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UNUSUAL REACTION OF THIOMALONAMIDE WITH 5,5-DIMETHYL-2-PHENYLAMINOMETHYLIDENE-1,3-CYCLOHEXANEDIONE

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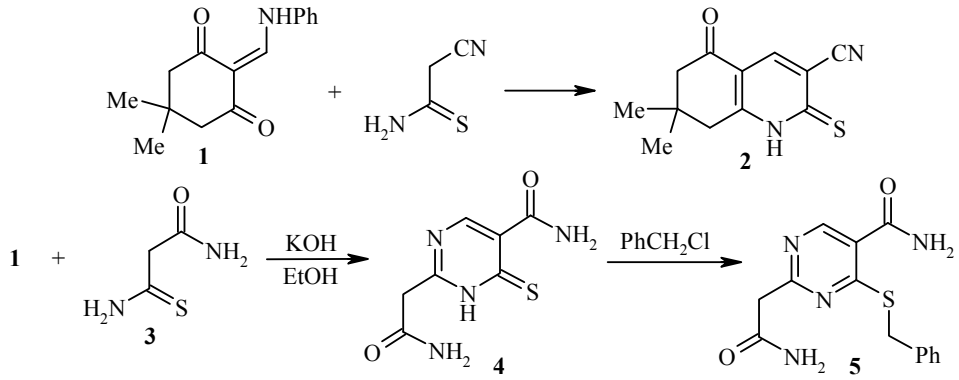
β-Enaminocarbonyl compounds are commonly used in heterocyclic synthesis as convenient and readily available 1,3-dielectrophile 3C synthones [1, 2]. In previous work [3], we showed that the reaction of 5,5-dimethyl-2-phenylaminomethylidenecyclohexane-1,3-dione (**1**) with cyanothioacetamide gives the quinoline derivative **2**. We established that the reaction of thiomalonamide **3** with dimedone derivative **1** yields 6-thioxopyrimidine-5-carboxamide **4** instead of the expected 3-carbamoyl analog of quinoline **2**. Alkylation of carboxamide **4** with benzyl chloride gives benzyl derivative **5**.

The structures of carboxamides **4** and **5** were supported by IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy, HPLC/MS, elemental analysis, and the results of a ^{1}H-^{13}C HMBC NMR experiment for carboxamide **4** (Fig. 1). The ^{1}H NMR spectrum of carboxamide **4** shows signals for two amide groups and one methylene group, as well as singlets for protons H-4 and NH. The HPLC/MS shows a peak $[M+H]^{+-}$ with *m/z* 213.6. Atom H-4 in the pyrimidine ring in the ^{1}H-^{13}C HMBC spectrum gives four correlation peaks: δ-8.78/127.1 (H-4/C-5), 8.78/159.6 (H-4/C-2), 8.78/163.7 (H-4/5-$CONH_2$), and 8.78/179.7 ppm (H-4/C-6). The CH_2 group protons give two cross peaks: δ-3.69/159.6 (CH_2/C-2) and 3.69/167.8 ppm (CH_2/CO). The finding of cross peaks at δ 7.17/41.1



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(CONH/CH_2), 7.17/167.8 (C(O)NH/C-2), 7.61/167.81 (CONH/C-2), and 7.86/127.08 ppm (CONH/C-5) permit unequivocal assignment of the amide group signals in the ^1H and ^{13}C NMR spectra.

In conclusion, we should note that this reaction demonstrates a fundamentally new approach to the construction of the pyrimidine ring and opens new possibilities for the preparation of functionally substituted pyrimidines. The mechanism of this reaction, optimization of its conditions, limitations, and scope of application will be covered in future studies.

The IR spectra were recorded on a Thermo Nicolet AVATAR 370 spectrophotometer for KBr pellets. The ^1H NMR, ^{13}C NMR, and ^1H-^{13}C HMBC spectra were recorded on a Bruker Avance II 400 spectrometer at 400 MHz for the ^1H nuclei and 100 MHz for the ^{13}C-nuclei in ~1:1 CCl_4–DMSO-d_6 with TMS as internal standard. The HPLC/MS analysis was carried out on a Shimadzu LC-10AD liquid chromatograph with a Shimadzu-SP D-10A UV-Vis (254 nm) detector, and Sedex 75 ELSD combined with a PE SCIEX API 150EX mass spectrometer using ES-API ionization. The elemental analysis was carried out on a Carlo-Erba 1106 Elemental Analyzer. The melting points were determined on a Koffler hot stage and not corrected. The purity of the products was checked by thin-layer chromatography on Silufol UV-254 plates with 1:1 acetone–hexane as the eluent and visualization by iodine vapor and UV radiation. 2-Anilinomethylene-5,5-dimethyl-1,3-cyclohexanedione (**1**) [3] and thiomalonamide **3** [4] were obtained according to reported procedures.

