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SYNTHESIS OF NOVEL PYRIMIDINE DERIVATIVES HAVING FLUORESCENT PROPERTIES

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ABSTRACT

The synthesis of novel pyrimidine derivatives have been reported from α-formylketene dithioacetals using guanidine followed by Knoevenagel condensation with malononitrile. Fluorescent study of the compounds revealed the possibility of fluorescent nature of the pyramidine derivatives.

Key words: α-Formylketene dithioacetals, Pyramidines, Knoevenagel condensation, Malononitrile.

INTRODUCTION

Pyrimidines are single-ringed, crystalline organic base that composes uracil, cytosine or thymine- an integral part of the genetic materials in DNA and RNA and is the parent compound of many drugs, including the barbiturates[1]. Pyrimidines had been obtained from 1,3-bifunctional compounds by reacting with 1,3-dinitrogen nucleophiles[2]. It was reported that formylketene dithioacetals when treated with guanidine produced pyrimidine-5-carbaldehyde[3]. The pyrimidines thus synthesized contained reactive groups and so we utilized them to prepare annulated pyrimidines by treating with malononitrile. But only Knoevenagel condensation products were obtained. In this paper, synthesis of some new pyrimidine derivatives have been described. The novel compounds were obtained from formylketene dithioacetals by treating with guanidine followed by the Knoevenagel condensation reaction on the product composed with malononitrile. Fluorescent study revealed the possibility of fluorescent nature of the incipient pyramidines. The α-formylketene dithioacetal could be prepared in quantitative yield from α-oxoketene dithioacetals by Vilsmeier-Haack reaction as reported by Asokan et al.[4]

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EXPERIMENTAL

Materials and reagents

All reagents were commercially available and were purified before use. The aroyl ketene dithioacetals were prepared by the known procedure[5]. Anhydrous sodium sulphate was used as drying agent. All purified compounds gave a single spot upon TLC analyses on silica gel 7GF using ethyl acetate/hexane mixture as eluent. Iodine vapors or $KMnO_4$ solution in water was used as developing agent for TLC.

Instrumentation

Melting points were determined on Buchi 530 melting point apparatus and were uncorrected. The IR spectra were recorded using KBr pellets on a Schimadzu IR-470 spectrometer and the frequencies are reported in cm^{-1}. The ^1H NMR spectra were recorded on a Brucker WM (500 MHz) spectrometer using TMS as internal standard and $CDCl_3$ or DMSO as solvents. The ^{13}C NMR spectra were recorded on a Brucker WM 300 (75.47 MHz) spectrometer using $CDCl_3$ or DMSO as solvent. Both ^1H NMR and ^{13}C NMR values are expressed as δ (ppm). The CHN analyses were done on an Elementar VarioEL III Serial Number 11042022 instrument.

General procedure for the synthesis of 2-amino-4-(methylsulfanyl)-6-phenyl-5-pyrimidine acrylaldehyde

Formylketene dithioacetal (2 mmol) was dissolved in DMF at room temperature. To this solution, guanidine hydrochloride (0.192 g, 2 mmol) and K_2CO_3 (0.55 g, 4 mmol) were added and refluxed for 15-20 hrs. The mixture was cooled and poured to ice cold water. Semisolid obtained was extracted in DCM (3 x 25 mL), dried and purified using column chromatography with ethyl acetate-hexane (3:7) mixture. The product was obtained as cream colored solid. The reaction was extended to various formylketene dithioacetals, to afford corresponding pyrimidine-5-carbaldehyde.

General procedure for the Knoevenagel condensation reaction of pyrimidines with malononitrile

A mixture of malononitrile (230 mg, 3.5 mmol), ammonium acetate (0.75 g, 10 mmol) and acetic acid (5 mL) were heated to 70°C. To this mixture, appropriate pyrimidine (2 mmol) was added, stirred for 2 hr at the same temperature and cooled to attain room temperature. The reaction mixture was diluted with ethyl acetate (100 mL) and then ice cold water was added. The organic layer was separated dried, over anhydrous sodium sulphate

and the solvent was evaporated. The crude product obtained was purified using column chromatography with ethyl acetate-hexane (3:7) mixture and the product was obtained as yellow solid.

Fluorescent study of 2-{[2-amino-4-(4-chlorophenyl)-6-(methylsulfanyl)-5-pyrimidinyl] methylene} malononitrile (2c)

Number of successful discoveries have been reported for pyrimidine ring system with extended conjugation as fluorescent materials[10]. Extended π-systems based on heteroatomic units like pyrimidines have been utilized as electron transport materials in organic electroluminescent devices[11]. The extensive conjugation of the malononitrile derivatives of pyrimidine carbaldehyde **(2)** having a shining appearance prompted us to study the fluorescent nature of these derivatives. For this proposal, their UV-visible absorption and fluorescence spectra were recorded. Absorption spectra were obtained with a Shimadzu UV-2400PC scanning spectrophotometer and emission spectra were recorded with a Shimadzu RF-5301PC spectrofluorophotometer, which was corrected for the instrumental response.

