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RESEARCH ARTICLE

LEW'S ACIDCATALYZED SYNTHESIS OF A NOVEL SERIES OF (1, 3, 4) THIADIAZOLO (3, 2-A) PYRIMIDINE-6-CARBOXYLATE DERIVATIVES

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ABSTRACT

A straightforward new path way and biological approach of a novel series of (1, 3, 4) thiadiazolo (3, 2-a) pyrimidine-6-carboxylate derivatives enhanced by transition metal chloride catalyst from starting moiety viz;2,4-dinitrobenzoic acid. The new adduct of this reaction was desired derivatives can be prepared by the reaction between 1, 3, 4-thiadiazol-2-amine interacted with ethylacatoacetate and substituted aromatic aldehyde and .The desired analogous are examined by advanced spectral data such as ^{1}HNMR, ^{13}CNMR and LCMS.

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1. INTRODUCTION

A fused heterocyclic compound is an integral part of the organic synthesis and constitutes a considerable part of the modern researches now days that are occurring presently throughout the world. The chemistry of heterocyclic moiety is as logical as the chemistry of either aliphatic or aromatic compounds. The complete study of heterocyclic systems is of great significant interest both from the theoretical and practical point of view. Heterocycles moiety was also played an important role in the design and discovery of new pharmacologically potent active compounds. Five membered aromatic systems having two heteroatoms at the symmetrical positions have been studied because of their interesting physiological properties. The sulphur and nitrogen containing heterocycles moiety are powerfully emergent form a designed in synthetic organic chemistry as well as medicinally chemistry. Several naturally compounded which is constructed by these hetero atoms and also numerous biological benefits biological. The exploration of the structures was established in drug discovery and it is a perpetually ongoing challenge in organic chemistry as well as medicinally chemistry. Pyrimidines are the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six membered rings.In addition to this, various analogs of pyrimidines have been found to possess Biological properties (Wafaa, 2024; Reza Moradivalikboni, 2015), Antimicrobial Activity (Abdelhamid, 2010; Ahmet Demirbas, 2009; Malleshappa, 2016), Antioxidant Activity (Canan Kus, 2008; Zainab Amer, 2022), Analgesic, Anti-inflammatory, Anti-Bacterial and Antitubercular Activity (Alok, 2011), Anti-inflammatory (Jie Hu), Alzheimer's disease (Haghighijoo, 2011; Mohamed, 2017), anti-diabetic (Kalyani Mallidi, 2025), anticancer (Sujaritha Jayaraj, 2024). Therefore, in this research, we further streamlined the reaction procedure by the use of a catalyst system and using The analogous of Ethyl 2-(2,4-dinitrophenyl)-7-methyl-5-phenyl-5H-(1,3,4) thiadiazolo(3,2-a)pyrimidine-6-carboxylate obtained by two steps involving the addition of 2-aminothiadiazole with ethyl acetoacetate and substituted aryl aldehydes and cyclization to give the ring-fused thiadiazolo (3, 2-a) pyrimidines in presence of $ZrOCl_2$.The reaction takes place between thiosemicarbazide and 2,4-dinitrobenzoic acid in the presence protic acid scaffold as intermediate (Abdelhamid, 2010).

2. EXPERIMENTAL

All the required startingchemicals, reagents, solvents for the reactions were procured from Fine chemicals with and used without further purification. The melting point of the all titled analogous were found out using an Agrawal thermal apparatus and uncorrected. The 1NMR spectra of particular analogous were estimated on a Bruker for 400 ^{1}H NMR spectra and 100 MHz for ^{13}C NMR spectra in $CDCl_3$ solvent using TMS as internal standard. The reaction was identified by thin layer

chromatography using silica gel as an adsorbent and ethyl acetate-hexane in different ratios as eluent. All the synthesized compounds find the molecular weight using LCMS.

