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# Molecular Iodine Catalyzed Synthesis of 9-Substituted Derivatives of 9-Phenyl-2,9-Diphenyl-5,9-Dihydro-6 *H*-Pyrimido[4,5-*d*] [1,3,4]Thiadiazolo[3,2-*a*] Pyrimidine-6,8(7*H*)-dione

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**ABSTRACT**

*A green, most efficient procedure has been developed for the synthesis of 9-substituted derivatives of 9-(4'-phenyl)-2-phenyl-5,9-dihydro-6H-pyrimido[4,5-d][1,3,4]thiadiazolo[3,2-a] pyrimidine-6,8(7H)-dione from a multicomponent one pot three component condensation of 2-amino-5-phenyl 1,3,4-thiadiazole, barbituric acid was refluxed independently in acetonitrile and molecular iodine with different substituted aldehydes. The formed compounds were screened potent Antioxidant activity.*

**Keywords:** 2-amino-5-phenyl-1,3,4-thiadiazole, Barbituric acid, Aromatic aldehyde

## INTRODUCTION

Heterocyclic compounds have broad attention towards organic chemistry due to availability in natural products and medical as well as biological properties [1]. The literature survey reveals that various thiadiazoles have resulted in many potential drugs and are known to exhibit a wide range of pharmacological and biological properties like antimicrobial [2], anti-inflammatory [3] and anticancer [4].

In a multicomponent reaction (MCRs) three or more reactant are converted into a higher molecular weight compound in a one pot method. The MCR has become very popular in the today's Chemistry. Thiadiazolo [3,2-*a*] pyrimidine dione derivatives occupies an important position in chemistry and biology. The most chemist widespread has growing interest to the development of thiadiazolo [3,2-*a*] pyrimidine dione due to the diverse pharmacological as well as biological properties such as antifungal activity [5], antitumor [6], antioxidant [7], anticonvulsant [8], antihypertensive [9], analgesic [10], anti-HIV activity [11], antibiotics [12]. In addition to these derivatives show diverse application in agrochemical industry and pharmaceutical industry.

Thiadiazolo [3,2-*a*] pyrimidine synthesis was reported using the various catalyst such as 2-[5-(4-methoxyphenyl) 4-*H*-1,2,4-triazole] acetic acid [13], NaOH in ethanol [14], SBA-15 [15]. Some of the method reported above use expensive catalysts, strong acidic conditions, higher temperature, require long reaction time, resulting cumbersome product isolation procedure.

Recent days, the use of iodine in fused heterocyclic organic compounds has considerable interest as a non-toxic, inexpensive and easily available agent with high selectivity in excellent yield. The mild Lewis acidity associated with iodine raised its usage to perform several organic transformation using stoichiometric levels to catalytic amounts. The Owing to advantages associated with eco-friendly iodine. So, in this present investigation we report the synthesis of 9-substituted derivatives of 9-(4'-phenyl)-2-phenyl-5,9-dihydro-6 *H*-pyrimido[4,5-*d*] [1,3,4] thiadiazolo [3,2-*a*] pyrimidine-6,8(7*H*)-dione having potent antioxidant activity.

## EXPERIMENTAL

Open capillary tubes were used for melting points of isolated synthesized compounds and are uncorrected. Perkin-Elmer FTIR spectrophotometer was used for IR (KBr) spectra of compounds. Mass spectral data were recorded on liquid chromatography mass spectrometer (Shimadzu 2010Ev) using ESI probe. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on various spectrometers at 300 and 400 MHz using TMS as an internal standard.

**General procedure for the synthesis of 9-substituted derivatives of 9-(4'-phenyl)-2-phenyl-5,9-dihydro-6 *H*-pyrimido[4,5-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6,8(7*H*)-dione(4a-e)**

A mixture of 2-amino-5-phenyl 1,3,4-thiadiazole (1) barbituric acid (2) was refluxed independently in acetonitrile and iodine with different substituted aldehydes (3a-e), to isolate the respective products (4a-e). The reaction mixture was cooled to room temperature and poured into ice cold water. The solid obtained was filtered, washed with water and recrystallized by ethanol to give (4a-e). The reaction was monitored by TLC. These synthesized products (4a-e) were completely characterized from IR, $^{1}$H-NMR, mass and $^{13}$C-NMR spectroscopic technique and also elemental analysis.

