*Available online at* www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

**Der Pharma Chemica, 2016, 8(3):222-224**
*(http://derpharmachemica.com/archive.html)*

# Silica Gel Catalyzed One Pot Synthesis and Antimicrobial Activity of 1,3,6-Trisubstitutedpyrimidine-2,4-dione Uracils

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

[1]*Department of Chemistry, Mahaveera Swami Institute of Technology, Jagdishpur, Sonepat, Haryana*
[2]*College of Pharmacy, Pt B D Sharma University of Health Sciences, Rohtak, Haryana,PIN-124 001*
[3]*Department of Chemistry, AIJHM PG College, Rohtak, Haryana, Pin-124001*
[4]*1167, Sector-1, Rohtak, Haryana, PIN-124 001*

---

**ABSTRACT**

*Silica gel catalyzes the synthesis of 1,3,6-Trisubstituted pyrimidine-2,4-diones by condensation of symmetrically disubstituted ureas with betaketoesters under solvent-free conditions.*

**Keywords**: silica gel, 1,3,6-Trisubstitutedpyrimidine-2,4-diones, 1,3,6-trisubstituted uracils, methylacetoacetate, ethylbenzoylacatate, solvent-free synthesis, dry media, rapid synthesis, closed Teflon vessell.

---

## INTRODUCTION

Heterocycles related to the title compounds are associated with attractive pharmacotherapeutic profiles such as analgesic, anti-inflammatory, and anti-pyretic biological profiles.[1-2]. 1,3,6-Trisubstitutedpyrimidine-2,4-diones, have been synthesized by methods like 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. One 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] However, 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.

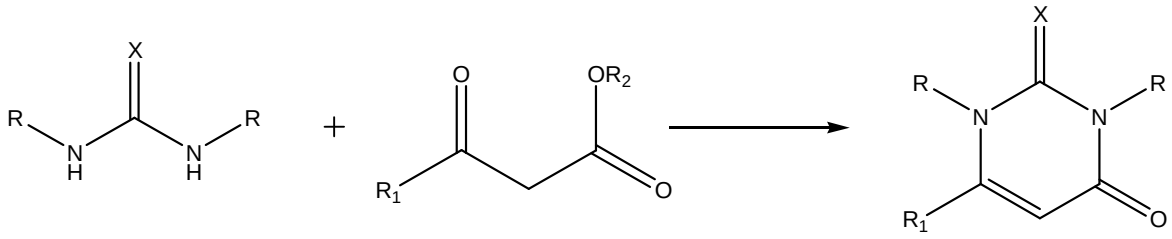
## METHODS AND MATERIALS

A 400 MHz Bruker NMR spectrometer was used for recording the Proton NMR spectra and the chemical shifts reported in ppm 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 silica gel (100mg) were taken in a 25 mL Pyrex beaker in a Teflon bath. The mixture was microwaved and the reaction monitored by thin Layer Chromatography and the crude product was purified by column chromatography (CCl4/ethylacetate, 94/6) as eluant over silica gel to afford the desired product. All the products were unambiguously characterized by spectroscopic and physical data.

## RESULTS AND DISCUSSION

Now-a-days we are interested in doing organic synthesis under solvent- free conditions, and using a catalyst if the reaction so demands and employing the technique of heating by microwaves that is under green chemistry conditions rather than under the classical reaction conditions that involves the use of solvents.[7-10] Hence, we aimed at developing the green rapid methods for the synthesis of the title pyrimidine-2,4-diones and we envisaged their rapid synthesis under dry media conditions from a betaketoester like methylacetoacetate, ethylbenzoylacetate and a symmetrically disubstituted urea.

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, silica gel, which is non-toxic, non-corrosive, inexpensive and environmentally benign substance. The silica gel was chosen in view of the presence of the carbonyl group in the betaketo ester in the condensation reaction with the urea. As the carbonyl group would get protonated in the presence of the silica gel which also contains Bronsted acidity, so the reaction was likely to get facilitated in the presence of the catalyst, silica gel.




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

We initiated by microwaving a mixture of ethylbenzoyl acetate (EBA) and 1,3-dimethylurea (DMU) (taken in 1:1 molar ratio) and silica gel in an open vessel at various temperatures. Reaction monitoring by thin layer chromatography (TLC) revealed that the reaction did not occur to any appreciable extent under these conditions and 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 79 % yield after column chromatography compared to 75% yield without the presence of a catalyst. Similarly, the condensation of diethylurea (DEU) with ethylbenzoyl acetate (EBA) gave the 1,3-diethyl-6-phenylpyrimidine-2,4-dione in 75% yield, while the yield of the product in the absence of the catalyst was 71% only. The 1,3-dibenzyl-6-phenylpyrimidine-2,4-dione from 1,3-dibenzylurea (DBU) and ethylbenzoyl acetate (EBA) was obtained in 83 % isolated yield compared to 80% in the absence of the catalyst. 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. Thhus, the condensation of DMU with MAA in the presence of the catalyst gave the 1,3,6-trimethylpyrimidine-2,4-dione in 76% yield, whereas the yield of the product obtained without the use of the catalyst was only 72%. Similarly, the yield of the condensation product, 1,3-diethyl-6-methylpyrimidine-2,4-dione from DEU and MAA was 67%, 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 73%. The yield of the products obtained in the presence and absence of the catalyst are collected in Table 1 below.

**Table 1: YIELDS OF THE PRODUCTS IN THE ABSENCE AND PRESENCE OF THE SILICA CATALYST**

| Urea | Betaketoester | No Catalyst | Silica Gel |
|---|---|---|---|
| DMU | EBA | 75 % | 82% |
| DEU | EBA | 72% | 76% |
| DBU | EBA | 80% | 83% |
| DMU | MAA | 71% | 76% |
| DEU | MAA | 62% | 67% |
| DAU | MAA | 73% | 83% |

From the table, it is clear that the yields of the title heterocyclic products, the 1,3,6-trisubstitutedpyrimidine-2,4-diones were, as anticipated better (67-83%) in the presence of the silica gel catalyst because of Bronsted acidity than those obtained in the absence (62-73%) of the silica gel.

As 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, 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 hours 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 and the other pharmacotherapeutic activities of the synthesized compounds are being explored.

## CONCLUSION

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 silica gel catalyst.

**Acknowledgement**
We are thankful to all those who helped us with chemicals used in this investigation.

## 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.