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Reaction of α-bis(methylthio)methylene cyclopropyl ketones with guanidine: Synthesis of 2-amino-4-alkoxy-6-(arylcyclopropyl)pyrimidines

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Cyclopropyl ketones **2** which are prepared from the cinnamoylketene dithioacetals **1** are transformed to the title pyrimidines **3** and **4** in good yields by cyclocondensation of the appropriate ketones **2** with guanidine nitrate, in the presence of sodium alkoxide/alkanol.

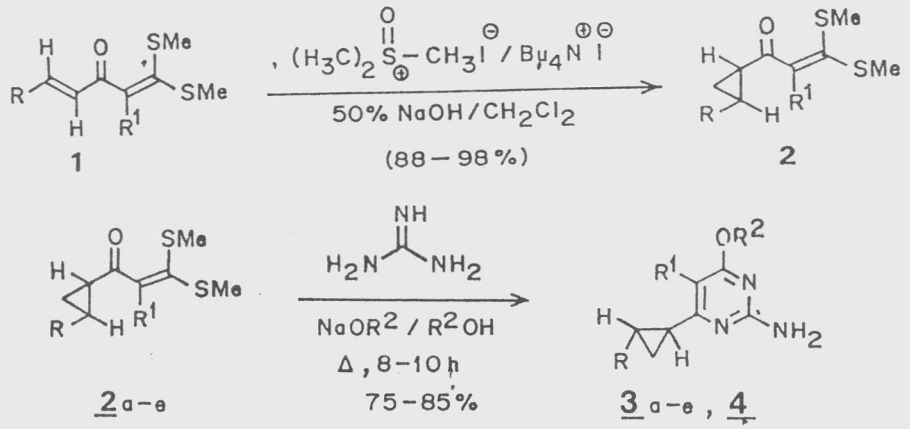
Cinnamoylketene dithioacetals have been reported[1] as useful synthetic intermediates for facile conjugate cyclopropanation regioselectively on the aryl substituted double bond. Thus, cyclopropyl ketones **2**[2] were prepared in quantitative yields by the addition of dimethyl oxosulphonium methylide to the corresponding α-cinnamoylketene dithioacetals in the presence of a phase transfer catalyst[3]. In the present investigation, these easily accessible bis(methylthio)methylene cyclopropyl ketones **2** have been utilized as three-carbon dielectrophilic intermediates to prepare cyclopropyl substituted pyrimidines in good yields by reacting with guanidine as the binucleophile. Cyclopropylimines has long been of synthetic interest[4] to undergo acid-catalyzed rearrangements for generating pyrrolines and a variety of alkaloid systems. Earlier works[1,5] have shown that cyclopropyl ketones **2** undergo acid-catalysed ring opening or thermal rearrangements to give substituted cyclopentanones. These studies prompted us to utilise these compounds (**3, 4**) as precursors for the synthesis of substituted pyrimido fused pyrrolines through Lewis acids-catalyzed ring opening of rigid cyclopropanes and through intramolecular rearrangements. However, after construction of the pyrimidine ring (in compounds **3** and **4**), it was observed that the cyclopropyl ring becomes very stable even though it is in conjugation with the imino nitrogen of the pyrimidine ring. It remains inert towards many Lewis acids (BF_3, $SnCl_4$) and also under thermal conditions.

Results and Discussion

The reaction of α-bis(methylthio)methylene cyclopropyl ketone **2a-e** with guanidine in the presence of the corresponding alkanol-alkoxide medium yielded the cyclopropyl substituted pyrimidines **3a-e**, **4** (Scheme I) in 75-85% overall yields. Guanidine reacts with the O,S-acetal formed *in situ* by displacement of methylthio group by alkoxide ion. The structure of **3a** as 2-amino-4-methoxy-6- (phenylcyclopropyl)pyrimidine was established on the basis of its IR, ^{1}H NMR and mass spectral data and the results of elemental analysis (see Experimental). Similarly, compounds **3b-e** were prepared in good yields. Incorporation of an appropriate alkoxy group in the ketene dithioacetal has been proved experimentally by using different alcohols. Thus, the homologous 4-ethoxypyrimidine **4** was prepared from **2b** by reacting with guanidine in the presence of sodium ethoxide in refluxing ethanol. Even though the compounds **3a-e**, **4**, prepared in the present investigation remain inert towards some Lewis acids i.e. BF_3. $SnCl_4$ etc., further investigations on the use of different Lewis acids and mineral acids as acid catalysts are in progress.

