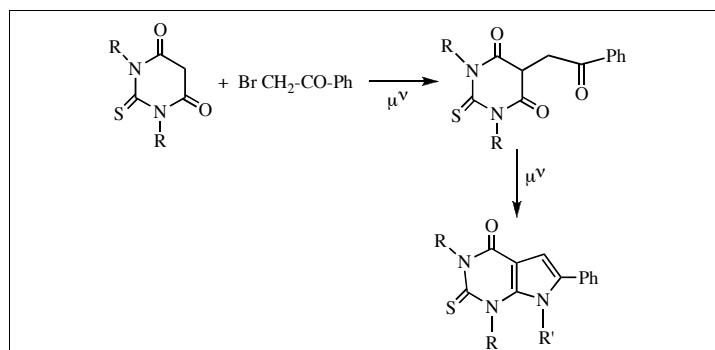# Paal Knorr Reaction for Novel Pyrrolo[2,3-d]pyrimidines

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An expeditious and convenient solid supported synthesis of 1,3,7-triaryl-6-phenyl-2-thioxo-1,2,3,7-tetra-hydropyrrolo[2,3-d]pyrimidin-4-one derivatives from readily accessible N,N-disubstituted thiobarbituric acids under microwaves utilising Paal Knorr reaction is described.

Pyrimidine and its derivatives have been studied for over a century due to its wide pharmaceutical applications as antimicrobial [1a], antitumor [1b], antihypertensive [1c] and anti-inflammatory [1d] agents. Also pyrroles constitute the core unit of many natural products including alkaloids, porphyrins and bile pigments [2]. The fusion of pyrrole with pyrimidines further constitutes a structural unit of nucleobases, which is of current interest to both chemists and biologists because of the enhanced biopotential. Pyrrolo[2,3-d]pyrimidines reveal significant biological profiles as broad-spectrum antitumors [3], antivirals, antibacterials [4], immunosuppressive agent and also has been useful in the treatment of Crohn's disease, Alzheimer's disease and leukemia [5]. They also possess significant inhibitory activity against *dihydrofolate reductase* (DHFR) [6] and *thymidylate synthase* enzymes [7].

Due to strict environmental legislation, there is an increasing awareness for the toxic effects of chemicals on the environment. In this endeavor, solid supported reactions [8,9] with microwaves [10] are widely explored for selective organic functional group transformations. These solid supports, which are usually of mineral origin, act as both catalyst [11] as well as an energy transfer media. Such dry media reactions are especially appealing as they provide an opportunity to work with open vessels avoiding the risk of high-pressure development with the possibility of up-scaling the reactions to industrial scale [12].

Paal Knorr reaction [13], a well known pathway, generalized mostly for the synthesis of highly substituted pyrrole rings and has not been explored much for fused systems. Thus, 1,4-diketones are synthesized using N,N-disubstituted thiobarbituric acid and finally condensed with amines used as nitrogen source to furnish novel pyrrolo[2,3-d]pyrimidines utilizing the Paal Knorr mechanistic approach.

No general method for the synthesis of titled compounds using Paal Knorr mechanism starting from N,N-disubstituted thiobarbituric acids and α-halo ketones has ever been reported. With a view to develop an environmentally benign green synthesis, biopotential of pyrrolopyrimidines and extending the applicability of Paal Knorr reaction, it was thought worthwhile to study the synthetic aspects of pyrrolo[2,3-d]pyrimidines with microwaves (MWs) under dry media. Conventional studies were also attempted to compare the reaction conditions and versatility of the supports.

Few strategies for the synthesis [14-15] of pyrrolo[2,3-d]pyrimidine backbone have been reported starting from uracil [16] or dimethyl acetal of uracils [17]. This employs harsh reaction conditions, use of toxicological chemicals and tedious work up procedure with unsatis-factory yields. Moreover, these multistep reactions include the limitations towards the structural diversity. For this reason, a great deal of effort has been devoted to the development of a facile and efficient method for the synthesis of pyrrolo[2,3-d] pyrimidines.

Our environmentally friendly approach involved the reaction of N,N-disubstituted thiobarbituric acids (**1a-d**) with phenacyl bromide (**2**), an α-halo ketone (step 1) over basic alumina [18] or anhydrous potassium carbonate

