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Reaction 2-Benzyl 5-Oxo 5-H 6-Ethyl carboxylate 7-phenyl -1,3,4-thiadiazolo- [3,2-a]- pyrimidine with Amin derivatives and study of Biological properties

Reza Moradivalikboni*, Sedigheh Tahereh Asadzadeh**, Mehdi Baghernejad, Zabialah Heidarnezhad**** and Heshmatollah Alinezhad****

**Faculty of Chemistry, University of Mazandaran, Babolsar, IRAN*
***Young Researchers Elite Club, Kazerun Branch, Islamic Azad University, Kazerun, IRAN*
****Young Researchers Elite Club, Gachsaran Branch, Islamic Azad University, Gachsaran, IRAN*
****Young Researchers Club, Andimeshk Branch, Islamic Azad University, Andimeshk, IRAN*

(Corresponding author: Reza Moradivalikboni)
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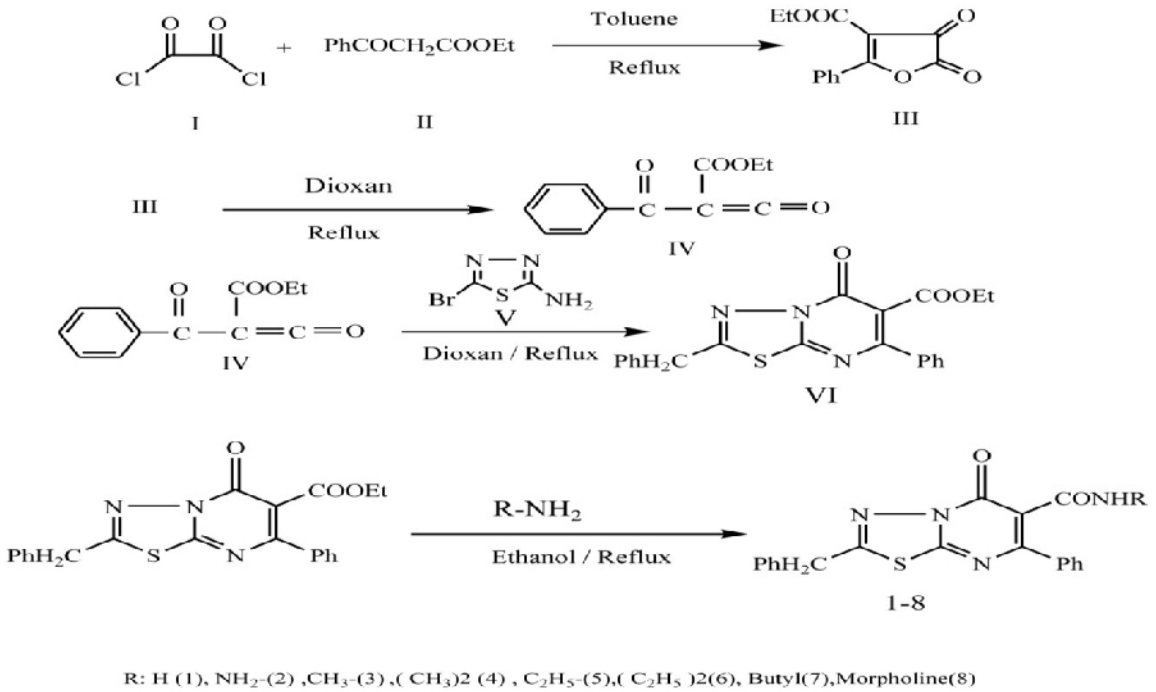
ABSTRACT: In this paper explain preparation of 2-Benzyl 5-Oxo 5-H 6 -R-amide derivatives 7-phenyl 1,3,4-thiadiazolo-[3,2-a]- pyrimidine through reaction of 2-Benzyl 5-Oxo 5-H 6- Ethyl Carboxilate 7-phenyl -1, 3,4 -thiadiazolo-[3,2-a]- pyrimidine with aminderivatives. The reactions are completed in Very short time with high yield. Interest in the synthesis of pyrimidine derivatives is due to their biological activities. The structures of all the newly synthesized compounds had been identified by elemental analysis, set NMR, ^{13}C, IR- spectroscopy.