2.1. Preparation of 5-(2,4-dinitrophenyl)-1,3,4-thiadiazol-2-amine(3): Take dry and clean four necks RBF. The mixture of 2, 4-dinitrobenzoic acid (1mol) and semithiocarbazide (1.5 mol) dissolved in the DMF (20mL) and few drops of phosphoric acid (H_3PO_4) into RBF at room temperature which is also fitted on the magnetic stirrer containing hot plate. The reaction mixture continuous carried the reaction for 5 hrs. at 60^0C . The progress of the reaction checked by the TLC (EtOAc: n-hexane = 5:5). After all the reactants were consumed and then cooled the reaction mixture at RT. The crude dissolved in ethyl acetate and washed with as saturated solution of sodium bicarbonate and separated the ethyl acetate layer and also washed with water separated the organic layer. The organic layer can be distilled off under vacuums and solid compound obtained

5-(2,4-dinitrophenyl)-1,3,4-thiadiazol-2-amine:
Paleredsolid; yield-92%, m.p-165-167^{0}C: ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 8.657(s, 1H), 8.589-8.358 (Ar, 2H, m), 6.854(s, 2H, NH_2).^{13}CNMR (400MHz, $CDCl_3$) δppm: 175.36, 162.58, 147.59, 145.92, 135.85, 129.56, 127.65, 121.38;; Weight of the derivative (m/z): 267.27(M^+); Formulae of compound: $C_8H_5N_5O_4S$.Elemental analysis: Calculated: C – 35.96, H -1.89, N – 26.21; Found: C-35.90, H-1.87, 26.28.

2.2.Preparation of Ethyl2-(2,4-dinitrophenyl)-7-methyl-5-phenyl-5H-(1,3,4) thiadiazolo (3,2-a)pyrimidine-6-carboxylate (6a-6g): A mixture of substituted aromatic aldehyde (1.110mole), 5-(2,4-dinitrophenyl)-1,3,4-thiadiazol-2-amine (1.125mol) and Ethylacatoacetate (1.50m) subjected catalytic amount of $ZrOCl_2$ in ethanol was taken in a50mL RB flask and continued the reaction was refluxed for 4 hrs. The reaction was recognized by TLC (5:5, Ethyl acetate: n-hexane). The reaction mixture was poured into crushed ice after all reactants consumed during the reaction. The solution was neutralized with aqueous solution of dilute $NaHCO_3$and product was extracted with ethyl acetate; the combined organic layer was washed with water and separated the Ethylacetae layer.The organic layer was dried on anhydrous sodium sulphate and the solvent was removed under reduced pressure with using vacuum pump to acquire the solid product. All the synthesized compounds were recrystallized from ethanol

2.2.1.Ethyl2- (2,4- dinitrophenyl)- 7- methyl-5-phenyl-5H-(1,3,4)thiadiazolo(3,2-a)pyrimidine-6-carboxylate (6a): Pale brown solid; M.p-256-258^{0}C;Yield-87%;^{1}HNMR (400MHz, $CDCl_3$)δppm:8.896 (s,1H),8.532-8.266 (m,2H,Ar-H),7.346-7.271 (m, 5H,Ar-H), 4.4381(s,1H), 4.026-3.195(q,2H, Ar-H), 1.044(t,J=8.0,3H), 1.776 (s,3H);^{13}C NMR (100 MHz,$CDCl_3$) δppm:168.74, 159.04, 152.19, 148.26, 145.09, 141.32, 139.06, 131.74, 129.85, 129.44, 128.83, 128.39, 128.05, 123.08, 119.84, 66.22, 60.26, 20.88, 13.48;Molecular formula: $C_{21}H_{17}N_5O_5$, Molecular weight :468.33(M+H);Elemental analysis C – 53.96, H -3.67, N – 14.98

