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Short Communication

Sodium Chloride Catalysed Rapid One Pot Synthesis of 1, 3, 6-Trisubstitutedpyrimidine-2,4-diones from Ureas and β-ketoesters

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ABSTRACT

Sodium Chloride catalyzes the one pot rapid synthesis of 1,3,6-Trisubstitutedpyrimidine-2,4-diones by condensation of symmetrically disubstituted ureas with betaketoesters like methylacetoacetate, ethyl aceto acetate under solvent-free closed vessel conditions, giving 72-89% yields.

Keywords: Ethylbenzoylacatate, methylacetoacetate, solvent-free synthesis, NaCl.

INTRODUCTION

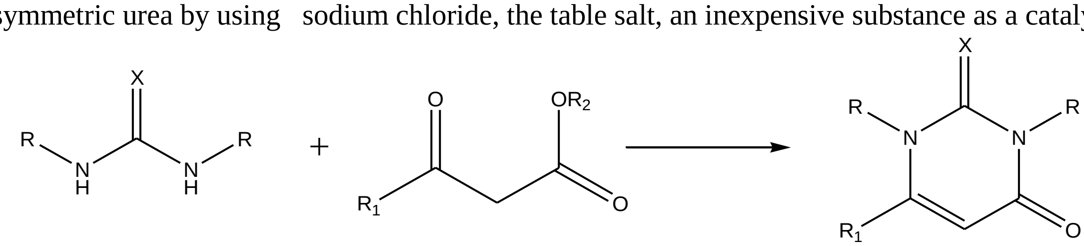
The likes of the title heterocycles have been found to be associated with attractive pharmacotherapeutic profiles such as analgesic, anti-inflammatory, and anti-pyretic biological profiles.[1-2] The title compounds, 1,3,6-trisubstitutedpyrimidine-2,4-diones, have been synthesized by methods such as by 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 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

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 methylacetoacatate (MAA) or ethyl benzoyl acetate (EBA) (1mmol) and 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.

RESULTS AND DISCUSSION

These days, we are 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.[7-13]. Similarly, it is very much advantageous to devise one pot synthesis of the targeted molecules from the point of view of yields, purity, convenience, labour and chemoeconomics. Therefore, we aimed at developing the green rapid one pot methods for the synthesis of the title pyrimidine-2,4-diones and we envisioned their rapid synthesis from a β-ketoester like methylacetoacetate, ethylbenzoylacetate and a symmetrically disubstituted urea under dry media conditions. In this paper, we report the synthesis of the title compounds by the condensation method from a β-ketoester and a dissymmetric urea by using sodium chloride, the table salt, an inexpensive substance as a 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 ethylbenzoyl acetate (EBA) and 1,3-dimethylurea (DEU) (taken in 1:1 molar ratio) and in the presence as well as absence of sodium chloride 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 84 % yield after column chromatography compared to 76% yield without the presence of the catalyst. Similarly, the condensation of diethylurea (DEU) with ethylbenzoyl acetate (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 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 89 % 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 80% 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 72%, 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 89% 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 sodium chloride

Urea	β-ketoester	No Catalyst	NaCl
DMU	EBA	76 %	84%
DEU	EBA	72%	78%
DBU	EBA	80%	89%
DMU	MAA	71%	80%
DEU	MAA	62%	72%
DAU	MAA	83%	89%

As can be seenfrom the table, the yields of the title heterocyclic products, the 1,3,6-tri substitutedpyrimidine-2,4-diones were better (72-89%) in the presence of sodium chloride than in its absence. Possibly,the sodium cations increase the electrophilicity of the carbonyl carbon in the betaketoester by attaching to the carbonyl oxygens and the chloride anions enhance the nucleophilicity of the nitrogen of the ureas, thereby facilitating the nucleophilic attack of the nitrogen on the electrophilic carbonyl carbon in the initial step as well as in the cyclizing step.

APPLICATIONS

Compounds related to the title heterocycles have been found to be associated with fascinative pharmaco therapeutic 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 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 thes 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

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 β-ketoester in high yields (72-89%) in the presence of the sodium chloride catalyst.

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