Keywords: 2-Benzyl 5-Oxo 5-H 6 -R-amide derivatives, pyrimidine, amin derivatives, Preparation , yield – Spectroscopy

INTRODUCTION

The introduction of a substituent at position 6 of the 1,3,4-thiadiazolo- [3,2-a] pyrimidine system efficiently enhances the physiological activity of the molecule [1-3]. This replacement occurs in the reactions of 1,3,4 –thiadiazolo- [3,2-a]- pyrimidine derivatives with electrophiles [4-10]. During recent years there have been intense investigations on fused thiadiazole systems. Literature survey revealed that 1,3,4- thiadiazolo-[3,2-a]- pyrimidine nucleus is associated with diverse pharmacodynamic and chemotherapeutic activities[11-19] including antimicrobial and antitumor activities. Pyrimidine derivatives have been found to be associated with diverse biological activities and numerous reports have appeared in the literature [20-22]. This highlighted their chemistry and use. The pyrimidine derivatives have Remarkable pharmacological activity [23,24] and widely used in the field of anti-microbial, antiviral, etc. Oxadiazoleandthiadiazole derivatives were shown to possess many biological activities including anti-inflammatory [25] Such medicinal utilities of the pyrimidine derivatives prompted to synthesize the new pyrimidine, thiosemicarbazide, 1,3,4-oxadiazole and 1,3,4-thiadiazole compounds. Literature data on fused heterocycles with athiadiazolo -[3,2-a]-pyrimidine system annelated with anotherring are scarce. These include 1,3,4-thiadiazolo –[3,2 -b]-quinozalhaes, [26,27] pyrazolol -[3 ,4-e] -1 ,3,4-thiadiazolo [3,2 -a]-pyrimidines and 1,3,4-thiadiazolo-[3, 2-a]- pyrido- [3,2, e]-pyrimidines. We have synthesized diravatives-1,3,4-thiadiazolo-[3,2-a]-pyrimidine. We synthesized 2-Benzyl 5-oxo 5-H 6 -Amid diravatives 7-phenyl 1,3,4-thiadiazolo-[3,2-a]-Pyrimidine in several stage. In continuation of our studies in developing efficient and simple benign methodologies for organic synthesis, we reveal herein the synthesis of 2- Benzyl 5-Oxo 5-H 6-R-amide derivatives 7-phenyl -1,3,4-thiadiazolo-[3,2-a]-pyrimidinein alcohols as a solvent (Scheme 1).



Scheme 1. Synthesis of 2-Benzyl 5-Oxo 5-H 6-R-amide derivatives 7-phenyl-1,3,4-thiadiazolo-[3,2-a]-pyrimidine.

EXPERIMENTAL

All the reagents and solvents were of the commercial quality and were used without purification. Elemental analysis was performed on a PE-2400 elemental analyze, the C, H and N analysis were repeated twice. ^{1}H NMR spectra were obtained with a Bruker AM-400 spectrometer with chemical shifts reported as ppm (in DMSO-d6, TMS as internal standard). Melting points were determined by an X-6 micro-melting point apparatus and were uncorrected.

A mixture of 2- Benzyl 5-Oxo 5-H 6-Ethylcarboxylate 7-phenyl 1,3,4- thiadiazolo -[3,2-a]-pyrimidine (1 mmol), amin derivatives (1 mmol) was stirred magnetically at 78^{o}C and the progress of the reaction was monitored by thin-layer chromatography (TLC).

For the example For the synthesis 2- Benzyl 5-Oxo 5-H 6-Carboxamide 7-phenyl -1,3,4-thiadiazolo-[3,2-a]-pyrimidine, At first: oxalic acid dichloride(I) (1mol,0.127g) and ethyl benzoylacetate(II) (0.86mmol,0.165g) reacted to gether in toluene at 110°C until is produced ethyl 4,5-dioxo 2-phenyl 4,5- dihydrofuran 3-carboxylateand(III). In another stage ethyl 4,5-dioxo 2-phenyl 4,5- dihydrofuran-3-carboxylate (1mmol,0.25g) in boiling dioxan converted to ethyl 2-formyl 3-oxo 3-phenyl propanoate(IV).

