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A NOVEL SERIES SYNTHESIS OF 2-SUBSTITUTEDIMINO-6-ETHYLAMINO-4-[2-ISOBUTOXY-5(4-METHYL-5-CARBOXY-1,3-THIAZO-2-YL)]-PHENYL-1,3,5-THIADIAZINES

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Various dichloroisothiocyanate, 2-(3-ethylthioamidoformamidino-4-isobutoxy- phenyl)-4-methyl-5-carboxy-1,3-thiazole.

Abstract

A simple, novel and suitable method has been developed for the synthesis of 2-substitutedimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazines **(VIIIa-h)** by the reaction of 2-(3-phenylthioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole **(IIIb)** and various dichloroisothiocyanate **(VIIa-h)** in 60% ethanol-acetone at 1:1 molar proportion for 2 hours. The method provides rapid and easy access to compounds in good yields by using 60% ethanol-acetone medium. The structures of all the synthesized compounds were justified on the basis of chemical characteristics, elemental analysis and spectral studies..

INTRODUCTION

Heterocyclic compounds are more intriguing due to their utility in various fields. The literature survey reveals that the compounds containing 1,3,5-thiadiazino molecule as a parent nucleus will enhance potency of that drug in medicinal, agricultural and industrial fields[1-9]. Now-a-days the drug containing 1,3,5-thiadiazino nucleus are widely used in the drug[8-12]. It has been reported that 1,3,5-thiadizino nucleus and its derivatives possesses antiviral[13], antifungal[14], antibacterial[15], anti-tuberculostatic[16] and anti-helminthic[17] activities. Several thiadiazines are used in the treatment of cancer[19] and some are anti-HIV[20-21] drugs and also used in agricultural such as fungicidal[22], insecticide[23].1,3,5-Thiadiazine and its derivatives industrial application in engineering field such as effective against copper corrosion[24] and used in lubricating oil[25].

The various researchers have been investigated briefly essential reactions for the synthesis of 1,3,5-thiadiazines from various substituted isocyanodichlorides and various dithiobiurates[26-28].

RESULTS AND DISCUSSION

By considering all these things, we have developed new research schemes. The main objective of this work is to synthesize a novel series of 2-substitutedimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazines **(VIIIa-h)** and also to set up new reaction condition to reduce the time span of such type of reactions and at the same time it was also thought to increase the yield of product by maintaining the purity and green chemistry parameters. During the study, it was observed that the 60% ethanol-acetone medium was the best solvent which curtails the time span. This work is useful to incoming researcher in organic chemistry. In the synthesized compound the 1,3,5-thiadiazines substituent may enhance the potency of the compounds **(Scheme 1).**

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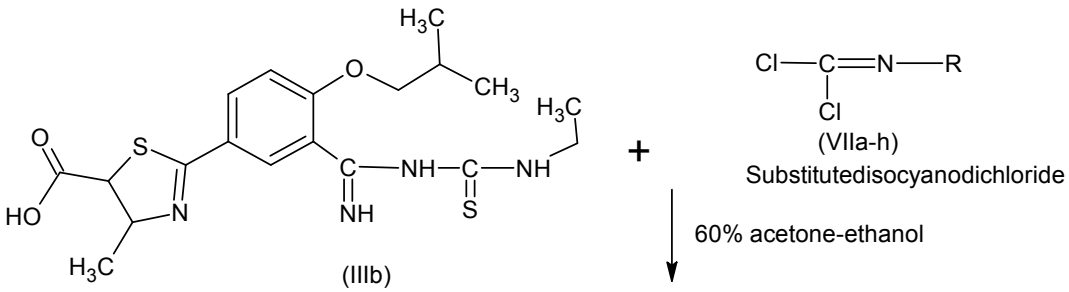

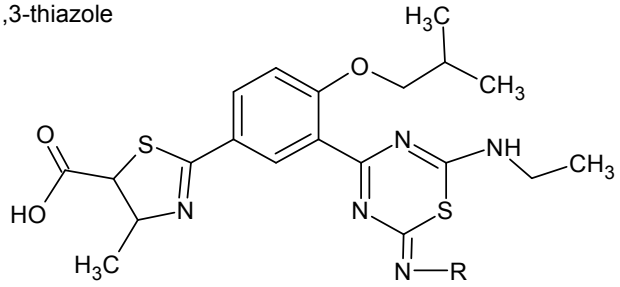

(VIIIa-h)
2-Substitutedimino-6-phenylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazine

Where: methyl, ethyl, tert-butyl, phenyl, p-chloro-phenyl, o-tolyl, m-tolyl, p-tolyl**.**