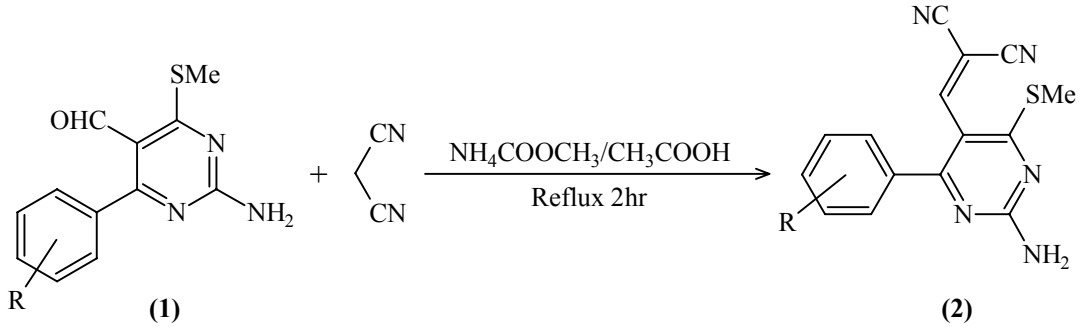
RESULTS AND DISCUSSION

Preparation of α-oxoketene dithioacetal: Methyl ketones in presence of base react vigorously with CS_2 and alkylating agent giving ketene dithioacetals[6]. Compounds were obtained as pure crystals after column chromatography and crystallization utilizing 3:7 ethylacetate-hexane amalgamation. Compounds were substantiated by comparing their R_f values with standard ketene dithioacetals.

The Vilsmeier-Haack reaction of α-oxoketene dithioacetals: **Synthesis of formylketene dithioacetals:** The benzoylketene dithioacetal with 1.5 equivalent Vilsmeier-Haack reagent led to the formation of 2-benzoyl-3,3-bis(methylsulfanyl)acrylaldehyde as the single product in 90% yield. The reaction was extended to various ketene dithioacetals to afford corresponding formylketene dithioacetals[4].

Synthesis of pyrimidine-5-carbaldehydes: The starting compound, formylketene dithioacetal could be considered as a combination of ketene dithioacetal as well as a 1,3-dicarbonyl compound[7]. Therefore, the reaction of formylketene dithioacetal with amidines should readily generate substituted pyrimidines. The only major product formed was pyrimidine-5-carbaldehyde[3].

Knoevenagel condensation reaction on pyrimidine-5-carbaldehyde: Pyrimidine-5-carbaldehydes had an aldehyde and $–SCH_3$ groups adjacent to each other. In order to engender fused pyrimidines, it was treated with malononitrile, an active methylene compound. Generally the reactions of aldehydes or ketones with active methylene compounds like malononitrile or ethyl cyanoacetate are carried out in the presence of impotent bases like an amine or a buffer of ammonium acetate or acetic acid[8]. In many cases, such reactions afford corresponding condensation adducts, which can be *in situ* cyclized to compose heterocyclic compounds especially functionalized pyridine derivatives[9]. When the 5-pyrimidinecarbaldehydes were subjected to Knoevenagel condensation reaction with malononitrile utilizing ammonium acetate or acetic acid as the buffer, the reaction afforded 2-{[2-amino-4-(methylsufanyl)-6-phenyl-5-pyrimidinyl]methylene}malononitriles in excellent yields. No cyclised product was obtanied and only the condensation product was obtained.



R = (a) H; (b) 4-CH_3; (c) 4-Cl; (d) 4-Br; (e) 4-OCH_3; (f) 3,4-$(CH_3O)_2$

The condensation products were heated with HCl/t-BuOH and also with sodium alkoxides. The reactions produced a mixture of compounds, which could not be separated to get pure compounds for analysis.

2-{[2-Amino-4-(methylsulfanyl)-6-phenyl-5-pyrimidinyl]methylene}]malononitrile(2a)

Deep yellow colored crystals; mp 184-186°C; yield 0.38 g (65%); IR (KBr) ν_{max} /cm^{-1} 3454, 3295, 3188, 2230, 1627, 1573, 1535, ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.6 (s, 3H, SC*H*$_3$), 5.5 (b, 2H, NH_2), 7.48-7.5 (m, 5H, Ar*H*), 7.93 (s, 1H, vinylic) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.7 (2C pyrimidine), 167.1 (4C pyrimidine), 162.4 (6C pyrimidine), 156.7 (vinylic), 141.8, 133.2, 129.9, 130.19 (phenyl carbons), 113.4 (5C pyrimidine), 111.5 (CN), 110.2 (CN), 88.1 ($C(CN)_2$), 13.0 (SMe) ppm., Anal: Found: C, 61.40%; H, 3.80%; N, 23.82%; S, 10.98%.