At more mixture of 2- Benzyl 5-amino-1,3,4-thiadiazole(V)(1mmol, 0.191g), ethyl-2-formyl-3-oxo-3-phenylpropanoate(1 mmol,0.218g) was stirred magnetically in toluene at 101^{o}C for 10-14 hours(14h) and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was filtered .In all the cases, the product 2- Benzyl5-Oxo 5-H 6-Ethylcarboxylate 7-phenyl 1,3,4- thiadiazolo-[3,2-*a*]- pyrimidine obtained(VI)((85%,0.332g).

A mixture of 2- Benzyl 5-Oxo 5-H 6-Ethylcarboxylate 7-phenyl 1,3,4- thiadiazolo -[3,2-a]-pyrimidine (1 mmol,0.391g) and NH_3(1 mmol,0.017g) was stirred magnetically at 78^{o}C for 11 hours and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was filtered . The product obtained after the usual work up gave satisfactory spectral data. And the product (2-Benzyl 5-Oxo 5-H 6-Carboxamide 7-phenyl -1,3,4-thiadiazolo-[3,2-a]- pyrimidine) is obtained in(0.284g, 90% yield).

Spectral data: 1)2-Benzyl5-Oxo5-H6-Carboxamide 7-phenyl -1,3,4-thiadiazolo -[3,2-a] –pyrimidine::^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):2,5(s,2H,CH_2); 5,9(s,2H,NH_2); 7,10-7,40 (10H, 2Ph); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):39,1(CH_2) ,118 (C), 126,4 (CH), 126,4 (CH) ,128(CH), 128,7(CH), 128,7(CH), 129,2(CH), 129,4(CH), 137 (C), 137,8 (C), 146 (C), 162 (C), 163 (C),168(C), 173 (C).

2)-2-benzyl 5-Oxo5-H 6-N-methylcarboxamide7-phenyl-1,3,4-thiadiazolo-[3,2-a]-pyrimidine::^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):2,6(s,3H,CH_3); 2,74(s,2H,CH_2); 8,1(s, H,NH); 7,15-7,65 (10H, 2Ph); -^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):28,3(CH_3),38,2(CH_2),118 (C),), 125,8 (CH), 126,4 (CH) , 126,4 (CH) ,128(CH), 128,7(CH), 128,7(CH), 129,2(CH),), 129,2(CH), 136,9 (C), 137,5 (C), 145 (C), 159.1 (C), 162 (C), 163 (C),168(C).

3)-2-benzyl5-Oxo5-H 6- N,N-dimethyl carboxamide7-phenyl-1,3,4-thiadiazolo-[3,2-a]-pyrimidine::^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):2,6(s,2H,CH_2); 2,9(s,6H,2CH_3); 8,1(s, H,NH); 7,15-7,65 (10H, 2Ph);-^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):37,1(CH_3),37,1(CH_3),38,2(CH_2),118 (C), 125,8 (CH), 126,4 (CH), 126,4 (CH),128(CH), 128,7(CH), 128,7(CH), 128,7(CH),128,7(CH),129,1(CH),), 129,1(CH), 136,9 (C), 137,5 (C), 145,8 (C), 160 (C), 162 (C), 163 (C),168(C).

4)-2-benzyl5-Oxo5-H 6- N-ethyl carboxamide7-phenyl-1,3,4-thiadiazolo-[3,2-a]-pyrimidine::^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):1,2(t,3H,CH_3); 2,6(t,2H,CH_2); 3,1(q,2H, CH_2); 8,1(s, H,NH); 7,15-7,65 (10H, 2Ph); -^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):15,1(CH_3),34,2(CH_2),38,2(CH_2),118 (C), 125,8 (CH , 126,4 (CH), 126,4 (CH),128(CH), 128,7(CH), 128,7(CH), 128,7(CH),128,7(CH), 129,1(CH),), 129,1(CH), 136,9 (C), 137,5 (C), 145,8 (C), 159,1 (C), 162 (C), 163 (C),168(C).

5)-2-benzyl5-Oxo5-H 6- N,N-diethyl carboxamide7-phenyl-1,3,4-thiadiazolo-[3,2-a]-pyrimidine::^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):1,2(t,6H,2CH_3); 2,6(s,2H,CH_2); 3,1(q,4H,2 CH_2); 8,2(s, H,NH); 7,15-7,60 (10H, 2Ph); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):12,9(CH_3),12,9(CH_3),38,2(CH_2),41(CH_2),41(CH_2),118 (C), 125,8 (CH), 126,4 (CH), 126,4 (CH) ,128(CH), 128,7(CH), 128,7(CH), 128,7(CH),128,7(CH), 129,1(CH), 129,1(CH), 136,9 (C), 137,5 (C), 145,8 (C), 159,1 (C), 162 (C), 163 (C),168(C).