Experimental Section

General. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 297 and 283 spectrophotometers. ^{1}H NMR spectra on a Varian EM-390 spectrometer using TMS as internal standard and mass spectra on a



2, 3, a, R = C_6H_5, R^1 = H, R^2 = OCH_3
b, R = 4-MeO, R^1 = H, R^2 = OCH_3
c, R = 3,4-$(MeO)_2C_6H_3$, R^1 = H, R^2 = OCH_3
d, R = 3,4-5$(MeO)_3C_6H_2$, R^1 = H, R^2 = OCH_3
e, R = 4-ClC_6H_4, R^1 = H, R^2 = OCH_3

2b, 4, R = 4-MeO, R^1 = H, R^2 = OC_2H_5

Scheme I

Jeol-D300 mass spectrometer. Elemental analyses were carried out on a Heraus CHN-O rapid Elemental Analyzer.

Preparation of 2a-e from α-cinnamoylketene dithioacetal. A suspension of an appropriate ketene dithioacetal (10 mmoles), dimethyl sulphoxonium iodide (13 mmoles), tetrabutylammonium iodide (15 mmoles) in an aqueous solution of 50% NaOH (70 mmoles) and CH_2Cl_2 (70 mmoles) was stirred at 50°C for 7 hr. The organic layer was separated and concentrated, the residue diluted with ethyl acetate to precipitate tetrabutylammonium iodide which was filtered off. The filtrate was evaporated to give the corresponding crude cyclopropyl ketone which was purified on a silica gel column using EtOAc-hexane(1:20) as eluant. The analytical and spectral data were in agreement with the reported[1,5] values.

Preparation of 2-amino 4-alkoxy-6(arylcyclopropyl)pyrimidines 3a-e. To solution of sodium methoxide [prepared by dissolving sodium (0.04 mole) in 75 mL of methanol], guanidine nitrate (2.44g,0.02 mole) was added and the reaction mixture stirred for 10-15 min. The appropriate cyclopropyl ketone **2** (0.2 mole) was then added and the reaction mixture refluxed for 8-9 hr. The solvent was distilled off under reduced pressure and the residue poured over crushed ice. It was extracted with chloroform, washed (H_2O), dried (Na_2SO_4) and the solvent distilled off to give the crude pyrimidine which was purified either by crystallisation or column chromatography. The characterization data of **3a-e**, thus prepared, are as follows:

2-Amino-4-methoxy-6- (phenylcylopropyl)pyrimidine 3a: Colourless needles (EtOAc), m.p. 102°, yield 83%; IR (KBr): 3297, 3143 (μNH), 1634, 1559 cm^{-1} (δNH), ^1H NMR (CCl_4): δ1.20-1.65 (m, 2H.CH_2), 1.75-2.1 (m, 1H, CH), 2.40-2.59 (m, 1H, CH), 3.89 (s, 3H, OCH_3), 5.0 (brs, 2H, NH), 6.50 (s, 1H, H-5), 7.15-7.50 (m, 5H, ArH). Anal. Calcd for $C_{14}H_{15}N_3O$ (241): C, 69.70; H, 6.2; N, 17.4, Found: C, 69.6; H, 6.2; N, 17.0%; MS: m/z (%) 241 (M^+, 70), 226 (M^+–15,100).

2-Amino-4-methoxy-6- (4-methoxyphenylcyclopropyl)pyrimidine 3b: Colourless needles (EtOH), m.p. 80°, yield 2.06g (82%); IR(KBr): 3390, 3180, (μNH), 1640, 1600 cm^{-1} (δ NH); ^1H

NMR (90 MHz, $CDCl_3$): δ1.15-1.68 (m, 2H, CH_2). 1.70-1.90 (m, 1H, CH), 2.30-2.55 (m, 1H, CH), 3.74 (s, 3H, OCH_3), 3.80(s, 3H, OCH_3), 4.75 (brs, 2H, NH, exchangeable with D_2O), 6.0 (d, 2H, *J*=9Hz,ArH). Anal. Calcd for $C_{15}H_{17}N_3O_2$(271) : C, 66.42; H, 6.27; N, 15.49, Found: C, 66.60, H, 6.10; N, 15.60; MS: m/z(%)271(M^+,73.4), 256(M^+–15, 100).