2-{[2-Amino-4-(4-methylphenyl)-6-(methylsulfanyl)-5-pyrimidinyl]methylene}] malononitrile (2b)

Yellow colored crystals; mp 188-190°C; yield 0.40 g (65%); IR (KBr) ν_{max}/cm^{-1} 3415, 3324, 3207, 2229, 1634, 1573, 1518, ^1H NMR (300 MHz, $CDCl_3$) δ = 2.3 (s, 3H, Me), 2.57 (s, 3H, SMe), 5.62 (s, 2H, NH_2), 7.25-7.38 (4H, Aromatic), 8.1 (s, vinylic) ppm., ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.7 (2C pyrimidine), 166.1 (4C pyrimidine), 161.4 (6C pyrimidine), 156.0 (vinylic), 141.0, 133.7, 129.4, 129.19 (phenyl carbons), 113.1 (5C pyrimidine), 111.76 (CN), 111.2 (CN), 88.2 ($C(CN)_2$), 21.3 (Me), 13.0 (SMe) ppm, Anal: Found: C, 62.48%; H, 4.31%; N, 22.80%; S, 10.41%.

2-{[2-Amino-4-(4-chlorophenyl)-6-(methylsulfanyl)-5-pyrimidinyl] methylene}] malononitrile (2c)

Deep yellow colored crystals; mp 182-184°C; yield 70%; IR (KBr) ν_{max}/cm^{-1} 3450, 3290, 3186, 2227, 1620, 1578, 1532. ^1H NMR (300 MHz, $CDCl_3$) δ = 2.6 (s, 3H, SC*H*$_3$), 5.6 (b, 2H, NH_2), 7.38-7.7 (m, 4H, Ar*H*), 7.9 (s, 1H, vinylic) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.3 (2C pyrimidine), 167.5 (4C pyrimidine), 162.7 (6C pyrimidine), 155.7 (vinylic), 140.8, 132.2, 128.9, 130.1 (phenyl carbons) ,113.4 (5C pyrimidine), 111.4 (CN), 110.3 (CN), 88.2 ($C(CN)_2$), 13.1 (SMe) ppm., Anal: Found: C, 54.92%; H, 3.11%; N, 21.30%; S, 9.48%; Cl,10.80.

2-{[2-Amino-4-(4-bromophenyl)-6-(methylsulfanyl)-5-pyrimidinyl] methylene}] malononitrile (2d)

Deep yellow colored crystals; mp 182-184 °C; yield 70%; IR (KBr) ν_{max}/cm^{-1} 3467, 3363, 3244, 2221, 1631, 1585, 1519, ^1H NMR (300 MHz, $CDCl_3$) δ = 2.6 (s, 3H, SC*H*$_3$), 5.4 (b, 2H, NH_2), 7.3 (d, J = 8.4 Hz, 2H, Ar*H*), 7.6 (d, J = 8.0 Hz. 2H, Ar*H*), 7.9 (s, 1H, vinylic) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.4 (2C pyrimidine), 166.5 (4C pyrimidine), 163.7 (6C pyrimidine), 154.7 (vinylic carbon), 141.8, 133.2, 129.8, 131.3 (phenyl carbons), 113.4 (5C pyrimidine), 111.5 (CN), 110.6 CN), 88.7 ($C(CN)_2$), 13.3 (SMe) ppm., Anal: Found: C, 48.50%; H, 2.71%; N, 18.90%; S, 8.58%; Br, 21.40.

2-{[2-Amino-4-(4-methoxyphenyl)-6-(methylsulfanyl)-5-pyrimidinyl] methylene}] malononitrile (2e)

Yellow colored crystals; mp 192-194°C; yield 77%; IR (KBr) ν_{max}/cm^{-1} 3410, 3308, 3182, 2934, 2225, 1648, 1582, ^1H NMR (300 MHz, $CDCl_3$) δ = 2.5 (s, SMe), 3.8 (s, OMe), 5.4 (s, 2H, NH_2), 6.94-6.96 (d, J = 8.4 Hz, phenyl), 7.45-7.42 (d, J = 8.7 Hz), 7.93 (1H, Vinylic) ppm, ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.8 (2C pyrimidine), 165.8 (4C pyrimidine), 161.6 (6C pyrimidine), 161.4 (vinylic carbon), 156.1, 131.0, 128.9, 114.3 (phenyl carbons),

113.1 (CN), 111.78, (CN), 88.0 ($C(CN)_2$), 55.41 (OMe), 13.13 (SMe) ppm, Anal: Found: C, 59.50%; H, 4.071%; N, 21.68%; S, 9.88%; O,4.93.