6)-2-benzyl 5-Oxo 5-H6-carbohydrazide 7-phenyl-1,3,4-thiadiazolo-[3,2-a]-pyrimidine:: ^{1}HNMR (400 MHz, $CDCl_3$, δ ppm):2,1(s,2H,NH_2); 2,6(s,2H,CH_2); 8.2(s, H,NH); 7,15-7,60 (10H, 2Ph); - ^{13}C NMR (100 MHz, $CDCl_3$,δ ppm):38,2(CH_2),118 (C), 125,8(CH), 126, 4(CH), 126, 4(CH), 128(CH), 128, 7(CH), 128,7(CH),128, 7(CH), 128, 7(CH), 129,1(CH), 129, 1(CH), 136,9 (C), 137, 5 (C), 145,8 (C), 162 (C), 163 (C),165,8(C),168(C).

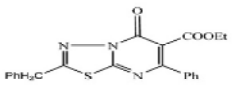
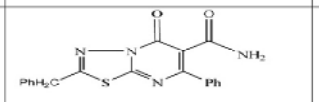
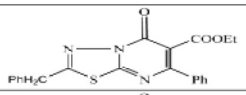
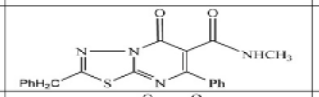
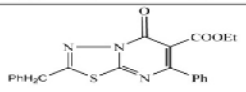
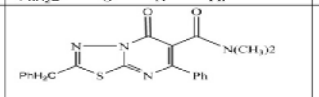
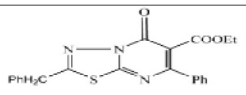
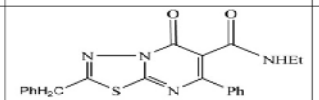
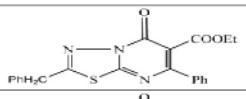
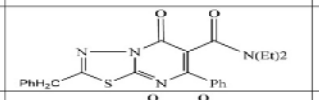
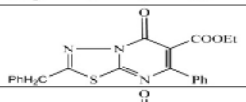
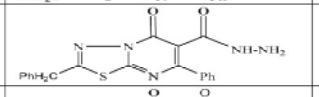
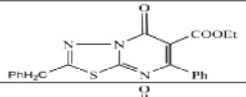
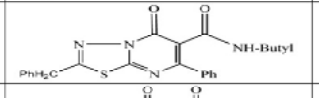
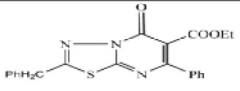
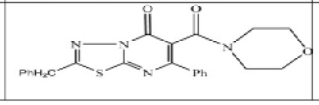
7)-2-benzyl5-Oxo5-H6-N-buthylcarboxamide7-phenyl-1,3,4-thiadiazolo-[3,2-a]-pyrimidine::^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):0,96(t,3H, CH_3); 1,3(s,2H, CH_2); 1,45(p,2H,CH_2); 2,55(t,2H,CH_2);2,7(s,2H,CH_2); 8,1(s, H,NH); 7,15-7,60 (10H, 2Ph);- ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):13,8(CH_3), 20, 2(CH_2), 32,5(CH_2), 38,2(CH_2),49,1(CH_2), 58(CH_2),118 (C), 124,8 (C), 125,8 (CH), 126,4 (CH), 126,4 (CH) ,128(CH), 128,7(CH), 128,7(CH), 128,7(CH),128,7(CH), 129,1(CH), 129,1(CH), 136,9 (C), 137,5 (C), 145,8 (C),), 161,2 (C), 163 (C),165,8(C),168(C),196,5(C).

8)-2-benzyl5-Oxo5-H6-carbomorpholin7-phenyl-1,3,4-thiadiazolo-[3,2-a]-pyrimidine:^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):2,6(s,2H, CH_2); 3,47(t,4H, 2CH_2); 3,67(t,4H,2CH_2); 7,15-7,65 (10H, 2Ph); - ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):38, 3(CH_2),45,6(CH_2),45,6(CH_2),66,3(CH_2),66,3(CH_2),118 (C), 125,8 (CH) , 126,4 (CH) , 126,4 (CH) ,128(CH), 128,7(CH), 128,7(CH), 128,7(CH),128,7(CH), 129,1(CH),), 129,1(CH), 136,9 (C), 137,5 (C), 145,8 (C),), 159,9 (C), 162,1 (C),163(C),168(C).