2.2.2. Ethyl 2-(2,4-dinitrophenyl)-5-(4-hydroxyphenyl) -7-methyl-5H-(1,3,4) thiadiazolo (3,2-a) pyrimidine-6-carboxylate (6b): Palebrowsolid;M.p-250-252^{0}C;Yield -90% ;^{1}HNMR(400MHZ,$CDCl_3$) ppm:9.246(s,1H, -OH), 8.762(s, 1H,Ar-H), 8.446-8.214(m,2H,Ar-H),6.976-6.816(m,4H), 4.132(s,1H,-CH), 4.024-3.894(q,2H,-CH_2-), 1.864(s,3H,-CH_3), 0.946 (t,J=8.0,3H,-CH_2);^{13}C NMR (100 MHz,$CDCl_3$)δppm: 165.29,157.36,151.06,148.32,144.44,140.02,130.98,130.42,129.87,123.49,121.05,66.96,59.17,20.02,12.74;Molecularformula :$C_{21}H_{17}N_5O_7S$,Molecular weight :484.719(M+H);Elemental analysis: C-52.17, H-3.54, N-14.49

2.2.3.Ethyl 2-(2,4-dinitrophenyl)-5-(4-methoxyphenyl)-7-methyl-5H-(1,3,4) thiadiazolo (3,2-a)pyrimidine-6-carboxylate(6c): Pale brown solid; M.p-260-262^{0}C; Yield -88%;^{1}HNMR(400MHz,$CDCl_3$)δppm:8.779(s,1H,Ar-H),8.536-8.346(m,1H,Ar-H),7.179-6.946(m,4H,Ar-H),4.236(s,-CH-,1H),4.036-3.966(q,2H,-CH_2-),3.710(s,OCH_3,3H),1.889(s,3H,-CH_2),1.026(t, J=7.1,3H,CH_3);^{13}C NMR (100 MHz,$CDCl_3$) δppm:166.24,158.04,153.28,148.36,146.62,141.77,140.03,134.55,131.45,130.02,129.74,128.36,127.672,123.02,119.08,64.82, 59.09,54.92,20.34,13.94;Molecular formula: $C_{22}H_{19}N_5O_7$, Molecular weight: 498.44(M+H);Elemental analysis: C- 53.12, H-3.85, N-14.08

2.2.4.Ethyl5-(4-chlorophenyl)-2- (2,4-dinitrophenyl)-7-methyl-5H-(1,3,4) thiadiazolo(3,2-a)pyrimidine-6-carboxylate(6d): Pale brown solid; M.p-265-267^{0}C;Yield-89%;1HNMR(400MHz,$CDCl_3$) δppm :9.049(s,1H), 8.636-8.4261(m,2H), 7.382-7.267(m,4H, Ar-H), 4.362(s,1H, -CH), 4.036-3.916(m,2H, -CH), 1.782(s,3H, -CH),1.126 (t,J=6.8,3H); 13C NMR (100 MHz,$CDCl_3$) δppm :168.37, 158.21, 152.06, 149.02, 147.11, 142.06, 139.76, 131.06, 130.26, 129.76, 128.62, 128.32, 127.04,121.26, 120.02, 66.62, 60.72,20.43, 13.24; Molecular formula: $C_{21}H_{16}ClN_5O_6S$, Molecular weight: 503.24(M+H);Elemental analysis: C-50.26, H-3.21, N-13.95

2.2.5.Ethyl5-(4-bromophenyl)-2- (2,4-dinitrophenyl)-7-methyl-5H-(1,3,4) thiadiazolo(3,2-a)pyrimidine-6-carboxylate(6e): Brown solid; M.p-247-249^{0}C;Yield -89% ;^{1}H NMR (400 MHz, $CDCl_3$) δppm :9.142(s,1H), 8.526-8.196(m,2H,Ar-H),7.726-7.306 (m,2H,Ar-H),4.336(s,1H,-CH),4.052-3.82 6(m,2H,-CH),2.664(s,3H,-CH_3),1.126(t,J=8.4Hz, 3H,CH3); ^{13}C NMR (100 MHz,$CDCl_3$) δppm :169.71, 158.04, 151.11, 149.02, 145.26, 141.05, 134.44, 131.04, 130.92, 129.88, 129.19, 128.66, 127.02, 123. 08, 121.15, 63.38, 58.28, 20.45, 12.76; Molecular formula: $C_{21}H_{16}BrN_5O_6S$, Molecular weight: 547.43(M+H); Elemental analysis: Calculated:C-46.17, H-2.95, N-12.82 ;Found:C-46.11, H-2.94, N-12.88.

