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Research Article

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One pot rapid synthesis of 1,3-diethyl-6-methyl uracil

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ABSTRACT

A rapid and facile one pot synthesis of 1,3-diethyl-6-methyluracil has been carried out in dry- media from 1,3-diethyl urea and methylacetoacetate in 62% yield .

Keywords: Uracils, Urea, Methylacetoacetate, Dry-media, MW

INTRODUCTION

Since the discovery of uracils from RNA, immense interest has gone into derivitizing uracils from the point of view of research into nucleic acids as well as from pharmacotherapeutic considerations.[1] Compounds related to the title heterocycle have been found to be associated with attractive pharmacotherapeutic profiles such as analgesic, anti-inflammatory, and anti-pyretic biological profiles.[2]

The title compound has been synthesized by methods such as by the condensation between the monosubstituted ureas and the diketene[2], by condensing the monosubstituted urea and ethylacetoacetate in the presence of conc. H_2SO_4 .[3]These methods yield 1 or 3-substituted -6-methyl uracils which are subsequently ethylated to give the 1,3-diethyl-6-methyluracil. A recent method for the synthesis of the title compound involves the condensation of a disubstituted urea with an excess of acetic anhydride in presence of 4-methylpyridine solution but it includes a series of tedious extractions and also gives moderate yields.[4]

In general, the reported method suffers from limitations like many steps, low yields and long reaction hours which prompted us to develop new methods for the synthesis of the title compound.

EXPERIMENTAL SECTION

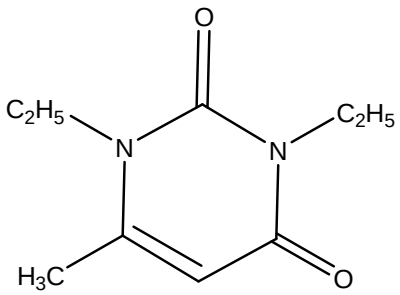
N,N-Diethylurea and methylacetoacetate were procured from Aldrich. The proton NMR spectra were recorded on a 400MHz NMR Spectrometer. All chemical shifts are expressed in parts per million with respect to tetramethylsilane(TMS) and in $CDCl_3$. The IR spectra were obtained on a FT Nicolet instrument.

N,N-Diethylurea DMU(1mmol) and methylacetoacatate (MAA)(1mmol) were taken in a 25 mL Pyrex beaker in a Teflon bath and the mixture microwaved at 50^0C for 10 min. The reaction was monitored by Thin Layer Chromatography using CCl4: ethylacetate (3:1). The crude product was purified by column chromatography

(CCl4/ethylacetate, 94/6) as an eluant over silica gel to afford the desired product in 62% yield. The reaction was also carried out at other conditions.

RESULTS AND DISCUSSION

We envisaged to synthesise the title compound in one pot by condensing 1,3-diethyl urea with methylacetoacetate which was unreported hitherto and that too under the green tool of irradiation by microwaves which is being increasingly used in organic synthesis.[6-9]In order to initiate the studies for the synthesis of the title compound, 1,3-diethylurea was mixed with methylacetoacetate in 1:1 ratio and irradiated in an open vessel in the absence of a catalyst. Irradiation was carried out at various temperatures but the yield obtained was very low. Monitoring of the reaction by TLC showed the spot due to methylacetoacetate had almost disappeared while that due to the urea remained intense. Therefore, we decided to enhance the amount of the ketoester to twice that of the urea. However, that did not improve the situation. We now decided to carry out the reaction under closed vessel conditions.



In the event, the reaction was carried out with the substrates being mixed in 1:1 ratio in a closed Teflon bath which was fitted with a security disk that could resist pressures up to 10 bars at a temperature of 50^0C. Monitoring of the reaction by TLC revealed that the reaction was complete after 10 minutes of irradiation. The crude product was separated by column chromatography to give the desired product in 62% ratio. The yield of the product could not be enhanced by carrying out the reaction under lower or higher temperatures or by increasing the substrate ratio of urea:methylacetoacatate from 1:1 to 1:1.5 or 1:2 or 1:3. The proton NMR of the isolated product showed the presence of two triplets at 1.17 and 1.25ppm corresponding to the two ethyl groups and two quartets centered at 3.87 and 3.96ppm due to the two methylene protons of the two ethyl groups. This led to the confirmation of the presence of the two ethyl units , one at each nitrogen in the product. A conspicuous singlet corresponding to three protons at 2.22ppm arising due to the methyl group present at C-6 of the desired uracil product could also be seen. An olefinic singlet of 1H intensity was also present at 5.57ppm. These data indicated the structure of the synthesized product corresponded to the desired compound. The infrared analysis showed the presence of the two carbonyl groups and C=C stretching frequencies as anticipated at 1700, 1665, and 1625 cm^{-1}. Further confirmation for the structure elucidated came from the m.p. which was observed to be 50^0C that agreed well with the literature.[4]Thus, it is obvious that we were able to realize the proposed synthesis of the title compound and that the synthetic strategy turned out to be very promising .

The antimicrobial activity of the synthesized compound was also assayed by agar well diffusion method as recommended by CLSI. 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. The other pharmacotherapeutic profiles of the title compound are in progress and will be reported in future

CONCLUSION

One pot synthesis of 1,3-diethyl-6-methyluracil has been carried out in dry- media from 1,3-diethyl urea and methylacetoacetate in 62% yield and has shown moderate antimicrobial activity .

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