**Spectral analysis**

**2,9-diphenyl-5,9-dihydro-6*H*-pyrimido[4,5-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6,8(7*H*)-dione (4a)**

M.P. 203-202°C, Yield 68%. IR (KBr/cm$^{-1}$ ) 3228 (-NH), 1701,1623 (2 C=O); $^{1}$H NMR (400 MHz, DMSO-$d_{6}$ / ppm ) δ 6.8 (s, 1H, -CH), δ 6.7-7.9 (m, 10 H, Ar-H), δ 10.8 and δ 11.4 (2 bs,2H,-NH); EI-MS (m/z: RA %): 375 ($M^{+\cdot}$, 100%),. Elemental analysis calculated data for $C_{19}H_{13}N_5O_2S$; C, 60.79; N, 18.86. Found: C, 60.81; N, 18.88.

**9-(4'-methoxyphenyl)-2-phenyl-5,9-dihydro-6*H*-pyrimido[4,5-*d*][1,3,4]thiadiazolo[3,2-*a*] pyrimidine-6,8(7*H*)-dione (4b)**

M.P. 210-212°C, Yield 85 %. IR (KBr/ cm$^{-1}$) 3209 (-NH), 1731,1674 (2 C=O),1269(-O-R); $^{1}$H NMR (400MHz, DMSO-$d_{6}$ / ppm) δ 3.07 (s, 3H, -Ar-OCH3), δ 6.40 (s, 1H, -CH), δ 7.0-8.5 (m, 9H, Ar-H), δ 11.1 and δ 11.3 (2 bs, 2H,-NH); EI-MS (m/z: RA %): 305 ($M^{+\cdot}$, 100%). $^{13}$C NMR (400 MHz, DMSO–$d_6$/ ppm ) δ: 163,160, 151, 150, 155, 143, 140, 128, 127, 90, 57, 51, 40, 39, 38. Elemental analysis calculated data for $C_{20}H_{15}N_5O_3S$; C, 59.25; N, 3.73. Found: C, 59.26; N, 3.75.

**9-(4'-hydroxyphenyl)-2-phenyl-5,9-dihydro-6*H*-pyrimido[4,5-*d*][1,3,4]thiadiazolo[3,2-*a*] pyrimidine-6,8(7*H*)-dione (4c)**

M.P. 340-342°C, Yield 82%. IR (KBr/cm$^{-1}$) 3450 (-OH), 3274(-NH) 1720, 1670 (2C=O); $^{1}$H NMR (400MHz, DMSO-$d_{6}$ / ppm ) δ 6.86 (s, 1H, -OH), δ 6.8 (s, 1H, -CH), δ7.4-8.3 (m, 9H, Ar-H), δ 10.8 and δ 11.1 (2 bs, 2H,-NH); EI-MS (m/z: RA %): 391 ($M^{+\cdot}$, 100%),. $^{13}$C NMR (400 MHz, DMSO–$d_6$/ppm) δ: 168,164, 163,155, 150, 138, 132, 129, 123,115,114. Elemental analysis calculated data for $C_{19}H_{13}N_5O_3S$ ; C, 58.30; N, 17.89. Found: C, 58.32; N, 17.92.

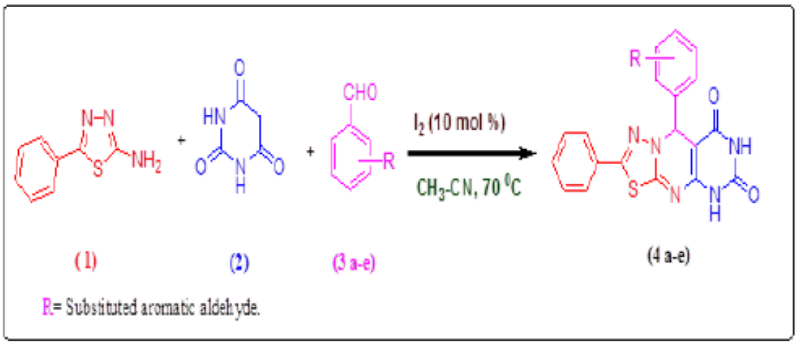
**9-(3'-bromophenyl)-2-phenyl-5,9-dihydro-6*H*-pyrimido[4,5-*d*][1,3,4]thiadiazolo[3,2-*a*] pyrimidine-6,8(7*H*)-dione (4d)**

M.P. 225-227°C, Yield 80%. IR (KBr/cm$^{-1}$) 3136 (-NH), 1697,1604 (2C=O); $^{1}$H NMR (400MHz, DMSO-$d_{6}$ / ppm) δ 5.7 (s, 1H, -CH), δ 7.0-8.2 (m, 9H, Ar-H), δ 10.4 and δ 11.1 (2 bs, 2H,-NH); EI-MS (m/z: RA %): 456 ($M^{+\cdot}$+3, 100),. $^{13}$C NMR (400 MHz, DMSO–$d_6$/ppm) δ: 169, 168,167, 164, 161,156, 152, 150, 146, 135,134, 130, 129,126, 121, 120. Elemental analysis calculated data for $C_{19}H_{12}N_5O_2BrS$ ; C, 50.23; N, 15.42. Found: C, 50.25; N, 15.44.