RESULTS AND DISCUSSION

In our research group, we have been interested in studying the design, synthesis, and biological activity of compounds containing the 2- Benzyl 5-Oxo 5-H 6-Amid diravatives7-Phenyl -1,3,4-thiadiazolo- [3,2-a]-pyrimidine. We tried synthesis of 2- Benzyl 5-Oxo 5-H 6- Amid diravatives7-Phenyl -1,3,4-thiadiazolo-[3,2-a]-pyrimidine with 2-Benzyl 5-Oxo5-H6Ethylcarboxylate7-Phenyl1,3,4-thiadiazolo-[3,2-a]-pyrimidine and amindiravatives in various solvent. But alcohols were the best solvents to this reactions. The alcohols such as methanol and ethanol have greater use of other alcohols. The key intermediate necessary for this study, was synthesized from ethyl 2-formyl 3-oxo 3- phenyl propanoate (compound IV). Because compound (IV) is crucial for the synthesis of derivatives of thiadiazolo pyrimidine . For example for the compound 2- Benzyl 5-Oxo 5-H 6-Carboxamide 7- Phenyl -1,3,4-thiadiazolo- [3,2-a]-pyrimidine , IR showed appearance of the aminoabsorption at 3250·3400 cm^{-1}, or carbonyl group appearance absorptionat 1715 cm^{-1} or phenyl group appearance absorption at 3085 cm^{-1} and cte (Table 1).

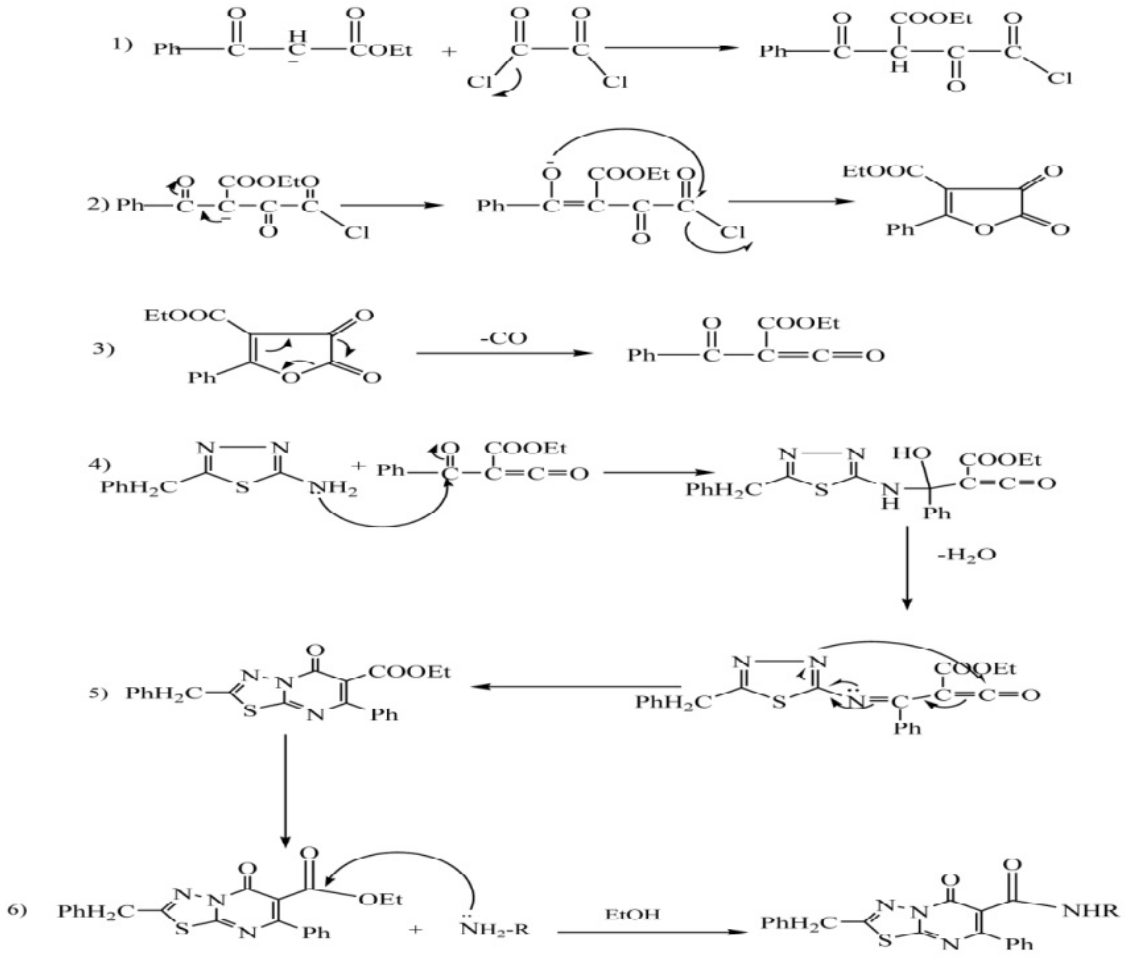
Table 1. Synthesis of 2- Benzyl 5-Oxo 5-H 6- Amid diravatives7-phenyl -1,3,4-thiadiazolo [3,2-a]-pyrimidine from 2- Benzyl 5-Oxo 5-H 6-Ethylcarboxylate 7-phenyl 1 ,3,4- thiadiazolo- [3,2-a]-pyrimidine and amine diravatives[a]