EXPERIMENTAL

General remarks

All reagents were purchased from commercial suppliers and used without further purification. All reactions were run in oven-dried round bottom flask or vial containing a teflon-coated stir bar and sealed with septum. Analytical thin layer chromatography was carried out on silica pre-coated glass plates (Silica gel 60 F254, 0.25 mm thickness) and visualized with UV light at 254 nm. ^{1}H NMR spectra were recorded on Bruker 400-MHz Ultrashield Advance II 400 model (400 and 100 MHz, respectively) at ambient temperature with $CDCl_3$ or DMSO-d6 as solvents. Data for ^{1}H are recorded as follows: δ chemical shift (ppm), multiplicity (s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), integration. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), DMSO-d6 (δ 2.50 ppm) or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. Liquid chromatography/mass spectrometry (LC/MS) data was obtained to verify molecular mass and analyze purity of products. The specifications of the LC/MS instrument are the following: Electrospray (+) ionization, mass range of 100-1000 Da, 20V cone voltage, Acquity BEH C-18 column (2.1 x 100mm, 1.7 µm), and gradient mobile phase consisting of 5 mm ammonium acetate in water and acetonitrile, and a flow rate of 0.5 mL/min.

General procedure for the synthesis of 2-methylimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazine (VIIIa):

A reaction mixture of 2-(3-phenylthioamidoformamidino-4-isobutoxyphenyl)-4-methyl-5-carboxy-1,3-thiazole **(IIIb)** and substituted isocyanodichloride (1.0 mmol) **(VIIa)** was refluxed in 60% ethanol-acetone medium (60 ml) on water bath for 2 h. The reaction mixture was concentrated under reduced pressure to remove medium and the

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residue was triturated in diethyl ether at 0°C to afford solids which was collected by filtration and washed with ice cooled diethyl ether to afford the pure product. Recrystallized from ethanol.

2-Methylimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazine (VIIIa):

white solid; melting point 166°C; ^{1}H NMR (400 MHz,DMSO-d_6): 11.1464 (1 H S), 8.1244-8 (1 H, S *J=14.8 Hz*), 8.3935 (1 H, S *J=14.8 Hz*), 8.203(1 H, S), 4.9180 (2 H S), 4.9269 (1 H S), 3.5111 (2 H d *J=12 Hz*), 1.0113 (1 H *J=12Hz* m), 1.0281 (6 H d), 1.213 (1 H S) ^{13}C :195, 192.2,164.3 162.5, 154.3, 148.5, 146.3, 143.1, 142, 138.5, 134.2, 130.2, 42.1, 35.2, 29.2, 25.8; IR: 3349.0 S, 1682.1 S, 1605 S, 1427.0 S, 1297.0 S, 1200 S; LCMS calcd for $C_{21}H_{27}N_5O_3S_2$ (M^+)421.09, found 421.16.

2-Ethylimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazine (VIIIb):

Brown solid; melting point 190 °C; ^{1}H NMR (400 MHz,DMSO-d_6): 11.4040 (1 H S), 7.1244-8 (1 H, S *J=14.8 Hz*), 7.435 (1 H, S *J=14.8 Hz*), 7.203(1 H, S), 6.756 (5 H S), 5.1312 (2 H S), 5.1402 (1 H S), 2.5041 (2 H d *J=12 Hz*), 1.6116 (1 H *J=12Hz* m), 1.483 (6 H d), 1.411 (1 H S) ^{13}C: 196.3, 190.2, 163.3 162.5, 155.3, 147.5, 144.3, 142.1, 141.2, 137.5, 132.4, 131.5, 128.0, 41.1, 34.2, 28.2, 24.8. IR: 3095.45 S, 1636.45 S, 1594.50 S, 1373.51 S, 1280.54.0 S, 1059.34 S; LCMS calcd for $C_{22}H_{29}N_5O_3S_2$ (M^+) 474.23, found 475.56.

2-Tert-butylimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazine (VIIIc):

Dark yellow solid; melting point 162 °C; ^{1}H NMR (400 MHz,DMSO-d_6): 11.3213 (1 H S), 7.1044 (1 H, S *J=12.8 Hz*), 7.345(1 H, S *J=12.8 Hz*), 7.203(1 H, S), 5.0323 (2 H S), 5.4402 (1 H S), 2.6423 (2 H d *J=12 Hz*), 1.6732 (1 H *J=12Hz* m), 1.483 (6 H d), 1.043 (1 H S) 13C: ^{13}C: 193.6,191.2,164.3 162.5, 155.3, 147.5, 145.3, 142.5, 140.5, 136.5, 134.2, 129.2, 41.1, 37.2, 28.2, 24.8, 20.2; IR: 3340.1 S, 1680.12 S, 1617.21 S, 1420.2 S, 1207.2 S,1145.2 S; LCMS calcd for $C_{24}H_{33}N_5O_3S_2$ (M^+)503.23, found 504.56.