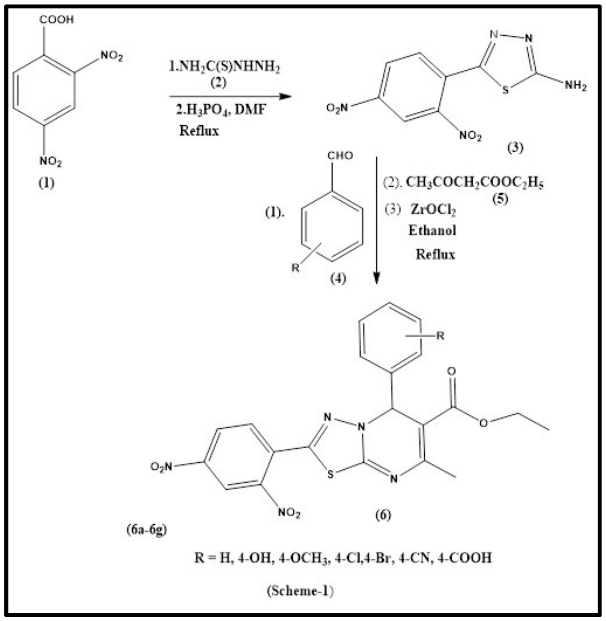
2.2.6.Ethyl5- (4-cyanophenyl)- 2-(2,4-dinitrophenyl)-7-methyl-5H -(1,3,4) thiadiazolo(3,2-a)pyrimidine-6-carboxylate (6f): Darkredcompound;M.p-258-260^{0}C;Yield-88%;1HNMR(400MHz,CDCl3)δppm:8.874(s,1H),8.417-8.124 (m,2H,Ar-H), 7.701-7.415(m,2H,Ar-H),4.387(s,1H,-CH), 4.021-3.894 (m,2H,-CH),2.126(s,3H,-CH_3),1.117(t,J=8.8 Hz, 3H,CH_3); ^{13}C NMR (100 MHz,$CDCl_3$) δppm : 165.95, 157.15, 152.06, 148.25, 144.03, 140.55, 133.85, 131.57, 130.21, 129.54, 128.84, 128.23, 127.56, 123. 43, 121.74, 118.01, 64.31, 58.07, 21.59, 13.07; Molecular formula: $C_{22}H_{16}N_6O_6S$, Molecular weight: 493.21(M+H); Elemental analysis: Calculated:C-53.66, H-3.27, N-17.02 ;Found: C-53.60, H-3.25, N-17.09.

2.2.7.4-(2-(2,4-dinitrophenyl)-6-(ethoxycarbonyl)-7-methyl-5H-(1,3,4)thiadiazolo(3,2-a) pyrimidin-5-yl)benzoic acid (6g): Pale brown solid; M.p-267-269^{0}C;Yield -85% ;^{1}HNMR(400MHz,$CDCl_3$)δppm:11.568(s,1H,-COOH), 8.975 (s,1H), 8.859-8. 104(m,2H,Ar-H),7.794-7.426(m,2H,Ar-H),4.413 (s,1H,-CH),4.045-3.887(m,2H,-CH),2.185(s,3H,-CH_3),1.107(t, J=9.6 Hz, 3H,CH_3); ^{13}CNMR (100 MHz,$CDCl_3$) δppm:170.35,166.84, 158.04, 151.54, 147.54, 143.75, 140.24, 134.08, 131.87, 130.02, 129.66, 128.79, 128.05, 127.14,

122.87, 120.47, 63.87, 59.46, 22.07, 14.07; Molecular formula: $C_{22}H_{17}N_5O_8S$, Molecular weight: 512.74(M+H); Elemental analysis: Calculated:C-51.66, H-3.35, N-13.69; Found: C-51.58, H-3.33, N-13.76.