Entry	Thiadiazol pyrimidine	amine diravatives	Product	Time(h)	Yield[b](%)	Melting point
1		NH_3		11	90	164-165
2		CH_3-NH_2		9	87	153-155
3		$(CH_3)2$-NH		8	90	157-159
4		Et -NH_2		6	88	155-157
5		(Et)2-NH		7	90	176-177
6		NH_2-NH_2		6	92	166-168
7		Butyl-NH_2		6	90	185-187
8		Morpholin		5	92	182-183

a Reactions were carried out with 2- Benzyl 5-oxo 5-H 6-ethylcarboxylate 7-phenyl 1 ,3,4-thiadiazolo-[3,2-a]- pyrimidine and amine diravatives

b Yields refer to isolated pure products

To show the generality and applicability of this procedure, we treated a wide variety 2-Benzyl-5-Oxo-5-H- 6-Amide derivatives-7-phenyl- 1,3,4-hiadiazolo-[3,2-a]-pyrimidine from 2- Benzyl-5-Oxo-5-H-6-ethyl carboxylate 7-phenyl 1,3,4-thiadiazolo- [3,2- a]-pyrimidine and amine diravatives in the presence of alcohol ethanol at 78°C and obtained the desirable products in good to excellent yields that, this compound have a lot of properties in parts of medicine (Scheme 2).



Scheme 2. Mechanism of reaction for Synthesis of 2-Benzyl 5-Oxo 5-H 6-R-amide derivatives 7-phenyl -1,3,4-thiadiazolo-[3,2-a]- pyrimidine.

CONCLUSION

In the present work, we design and discover a new class of 2-Benzyl5-Oxo 5-H 6-Amide derivatives7-phenyl 1 ,3,4- thiadiazolo- [3,2-a]- pyrimidine. The preliminary results showed that most of this synthesis ,various alcohol have been employed as a mild and highly efficient solvent system for the convenient preparation of 2- Benzyl 5-Oxo 5-H 6- Amide derivatives7-phenyl -1,3,4-thiadiazolo- [3,2-a]- pyrimidine in excellent yields from 2- Benzyl 5-Oxo 5-H 6-ethylcarboxylate 7-phenyl 1 ,3,4- thiadiazolo- [3,2-a]- pyrimidine and amin derivatives. The advantages include low cost, mild reaction conditions and with excellent yields. The antimicrobial activity of 2-Benzyl5-Oxo 5-H 6-Amide derivatives7-phenyl 1,3,4- thiadiazolo- [3,2-a]- pyrimidine (1-8) was studied with respect to a series of test microbes.

The data obtained show that compounds 2- Benzyl 5-Oxo 5-H 6- amid diravatives7-phenyl -1,3,4-thiadiazolo- [3,2-a]- pyrimidine, have antimicrobial such as anti- Staphylococcus aureus, anti-Pseudomonas aeruginosa and etc.

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