**9-(2',4'-dichlorophenyl)-2-phenyl-5,9-dihydro-6*H*-pyrimido[4,5-*d*][1,3,4]thiadiazol[3,2-*a*] pyrimidine-6,8(7*H*)-dione (4e)**

M.P. 230-232°C, Yield 75%.IR (KBr/cm$^{-1}$) 3132 (-NH), 1693,1600 (2C=O); $^{1}$H NMR (400MHz, DMSO-$d_{6}$ / ppm ) δ 5.7 (s, 1H, -CH), δ 7.11-8.39 (m, 8H, Ar-H), δ 10.47 and δ 11.29 (2 bs, 2H,-NH); EI-MS (m/z: RA %): 443 ($M^{+\cdot}$ +1, 100%),. $^{13}$C NMR (400 MHz, DMSO–$d_6$/ppm) δ: 168, 167 (C=O), 160,149 (C-4b), 135, 134,133,130,129 128, 126, 121, 78,40,39,38. Elemental analysis calculated data for $C_{19}H_{11}Cl_2N_5O_2S$; C, 51.36; N, 15.76. Found: C, 51.38; N, 15.78.

## RESULT AND DISCUSSION




**Scheme 1: Model reaction**

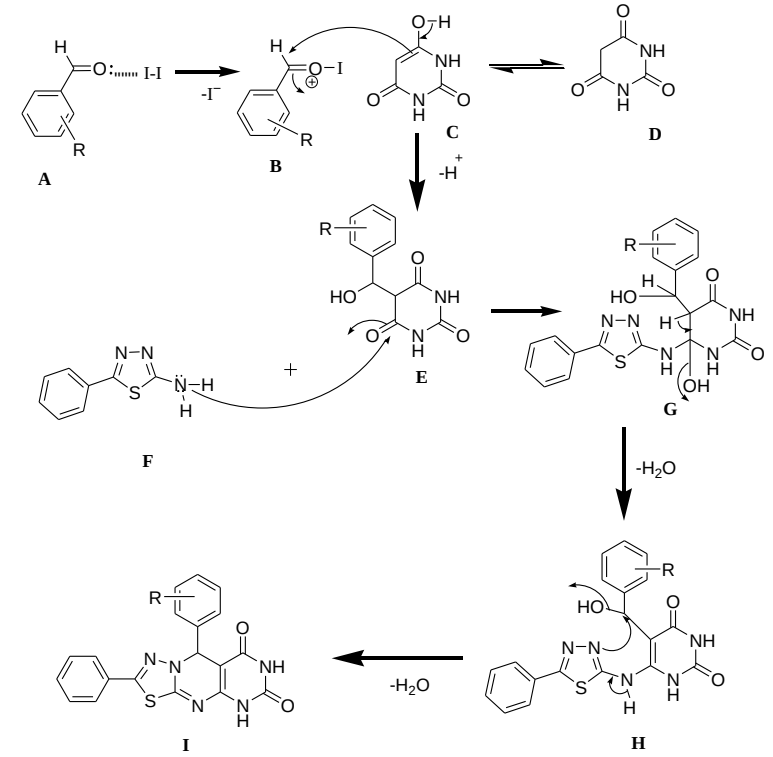
Our firstly efforts were focused on optimization reaction condition. The reaction mixture of 2-amino-5-phenyl 1,3,4-thiadiazole, barbituric acid was refluxed independently in acetonitrile and iodine with different substituted aldehydes, was considered as a model reaction (Scheme 1) for investigating the effectiveness of different polar and non-polar solvent using catalytic amount of molecular iodine (10 mol%). Solvent optimization clearly suggested that acetonitrile is the best solvent for the desired transformation due to fast reaction rate and high yield (Table 1, entry 6). The other polar protic solvents gives moderate yield (Table 1, entry 5). While other aprotic solvent like tetrahydrofuran (THF), Dimethylformamide (DMF), ethylene dichloride and 1,4-dioxane displayed slow reaction rates leading lower yield (Table 1, entry 1-4).