3. RESULTS AND DISCUSSION

Initially, it was improved the synthesis of desired derivatives by using Lew's acid catalyst like $ZrOCl_2$, this catalyst was imposed during the reaction due to the impact of the rate of reaction, developed the percentage of product as well as reduced the time factor of the completion of the reaction. In addition to commercially available, easily handling and also workup procedure was simplicity. An effective catalyst was designed and synthesized based on (1, 3, 4) thiadiazolo (3, 2-a) pyrimidine-6-carboxylate of $ZrOCl_2$ as shown scheme-1.



(Scheme-1)

The different Lewsacd catalysts were applied during the completion of the reaction such as $FeCl_3$, $ZnCl_2$, $AlCl_3$, CAN and $ZrOCl_2$. An excellent effective role was played by the catalyst among the Lew's acid catalyst such as $ZrOCl_2$. The Yield of the product as well as minimized the time factor is considered mainly important for the preparation of desired product as shown in Table-I.

Table I. ffect of the catalyst for synthesis of titled derivative (6b)

Entry	Catalyst	Time (min)	Yield (%)
1	$FeCl_3$	220	67
2	$AlCl_3$	180	70
3	CAN	150	60
4	$ZrOCl_2$	120	90

The main objective of the synthesis of titled derivatives is an impact of the solvent in this reaction. The key role is played an significant part of the solvent in during the reaction, all the reactants were completely soluble above and also effect of the starting materials was finished appropriate timeas shown in Table-II.

Table-II. Effect of solvent for synthesis of titled derivative (6b)

Entry	Catalyst	Time (min)	Yield (%)
1	MeOH	150	70
2	MDC	150	52
3	CH_3CN	150	74
4	EtOH	150	90

The amount of the catalyst is another parameter of this reaction, even there is no progressive development of the reaction if absence of the catalyst. The amount of catalyst was added gradually, and then the rate of reaction was increased by percentage of the yield up to 90% by using 0.8 moles as shown in Table-III.

Table-III:- Effect of amount catalyst for synthesis of titled derivative (6b)

Entry	Loaded catalyst(mole)	Time (min)	Yield (%)
1	0.1	150	Traces
2	0.2	150	45
3	0.4	150	52
4	0.8	150	90

The structures of the desired (6a-6g) analogous were analyzed by ^{1}HNMR, ^{13}CNMR, mass spectral. ^{1}HNMR spectrum of the titled derivatives exhibited in various aromatic protons appears at δ 9.425 to 6.946 ppm. The acid protons appear at □11.568 , amine protons at δ6.854, quaternary protons appears at δ 4.413and 4.132 and the methoxy protons showed at 3.745 and the methyl protons appeared at 1.915ppm. The mass spectrum of halogen derivatives exhibited molecular ion peak at (m/z)(M+2). Overall the reaction, we also identified that the highest yield acquired during synthesis, the product analogous bearing electron releasing group (6b) greater than the product of the derivatives having electron attracting group (6g) and the compounds was bearing including the halogen containing group (6d-6f) also got good yield .

4. CONCLUSIONS

In summary, we have been approached to follow the protocol of process for the synthesis of titled compounds (6a-6g) incorporated in an excellent yield. Our observation mainly focused the enhancement of the yield of this multistep synthesis. The beneficial of the catalyst is simple experimental workup procedure, all of which make it a useful method for the synthesis of the titled derivatives. The mildness of the conversion, the experimental simplicity, compatibility with various functional groups, excellent product yields and the easy work-up procedure make this approach attractive for synthesizing a variety of such derivatives

5. ACKNOWLEDGEMENTS

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6.CONFLICTOF INTEREST

We declare that we have no conflict of interest

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