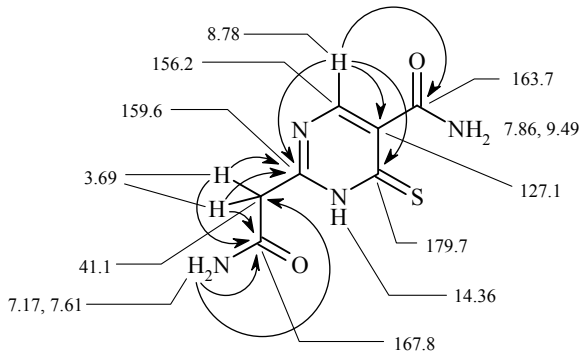

Fig. 1. Observed correlations in the ^1H-^{13}C HMBC spectrum of carboxamide **4**.

2-Carbamoylmethyl-6-thioxo-1,6-dihydropyrimidine-5-carboxamide (4). Thiomalonamide **3** (4.00 g, 33.9 mmol) and enaminodiketone **1** (8.24 g, 33.9 mmol) were put into a 100-ml beaker, and 96% ethanol (50 ml) was added. Potassium hydroxide (3.80 g, 67.9 mmol) was added to the obtained suspension with vigorous stirring. The starting reagents dissolved, and a precipitate of the product **4** potassium salt formed after about 30 min. The reaction mixture was stirred for 6 h, maintained for ~16 h at 25°C, and, then, an excess of concentrated hydrochloric acid (10 ml) was added with stirring. Note: H_2S is liberated! The mixture was stirred for 2 h. The precipitate was filtered off and washed with ethanol, water, and acetone. The sample obtained contained a trace of starting enaminodiketone **1**. In order to obtain an analytically pure sample, the crude product was heated at reflux in acetone for 0.5 h or recrystallized from DMF. Yield 1.90 g (53%). Yellow powder; decomp. temp. 245-250°C. IR spectrum, ν, cm^{-1}: 3391, 3188, 3075 (N–H), 1660, 1650 (C=O). ^1H NMR spectrum, δ, ppm: 3.69 (2H, s, 2-CH_2); 7.17 (1H, br. s) and 7.61 (1H, br. s, CH_2CONH_2); 7.86 (1H, br. s) and 9.49 (1H, br. s, 5-$CONH_2$); 8.78 (1H, s, H-4); 14.36 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 40.9 (CH_2CONH_2); 127.2 (C-5); 156.2 (C-4); 159.5 (C-2); 163.9 (5-$CONH_2$); 167.8 (CH_2CONH_2); 180.1 (C-6). Mass spectrum, *m*/*z*: 213.6 $[M+H]^+$, 425.5 $[2M+H]^+$. Found, %: C 39.50; H 3.93; N 26.62. $C_7H_8N_4O_2S$. Calculated, %: C 39.62; H 3.80; N 26.40.

4-Benzylsulfanyl-2-carbamoylmethylpyrimidine-5-carboxamide (5). A 10% aqueous potassium hydroxide solution (2.40 ml, 4.7 mmol) was added with stirring to a suspension of thioxopyrimidine **4** (1.00 g, 4.7 mmol) in ethanol (20 ml) cooled to 5-7°C. After 2 min, benzyl chloride (0.54 ml, 4.7 mmol) dissolved in ethanol (5 ml) was added dropwise to the solution obtained. The reaction mixture was stirred at this temperature

for 2 h and, after ~16 h, diluted with an equal volume of water. The precipitate was filtered off and recrystallized from ethanol. Yield 0.53 g (37%). White powder; mp 205-208°C. IR spectrum, ν, cm^{-1}: 3366, 3191, 3085 (N–H), 1661 (C=O). ^1H NMR spectrum, δ, ppm: 3.38 (2H, br. s, SCH_2); 3.74 (2H, s, 2-CH_2); 6.85 (1H, br. s) and 7.11 (1H, br. s, CH_2CONH_2); 7.17-7.28 (3H, m, H Ph); 7.40-7.44 (3H, m, H Ph, 5-$CONH_A$); 7.98 (1H, br. s, 5-$CONH_B$); 8.69 (1H, s, H-4). Mass spectrum, *m*/*z*: 303.8 $[M+H]^+$, 605.7 $[2M+H]^+$. Found, %: C 55.48; H 4.83; N 18.70. $C_{14}H_{14}N_4O_2S$. Calculated, %: C 55.62; H 4.67; N 18.53.

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