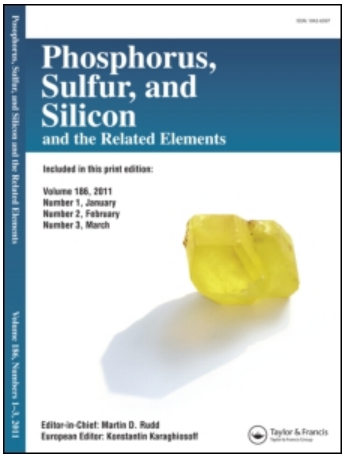

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A SIMPLE AND EFFICIENT METHOD FOR THE UNUSUAL REGIOSELECTIVE SYNTHESIS OF THIAZOLOPYRIMIDINES

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The addition of dimethyl acetylenedicarboxylate (DMAD) to 2-thio-uracils **1** afforded in good yield cycloadducts which were characterized to be new thiazolo [2,3-b] pyrimidines.

Keywords: Thiazolopyrimidines

Acetylenic esters have proven to be very versatile reagents for heterocyclization and many divers products can be prepared from the addition of this compound to nitrogen and sulphur containing heterocycles[1-4].

In 1984, S. Palazzo et al.[5] have reported the reaction of dimethyl acetylenedicarboxylate (DMAD) and 3-thioxo-1,2,4-triazin-5-ones to afford a single compound. On the basis of ^{13}C-chemical shifts and C, H coupling constant measurments, they characterized the product to be 6-substituted (z)-2-(methoxycarboxylmethylene) thia-zolo[2,3-b] 1,2,4-thiazine-3,7-dione.

We were interested in the chemistry of heterocyclic compounds containing nitrogen and sulphur atoms[6]. Uracil derivatives are an important class of compounds which are interesting from the chemical[7] and biological[8] point of view. As a part of a research program on synthesis of heterocyclic compounds containing nitrogen and sulphur and with a view to extending the synthetic utility of dimethyl acetylenedicarboxylate[9] (DMAD) we

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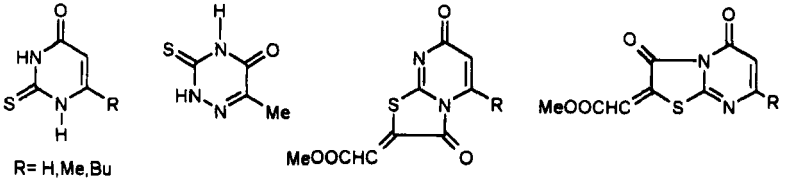
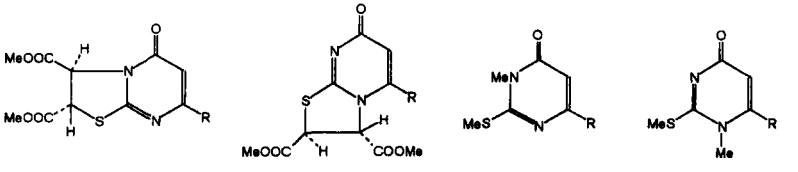
have investigated the addition of the latter to substituted 2-thiouracil. We herein report our results. 6-Methyl-2-thiouracil (**1**, R=Me) reacted readily with DMAD in acetonitrile to give the adduct which was expected to be either **3** or **4**[5] by considering the similar chemical behaviour of **1** with 6-methyl-3-thioxo-1,2,4-triazin-5(4H)-one **2**.



1 2 3 4

IR spectra of this adduct showed three carbonyl absorptions but no NH bands. But interestingly ^{1}H-NMR of this compound exhibited a signal corresponding to two methyl ester groups at δ 3.55 and CH doublets (both with J ca. 1.2 Hz) at δ 4.8 and 5.6 respectively besides a singlet at δ 2.1 for Me and δ 5.9 for H-5, no signals exchanged with D_2O. The mass spectrum of this compound showed moderate intensity of molecular ion peak corresponding to 1:1 molar adduct without elimination. Conventional simple fragmentation such as loss of -CO_2Me is also observed. These data indicated that a cyclization process had occurred by two nucleophilic additions to the triple bond in the presence of the ester groups. The above data was consistent with two possible structures **5** and **6** but was not sufficient to distinguish between them. The geometry of the thiazolidine 2,3-dicarboxylate ring was fixed by the small value (ca. 1.2 Hz) of the vicinal coupling constant between the alicyclic C-H protons observed in the ^{1}H NMR spectrum. It agrees with a trans diequatorial configuration assigned for similar compounds[10].



5 6 7 8

Structures **5** and **6** were easily descernible by comparison of their UV spectra with those of 2,3-disubstituted pyrimidinone **7** and 1,2-disubsti-

tuted pyrimidinone **8**. It has been reported that **7** with a dienone structure shows the absorption maxima uniformaly at longer wavelengths compared with that of **8** with a quinone structure[11]. The bicyclic derivative (**5** or **6**) showed an extremly similar absorption and maxima to **7**. This observation ruled out the possibility of formation of **6**. We therefore concluded that the nucleophilic groups attack to the triple bond of DMAD twice and regioselective cyclization occurs.

In a typical experimental procedure, 6-methyl-2-thiouracil **1** was dissolved in warm acetonitrile (25 mL). To this solution DMAD (1.47 mL, 12 mmol) in acetonitrile (15 mL) was added. The reaction mixture was refluxed for 2h. The solvent was evaporated to dryness under reduced pressure and the crude product was crystallized from EtOAc to afford 5, R=Me. Yield: 60%; mp.: 144–146°C; ^{1}H-NMR (δ, d_6-DMSO): 2.1 (s, 3H, Me), 3.6 (s, 6H, 2 COOMe), 4.8 (d, J=1.2 Hz, 1H, CH), 5.6 (d, J=1.2 Hz, 1H, CH); 5.9 (s, 1H CH5)^{13}C-NMR (δ): 20.15, 42.33, 52.23, 53.70, 62.25, 152.97, 155.72, 159.53, 165.43, 165.84, 170.66; UV (MeOH, λ_{max}/nm): 285; MS (m/z, M^+): 284(5), 227(15), 226(65), 225(100), 224(45), 182(45), 140(45), 139(17), 49(30).

Further study of this unusual, efficient and regioselective synthetic method is in progress.

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