(K_2CO_3) as solid support under MW irradiation (Method A) resulting in 1,4-diketone (intermediate) (**3a-d**) which further cyclised with numerous aromatic/heteroaromatic amines (**4a-c**) over acidic alumina [19] / montmorillonite K-10 clay [20] furnishing 1,3,7-tetraryl-6-phenyl-2-thioxo-1,2,3,7-tetrahydropyrrolo[2,3-*d*]pyrimidin-4-one (**5a-l**) as the required product in step 2. The property of thiobarbituric acid (TBA) and barbituric acid (BA) to act as cyclic active methylene moiety was utilized to synthesize a series of intermediates. Initially, to synthesize novel pyrrolo[2,3-*d*]pyrimidines, alkylation of thiobarbituric acid (TBA) and barbituric acid (BA) with phenacyl bromide was attempted. This resulted in the formation of aromatized pyrimidine ring in which the two hydroxy groups were placed at 4 and 6 positions. This configuration is generated *in situ* as the carbonyl groups of TBA and BA at 4 and 6 positions undergo tautomerisation. Thus thiobarbituric acid and barbituric acid upon reaction with phenacyl bromide gave 4,6-dihydroxy ketone instead of the respective 1,4-dicarbonyl (triketone) as an intermediate, which in turn failed to react in step 2 with amines. In another attempt, in place of TBA and BA, *N,N*-disubstituted thiobarbituric acids (**1a-d**) were used with a view to utilize its active methylene group as in this case, there are no chances of tautomerisation. *N,N*-Disubstituted thiobarbituric acids upon reaction with α-halo ketones resulted in 1,4-diketone as intermediates (**3a-d**) (**Table 1**). Furthermore, some specific intermediates were selected according to the reaction condition, which were reacted smoothly with some of the aromatic/heteroaromatic amines (**4a-c**) *via* Paal Knorr reaction to afford pyrrolo[2,3-*d*]pyrimidines (**5a-l**) in

just a few minutes with higher yield. However, it was observed that the reactivity of different amines varied in the reaction conditions employed. In the case, where amines with electron withdrawing groups were used, the reaction did not proceed, giving negative results.

Scheme

R = Phenyl, furyl, m-tolyl, p-chlorophenyl
R' = Phenyl, furyl, m-tolyl
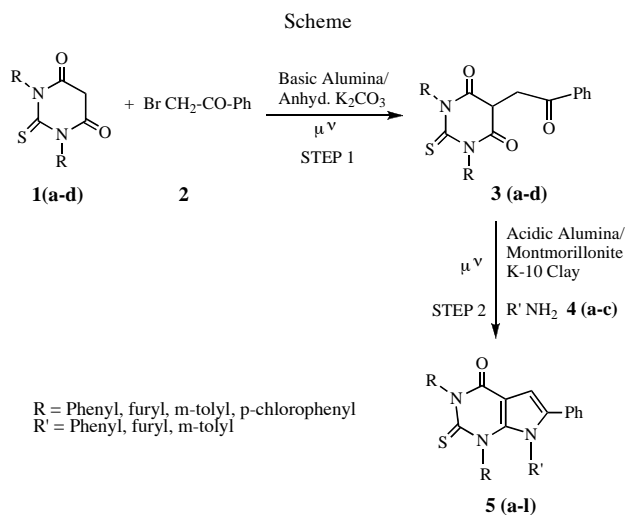
For comparative studies, the conventional reaction conditions were also developed (Method B), in which piperidine and glacial acetic acid were used in step 1 and step 2 respectively. In step 2 (**Table 2**), the reaction catalyzed by montmorillonite K-10 clay was found to give the required products (**5a-l**) more beneficially in reduced time with satisfactory yields. This was attributed to the ditopic nature [21] of montmorillonite K-10 clay. Finally,

Table 1

Comparison of Reaction Time and Yield for the Synthesis of 1,4-Dicarbonyl

Compounds (**3a-d**) in Step 1

Compd. No.	R	METHOD A		METHOD B	Recrystallisation
		Time (min)/Yield(%)		Time(hrs)/Yield (%)	Solvent
		Basic Alumina	Anhydrous Potassium carbonate		(v/v)
3a	(phenyl)	6/80	4.5/78	7.5/67	CHCl₃/Et₂O 2 : 8
3b	(furyl)	4.5/78	3.5/82	5/72	CHCl₃/Et₂O 1 : 9
3c	(m-tolyl, CH₃)	5/80	4/85	6/75	CHCl₃/Et₂O 1 : 9
3d	(Cl-phenyl)	6/76	6/80	7.5/65	CHCl₃/Et₂O 2 : 8

Table 2

Comparison of Reaction Time and Yield for the Synthesis of (**5a-l**) in Step 2

S. No.	R	R'	METHOD A Time (min) / Yield (%)		METHOD B Time (hrs) / Yield (%)
			Acidic Alumina	Montmorillonite K-10 Clay	
5a			8/74	6.5/80	10.5/63
5b			7.5/80	7/80	1s4.5/60
5c			7/76	7/78	12/68
5d			7/74	5/82	7/68
5e			5/76	6.5/80	10/65
5f			5.5/76	4/77	10/70
5g			10/80	7/85	12/64
5h			7.5/65	6.5/74	13.5/58
5i			5/78	5/84	12/70
5j			7/80	6.5/78	13/65
5k			5.5/76	3.5/88	10/70
5l			8/74	7/80	11.5/62

anhydrous potassium carbonate and montmorillonite K-10 clay were found to be the best catalytic support for step 1 and step 2 respectively. The observed optimal yield for this sequential process indicated that Paal Knorr reaction is about 80% efficient on average under MWs. In addition, the condensation steps in which anhydrous conditions are desirable can be achieved with the use of these solid supports.

