media conditions. 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, silica gel, sodium chloride, Mont-K10, Mont KSF 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 toluene-p-sulfonic acid as the acidic catalyst.



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

The investigations were initiated by microwaving a mixture of ethylbenzoylacetate (EBA) and 1,3-dimethylurea (DEU) (taken in 1:1 molar ratio) and MontK-10 (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 93 % 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 85% 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 94 % 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 87% 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 80%, 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 94% 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 TsOH

| Urea | Betaketoester | No Catalyst | TsOH |
|---|---|---|---|
| DMU | EBA | 76 % | 93% |
| DEU | EBA | 72% | 85% |
| DBU | EBA | 80% | 94% |
| DMU | MAA | 71% | 87% |
| DEU | MAA | 62% | 80% |
| DAU | MAA | 83% | 94% |

As can be seen , the yields of the title heterocyclic products, the 1,3,6-trisubstitutedpyrimidine-2,4-diones were as anticipated better (80-94%) 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. In fact, the organic catalyst, TsOH has proved to be a better catalyst compared to the inorganic acidic catalysts, Mont-k10 catalyst (77-92%) and Mont- KSF (74-90%) catalysts already reported by us.

## 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 $37^0$C 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 publications.

## CONCLUSIONS

We have developed a new green rapid one-pot method for the synthesis of 1,3,6-tri substituted pyrimidine-2,4-diones from the condensation between a 1,3-dialkyl urea and a beta ketoester in high yields (70-88%) in the presence of the TsOH catalyst.

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