We have carried out the model reaction using different stoichiometric amount of catalyst. The catalyst screening result are summarized in Table 2. It was observed that the excellent yield was achieved by using 10 mol% of molecular iodine (Table 2, entry 5).

After investigating the influence of different parameters on the model reaction, we turned our attention towards the 9-substituted derivatives of 9-(Substituted phenyl)-2-phenyl-5,9-dihydro-6*H*-pyrimido [4,5-*d*] [1,3,4] thiadiazolo [3,2-*a*] pyrimidine-6,8(7*H*) dione (4a-e) using one pot three component reaction of 2-amino-5-phenyl 1,3,4-thiadiazole (1) barbituric acid (2) was refluxed independently in acetonitrile and iodine with different substituted aldehydes (3a-e), and the result are summarized in Table 3.

With the both electron-poor and electron-rich benzaldhydes (Table 3, entries 1-3 and 4-5 ), the corresponding 9-substituted of pyrimido [4,5-*d*] [1,3,4] thiadiazolo [3,2-*a*] pyrimidine-6,8(7*H*) dione derivatives (4a-e) were obtained to excellent yields. These synthesized products (4a-e) were completely characterized from IR, $^{1}$H-NMR, Mass and $^{13}$C-NMR spectroscopic technique and also elemental analysis.

The molecular iodine has acting remarkable reagent properties like hard-soft reagent that's why reaction mechanism was accelerated. On the basis of all our experimental analysis result, we proposed tentative plausible mechanism for the formation of thiadiazolo [3,2-*a*] pyrimidine-6,8(7*H*) dione (4a-e) in the presence of molecular iodine. The hypothesis supported the fact that reaction initiated from iodine. The overall, mechanism takes place according to Knoevenagels-Micheal reaction (Scheme 2).




**Scheme 2:** Knoevengels- Micheal types of Mechanism

**Table 1: Optimization of the reaction conditions using different solvents[a]**

| Entry | Solvent | Reaction time (h) | Yield (%)[b] |
|---|---|---|---|
| 1 | 1,4-dioxane | 6.0 | 35 |
| 2 | Ethylene dichloride | 8.0 | 40 |
| 3 | THF | 9.0 | 45 |
| 4 | DMF | 6.0 | 50 |
| 5 | Ethanol | 5.5 | 65 |
| 6 | Acetonitrile | 4.0 | 85 |

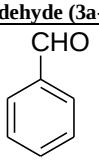
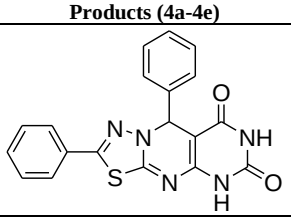
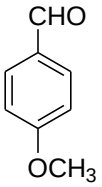
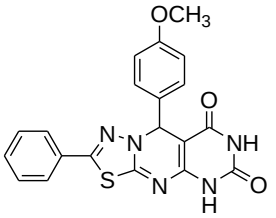
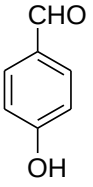
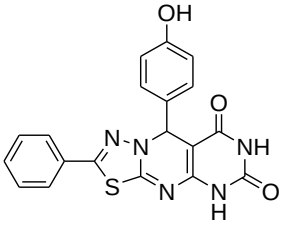
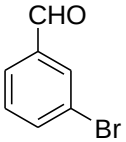
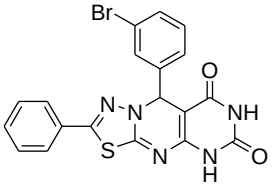
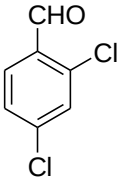
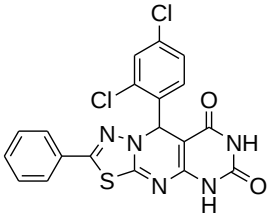
[a]Reaction conditions: 2-amino-5-phenyl 1,3,4-thiadiazole (1 mmol), barbituric acid (1 mmol) with substituted benzaldehydes (1 mmol) and acetonitrile in Iodine were refluxed at 70°C. [b]Isolated yields