The structures of the intermediates (**3a-d**) and the final product pyrrolo[2,3-*d*]pyrimidines (**5a-l**) were established on the basis of elemental analysis and spectral data. IR spectral absorption bands at 1715-1725 cm^{-1} and 1680-1700 cm^{-1} suggested the presence of carbonyl group in *N,N*-disubstituted thiobarbituric acids (**1a-d**) and intermediates (**3a-d**) respectively. Further, in the case of pyrrolo[2,3-*d*]pyrimidines, absorption band was observed at 1640-1660 cm^{-1}. This shift of about 40-50 cm^{-1} in the carbonyl band towards the lower frequency region was attributed to the presence of α,β-unsaturated carbonyl group, which confirmed the structure of the final products (**5a-l**). In the ^{1}H NMR spectrum of intermediates (**3a-d**), a triplet for one proton and a doublet for two protons were observed at δ 3.9

and δ 3.65 respectively along with other usual signals. The disappearance of these peaks with the appearance of a new singlet at δ 6.4-6.6 value further supported the Paal Knorr reaction mechanism, which involved the heterocyclisation of 1,4-dicarbonyl compounds to the pyrrole ring.

In conclusion, Paal Knorr reaction was explored using different inorganic solid supports under MW irradiation for the synthesis of pyrimidine fused N-substituted pyrroles and to make this important moiety available for biological screening in the search for better medicinal agents. The proposed methodology thus, offered the advantages of being simple and practically convenient and environmentally benign, cost effective protocol with excellent yield of the products in lesser reaction time.

EXPERIMENTAL

Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. IR (in Nujol) spectra were recorded on a model Perkin-Elmer FTIR-1710 spectrophotometer, ^{1}H NMR spectra were recorded on a Bruker Avance Spectrospin 300 (300 MHz) using TMS as internal standard. Elemental analysis was performed on a Heraeus CHN Rapid Analyser. The purity of compounds was checked on silica gel coated aluminium plates (Merck). A Kenstar microwave oven, Model No. OM9925E at (2450 MHz, 800W) was used for MWI. Temperature of the reaction was measured through AZ, Mini Gun Type, Non-Contact IR Thermometer, Model No. 8868.

General procedure for the synthesis of Pyrrolo[2,3-d]pyrimidines (5a-l).

Method A (Microwave Assisted Solid Supported Synthesis).

Synthesis of 1,4-Dicarbonyl Compound (Intermediate) (3a-d) Step 1.

To the solution of N,N-disubstituted thiobarbituric acids (1a-d) (0.012 mol) and phenacyl bromide (2) (0.01 mol) in chloroform, anhydrous K_2CO_3/basic alumina (20 g) was added. The reaction mixture was air-dried. This was then placed in an alumina bath [22] and subjected to MWI for the time interval of 30 sec. Upon completion of reaction as monitored by TLC, the reaction mixture was cooled and products (3a-d) were extracted using (3x10 ml) of ethanol and recrystalized using appropriate solvents to afford intermediate (3a-d) in high yield.

Reaction of 5-(2-Oxo-2-phenylethyl)-1,3-diaryl/heteroaryl-2-thioxo-1,3-dihydropyrimidin-4,6-dione (intermediate) (3a-d) with Aromatic/Heteroaromatic Amines (4a-c) Step 2.

Acidic alumina/montmorillonite K-10 clay was added to the equimolar solution of intermediate (3a-d) (0.01 mol) in $CHCl_3$ and amines (4a-c) (0.01 mol) at room temperature. The reaction mixture was thoroughly mixed and dried in air. It was then placed in an alumina bath and subjected to MWI. Temperature of the reaction mixture was 130-140 $^\circ$C. At every interval of 30 sec, the reaction was monitored by TLC, after completion, the product pyrrolo[2,3-d]pyrimidines (5a-l) were extracted using (3 x 10 ml) of chloroform, which was further purified by column chromatography [column of SiO_2; preadsorption of the crude product at SiO_2; elution with benzene/ethyl acetate = 90:10 v/v].

Method B (Conventional Procedure).

Synthesis of intermediates (3a-d) Step 1.

N,N-Disubstituted thiobarbituric acids (1a-d) (0.012 mol), phenacyl bromide (2) (0.01 mol) and piperidine (few drops) in chloroform (20 ml) were refluxed on a steam bath. The heating was continued for appropriate time of approximately 5-7.5 hrs and the reaction was monitored by TLC. Upon completion of the reaction, the solvent was evaporated. The crude mass isolated by suction is then dried and recrystalized from appropriate solvent.