2-{[2-Amino-4-(3,4-dimethoxyphenyl)-6-(methylsulfanyl)-5-pyrimidinyl]methylene}] malononitrile (2f)

Deep yellow colored crystals; mp 178-180°C; yield 70%; IR (KBr) ν_{max}/cm^{-1} 3412, 3305, 3182, 2221, 1631, 1577, 1531, ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.6 (s, 3H, SC*H*$_3$), 3.93 (s, 3H, -OMe and 3.95 (s, 3H, -OMe), 5.48 (s, 2H, NH_2), 6.9-7.1 (m, 3H, Ar*H*), 7.9 (s, 1H, vinylic) ppm, ^{13}C NMR 75 MHz, $CDCl_3$ δ = 171.82 (2C pyrimidine), 165.81 (4C pyrimidine), 161.40 (6C pyrimidine), 156.25 (Vinylic), 151.33, 149.36, 129.09, 123.00, 113.21, 112.27, (phenylic), 111.85 (CN), 111.35 (CN), 110.84, (5C pyrimidine), 88.15 ($C(CN)_2$), 56.1, 56.0, ($(OMe)_2$), 13.17 (SMe), Anal: Found: C, 57.75%; H, 4.27%; N, 19.88%; S, 9.08%; O, 9.08.

Fluorescent study of 2-{[2-amino-4-(4-chlorophenyl)-6-(methylsulfanyl)-5-pyrimidinyl] methylene}malononitrile (2c)

It was noticed that the compound **(2c)** in $CHCl_3$ showed three absorption maxima at 379.60, 300.60 and 249.00 nm. Thus, these wavelengths were used to study its fluorescent behaviour. The emission maximum was found to be at 429 nm, when the excitation was carried out at 379 nm. Similarly, fluorescent study using other two frequencies also gave emission spectra near 429 nm (Fig. 1).

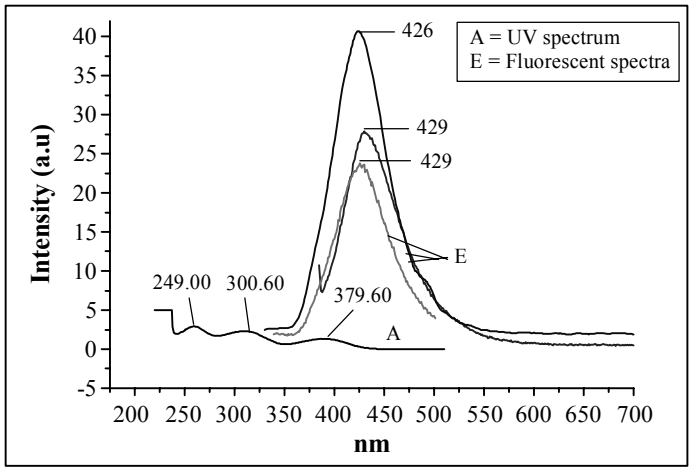


Fig. 1: Absorption spectrum and emission spectrum (excited at 379, 300 and 249 nm) of 2-{[2-amino-4-(4-chlorophenyl)-6-(methylsulfanyl)-5-pyrimidinyl] methylene}malononitrile

It was revealed that the emission maximum was a constant value in all the three excitation experiments. It clearly indicated that when pyrimidine derivative was excited, it could emit radiation in the visible region; thus, showing the fluorescent nature of 2-{[2-amino-4-(4-chlorophenyl)-6-(methylsulfanyl)-5-pyrimidinyl] methylene}malononitrile. Fluorescent study on other malononitrile derivatives of pyrimidines also gave the emission maxima in the higher wavelength region confirming the above observation. Further detailed studies on the quantum yield of the fluorescence and variation in emission maxima with respect to different solvents will be done in future.

CONCLUSION

In this paper, the synthesis of novel hitherto 2-{[2-amino-4-(methylsufanyl)-6-phenyl-5-pyrimidinyl]methylene}malononitriles has been reported starting from formylketene dithioacetals. It was tried to prepare annulated pyramidines from the condensation adduct, but the reactions did not give any positive results. A study was carried out on the products about their fluorescent nature. The initial study revealed a possibility of fluorescent nature of the pyrimidines. Hence, synthetic potential of the novel pyrimidines prepared are to be investigated further.

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