**Table 2: Optimization Study for the amount of Molecular Iodine[a]**

| Entry | Catalyst (mole %) | Temperature (°C) | Reaction time (h) | Yield %[b] |
|---|---|---|---|---|
| 1 | 01 | 70 | 4.0 | 40 |
| 2 | 02 | 70 | 4.0 | 50 |
| 3 | 05 | 70 | 4.0 | 60 |
| 4 | 08 | 70 | 4.0 | 72 |
| 5 | 10 | 70 | 4.0 | 85 |
| 6 | 15 | 70 | 4.0 | 85 |
| 7 | 20 | 70 | 4.0 | 85 |

[a]Reaction conditions: 2-amino-5-phenyl 1,3,4-thiadiazole (1 mmol), barbituric acid (1 mmol) with substituted benzaldehydes (1 mmol) and acetonitrile in Iodine were refluxed at 70°C. [b] Isolated yields

**Table 3: Three component reaction of 2-amino-5-phenyl 1,3,4-thiadiazole (1), barbituric acid (2), and aromatic aldehydes (3a-e) for the synthesis of (4a-4e)[a]**

| Entry | Aldehyde (3a-e) | Products (4a-4e) | Time (h) | Yield (%)[b] | M.P. (°C) |
|---|---|---|---|---|---|
| 1 |  |  | 3.0 | 68 | 203-202 |
| 2 |  |  | 3.5 | 85 | 210-212 |
| 3 |  |  | 4.0 | 82 | 340-342 |
| 4 |  |  | 3.5 | 80 | 225-227 |
| 5 |  |  | 3.0 | 75 | 230-232 |

[a]Reaction conditions: (1) (1 mmol), (2) (1 mmol), (3a-e) (1 mmol) and acetonitrile in Iodine were refluxed at 70°C. [b] Isolated yields

## BIOLOGICAL ACTIVITY

### Antioxidant activity

### DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging assay

DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay was performed as per earlier reported method [16]. The reaction cocktail was prepared by mixing individual newly synthesized organic compounds is added to equal volume of 0.1 mM solution of DPPH radical in absolute ethanol. After 20 min of incubation at room temperature, the DPPH reduction was calculated by reading the absorbance at 517 nm using UV-Visible spectrophotometer. Ascorbic acid (1mM) was used as reference compound. The compound (4d and 4e) shows remarkable antioxidant activity against DDPH radical scavenging activity with reference of ascorbic acid (91.4 ± 0.021).

### *OH radical scavenging assay*

Hydroxy radicals scavenging activity was measured with Fenton's reaction (Rollet –Labelle et al.). The reaction mixture contained 60 µl of $FeCl_2$ (1 mM), 90 µl of 1,10-phenanthroline(1mM), 2.4 ml of phosphate buffer (pH 7.8), 150 µl of 0.17 M $H_2O_2$ and 1.5 ml of individual newly synthesized organic compounds (1 mM). The reaction mixture was kept at room temperature for 5 min incubation and the absorbance was recorded at 560 nm using UV-Visible spectrophotometer. Ascorbic acid (1 mM) was used as the reference compound. The compound (4c, 4d and 4e) shows good OH radical scavenging activity as compared with Ascorbic acid (89.5 ± 0.021) (Table 4).

**Table 4: Antioxidant activity of tested compounds (4a-4e)**

| Entry | Compound code | % Radical scavenging activity | |
|---|---|---|---|
| | | DPPH radical scavenging | OH radical scavenging |
| 1 | 4a | 40.2 ± 0.60 | 51.1 ± 1.22 |
| 2 | 4b | 66.6 ± 0.84 | 64.2 ± 1.65 |
| 3 | 4c | 63.9 ± 1.79 | 71.2 ± 1.32 |
| 4 | 4d | 85.4 ± 1.36 | 80.9 ± 0.21 |
| 5 | 4e | 70.4 ± 0.70 | 79.2 ± 1.40 |
| 6 | Ascorbic acid (Standard) | 91.4 ± 0.021 | 89.5 ± 0.021 |

## CONCLUSION

In conclusion, we have developed an efficient, green and easy protocol for synthesis of 9-substituted derivatives of 9-(Substituted phenyl)-2-phenyl-5,9-dihydro-6*H*-pyrimido[4,5-*d*] [1,3,4] thiadiazolo [3,2-*a*] pyrimidine-6,8(7*H*) dione by reaction of corresponding substituted aldehydes, 2-amino-5-phenyl 1,3,4-thiadiazole and barbituric acid in presence iodine in acetonitrile. The product can be easily isolated by simple workup technique, requires ambient reaction condition, short time, less expensive and give excellent yield. Among these synthesized compounds shows potent Antioxidant activity.

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