2-Amino-4-methoxy-6-(3, 4-dimethoxyphenylcyclopropyl)pyrimidine 3c: Needles (EtOH), m.p. 110°, yield 2.20g(75%); IR(KBr): 3401, 3185 (NH), 1590 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): 1.20-1.61(m, 2H, CH_2), 1.80-2.10 (m, 1H, CH), 2.35 (m, 1H, CH), 3.87 (s, 3H, OCH_3), 3.95(s, 6H, 2×OCH_3), 5.20 (brs, 2H, NH), 6.10 (s, 1H, H-5), 6.85 (m, 3H, ArH), Anal. Calcd for $C_{16}H_{19}N_3O_3$ (301): C, 63.78; H, 6.31; N, 13.95. Found C, 63.65; H, 6.32; N, 14.0%.

2-Amino-4-methoxy-6-(3, 4, 5-trimethoxyphenylcyclopropyl)pyrimidine 3d: Colourless crystals (EtOH), m.p. 112°, yield 2.35g (78%); IR(KBr): 3481, 3173, (μNH), 1559 (δNH), 1446 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.10-1.65, (m, 2H, CH), 1.75-1.90 (m, 1H, CH), 2.30-2.50 (m, 1H, CH), 3.65 (s, 3H, OCH_3), 3.85 (s 6H, 2×OCH_3), 5.15(brs, 2H, NH) 5.95 (s, 1H, H-5), 6.30(s, 2H, ArH). Anal. Calcd for $C_{17}H_{21}N_3O_4$ (331): C, 61.63; H, 6.34; N, 12.68. (Found: C, 62.5; H, 6.10; N, 12.65%.

2-Amino-4-methoxy-6- (4-chlorophenylcyclopropyl)pyrimidine 3e: Colourless crystals (EtOAc-hexane), m.p. 105°, yield 2.0g(80%); IR(KBr): 3465, 3147, (μ NH_2), 3131, 1559, (δ NH_2) 1454 cm^{-1}; ^1H NMR (90 MHz,CCl_4): δ0.85-1.0(m,1H,CH), 1.15-1.65 (m, 2H, CH_2), 1.95-2.15 (m, 1H, CH), 3.45(s, 3H, OCH_3), 4.55(brs, 2H, NH_2), 5.55(s,1H,H-5), 6.75(d, 2H, *J*=9Hz, ArH), 6.95 (d, 2H, *J*=9Hz, ArH). Anal. Calcd for $C_{14}H_{14}N_3OC1$ (275.5); C, 60.98; H, 5.08; N, 15.24. Found: C, 61.0; H, 5.12; N, 15.05%.

2-Amino-4-ethoxy-6- (4-methoxyphenylcyclopropyl)pyrimidine 4. To a solution of sodium ethoxide (0.04 mole) in ethanol, guanidine nitrate (0.02 mole) was added followed by the addition of cyclopropyl ketone **2b** (0.2 mole) and the reaction mixture refluxed for 8 hr. After complete evaporation of the solvent, the residue was washed (H_2O), and extracted with chloroform, dried (Na_2SO_4) and crystallized from ethanol to give **4** as a crystalline product. Its characterization data are as follows:

Colourless needles (ethanol), m.p. 195°, yield 2.14g (75%); IR (KBr): 3400, 3210 (μNH_2), 1645, 1601 cm^{-1} (δ NH_2); ^1H NMR (90 MHz, CCl_4): δ 1.25 (t, 3H, *J*=7Hz,OCH_2CH_3), 1.39-1.55 (m,2H,CH), 1.65-1.85 (m, 1H, CH), 2.20-2.30 (m, 1H, CH),3.69 (s, H, OCH_3), 4.25 (q, 2H, *J*=7Hz, CH_2-CH_3), 5.15 (brs, 2H, NH), 5.89 (s, 1H, H-5), 6.65 (d, 2H, *J*=9Hz, ArH). Anal. Calcd for $C_{16}H_{19}N_3O_2$ (285): C, 67.36; H, 6.6; N, 14.73. Found: C, 66.50; H, 6.5; N, 14.95%; MS: m/z(%) 285 (M^+,85), 270 (M^+–15, 100).

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