2-Phenylimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazine (VIIId):

Faint yellow solid; melting point 168°C; ^{1}H NMR (400 MHz,DMSO-d_6): 10.141 (1 H S), 8.2743 (1 H, S *J=13 Hz*), 6.234 (1 H, S *J=14 Hz*), 6.023(1 H, S), 4.1312 (2 H S), 4.021 (1 H S), 2.9842 (2 H d *J=12 Hz*), 1.3532 (1 H *J=12Hz* m), 1.012 (6 H d), 1.043 (1 H S); ^{13}C: 196, 192.2,164.3, 162.5, 155.3, 149.5, 145.3, 142.1, 141.7, 139.5, 135.2, 131.2, 41.1, 36.2, 31.2, 26.8, 24.5, 20.2; IR: 3204.54.0 S, 1787.32 S, 1604.2 S, 1457.0 S, 1356.53.0 S, 1178.58 S; LCMS calcd for $C_{26}H_{29}N_5O_3S_2$ (M^+)522.43, found 523.75.

2-p-Chlorophenylimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazine (VIIIe):

Yellow solid; melting point 168°C; ^{1}H NMR (400 MHz,DMSO-d_6): 11.421 (1 H S), 7.2743 (1 H, S *J=14 Hz*), 7.234 (1 H, S *J=14 Hz*), 7.103(1 H, S), 5.1312 (2 H S), 5.021 (1 H S), 2.3042 (2 H d *J=12 Hz*), 1.7632 (1 H *J=12Hz* m), 1.632 (6 H d), 1.043 (1 H S); ^{13}C: 196, 192.2,164.3, 162.5, 155.3, 149.5, 145.3, 142.1, 141.7, 139.5, 135.2, 131.2, 41.1, 36.2, 31.2, 26.8, 24.5, 20.2; IR: 3294.54.0 S, 1762.32 S, 1654.2 S, 1502.0 S, 1280.53.0 S, 1124.58 S; LCMS calcd for $C_{26}H_{28}ClN_5O_3S_2$ (M^+)558.43, found 556.75.

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2-o-Tolylimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazine (VIIIf):

Ivory solid; melting point 188^{0}C; ^{1}H NMR (400 MHz,DMSO-d_6): 12.6523 (1 H S), 7.6543 (1 H, S *J=14 Hz*), 7. (1 H, S *J=14 Hz*), 7.432(1 H, S), 5.234 (2 H S), 5.643 (1 H S), 2.642 (2 H d *J=12 Hz*), 1.654 (1 H *J=12Hz*m), 1.2121 (6 H d), 1.456 (1 H S); ^{13}C: 195.5,188.2,165.3, 162.5, 152.3, 148.5, 142.3, 141.1, 140, 139.5, 132.2, 130.2, 78, 54.2, 41.2, 36.9, 28.4, 24.8.19.9; IR: 3813.10 S, 1715.19 S, 1620.2 S, 1490.3 S, 1197.2 S, 1112.55 S; LCMS calcd for $C_{27}H_{31}N_5O_3S_2$ (M^+) 536.43, found 537.75.

2-m-Tolylimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazine(VIIIg)

white solid; melting point 158^{0}C; ^{1}H NMR (400 MHz,DMSO-d_6): 11.7823 (1 H S), 8.2165 (1 H, S *J=16 Hz*), 8.1568 (1 H, S *J=16 Hz*), 7.4757 (1 H, S), 7.1152 (5H, S), 5.0043 (1 H S), 3.5022 (2 H d *J=12 Hz*), 1.7684 (1 H *J=12Hz* m), 1.8264, (6 H d), 1.2185 (3 H S), 1.0233 (1 H S) 1.0066 (1 H S); ^{13}C: 198, 192.2, 175.3, 162.3, 164.5, 154.3, 152.5, 148.5, 146.3, 143.1, 142, 138.5, 134.2, 130.2, 128.0, 42.1, 36.2, 29.2, 25.8; IR: 3212.06 S, 1645.9 S, 1599.11 S, 1338.10 S, 1426.11 S, 1035.06 S; LCMS calcd for $C_{27}H_{31}N_5O_3S_2$ (M^+) 537.43, found 538.89.

2-p-Tolylimino-6-ethylamino-4-[2-isobutoxy-5(4-methyl-5-carboxy-1,3-thiazo-2-yl)]-phenyl-1,3,5-thiadiazine(VIIIh):

Brown solid; melting point 166^{0}C; ^{1}H NMR (400 MHz,DMSO-d_6): 11.1760 (1 H S), 8.2350 (1 H, S *J=16 Hz*), 8.1582 (1 H, S *J=16 Hz*), 8.5264 (1 H, S), 5.0681 (1 H S), 3.0421 (2 H d *J=12 Hz*), 1.6671 (1 H *J=12Hz* m), 1.1292, (6 H d), 1.4704 (3 H S), 1.1432, (1 H S), 1.1114 (1 H S), 1.0014 (9 H S) ^{13}C: 198, 190.2, 177.3, 163.3, 165.5, 155.3, 153.5, 144.5, 142.3, 141.1, 140, 138.5, 133.2, 130.2, 74, 42.1, 36.2, 29.2, 25.8 21.4; IR: 3353.70 S, 1623.12 S, 1511.17 S, 1426.14 S, 1298.15 S, 1060.10 S. LCMS calcd for $C_{27}H_{31}N_5O_3S_2$ (M^+) 536.43, found 537.56.

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