Synthesis of pyrrolo[2,3-d]pyrimidines (5a-l) Step 2.

An equimolar mixture of intermediate (3a-d) (0.01 mol) and aromatic/heteroaromatic amines (4a-c) (0.01 mol) in glacial acetic acid (15 ml) was stirred at refluxing temperature for 7-15 hrs. Upon completion of the reaction, the reaction mixture was cooled, concentrated and left at room temperature. Ice-cold water and aqueous ammonia solution was added to neutralize the reaction mixture and the solid that separated was collected by filtration, dried and recrystallised to get pyrrolo[2,3-d]pyrimidines (5a-l).

1,3,6,7-Tetraphenyl-2-thioxo-1,2,3,7-tetrahydropyrrolo[2,3-d]-pyrimidin-4-one (5a).

This compound has the following spectral properties: mp 206-210°; ir: 1664.35 (C=C-C=O), 1605.02 (C=C arom), 1300.65 (C=S) cm^{-1}; ^{1}H nmr: (300 MHz, deuteriochloroform): δ 6.41 (1H, s, C_5-H), 7.18-7.59 (20 H, m, arom)

Anal. Calcd. for $C_{30}H_{21}N_3OS$: C, 76.43; H, 4.45; N, 8.91. Found: C, 76.49; H, 4.37; N, 8.98.

7-(Furan-2-yl)-1,3,6-triphenyl-2-thioxo-1,2,3,7-tetrahydropyrrolo-[2,3-d]pyrimidin-4-one (5b).

This compound has the following spectral properties: mp 198-200°; ir: 1638.34 (C=C-C=O), 1596.38 (C=C arom), 1263.81 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 6.35 (1H, s, C_5-H), 7.26-7.59 (18 H, m, arom).

Anal. Calcd. for $C_{28}H_{19}N_3OS$: C, 75.50; H, 4.26; N, 9.43. Found: C, 75.61; H, 4.35; N, 9.49.

7-(m-Tolyl)-1,3,6-triphenyl-2-thioxo-1,2,3,7-tetrahydropyrrolo-[2,3-d]pyrimidin-4-one (5c).

This compound has the following spectral properties: mp 260-264°, ir: 1649.72 (C=C-C=O), 1590.02 (C=C arom), 1281.63 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 2.35 (3H, s, CH_3), 6.38 (1H, s, C_5-H), 7.21-7.58 (19 H, m, arom).

Anal. Calcd. for $C_{31}H_{23}N_3OS$: C, 76.70; H, 4.74; N, 8.65. Found: C, 76.66; H, 4.82; N, 8.56.

1,3-Di(furan-2-yl)-6,7-diphenyl-2-thioxo-1,2,3,7-tetrahydropyrrolo-[2,3-d]pyrimidin-4-one (5d).

This compound has the following spectral properties: mp 222-225°; ir: 1652.81 (C=C-C=O), 1596.19 (C=C arom), 1267.01 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 6.49 (1H, s, C_5-H), 7.30-7.59 (16 H, m, arom).

Anal. Calcd. for $C_{26}H_{17}N_3O_3S$: C, 69.17; H, 3.76; N, 9.31. Found: C, 69.24; H, 3.88; N, 9.44.

1,3,7-Tri(furan-2-yl)-6-phenyl-2-thioxo-1,2,3,7-tetrahydro-pyrrolo[2,3-d]pyrimidin-4-one (5e).

This compound has the following spectral properties: mp 246-248°, IR: ν (cm^{-1}) 1654.68 (C=C-C=O), 1608.77 (C=C arom),

1298.90 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 6.46 (1H, s, C$_5$-H), 7.32-7.54 (14 H, m, arom).

Anal. Calcd. for C$_{24}$H$_{15}$N$_3$O$_4$S: C, 65.30; H, 3.40; N 9.52. Found: C, 65.19; H, 3.32; N, 9.64.

1,3-Di(furan-2-yl)-6-phenyl-7-(*m*-tolyl)-2-thioxo-1,2,3,7-tetra-hydropyrrolo[2,3-*d*]pyrimidin-4-one (**5f**).

This compound has the following spectral properties: mp 200-202°, IR: ν (cm^{-1}) 1651.09 (C=C-C=O), 1611.83 (C=C arom), 1274.31 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 2.38 (3H, s, CH$_3$), 6.46 (1H, s, C$_5$-H), 7.28-7.59 (15 H, m, arom).

Anal. Calcd. for C$_{27}$H$_{19}$N$_3$O$_3$S: C, 69.67; H, 4.08; N, 9.03. Found: C, 69.74; H, 4.20; N, 9.11.

1,3-Di(*m*-tolyl)-6,7-diphenyl-2-thioxo-1,2,3,7-tetrahydropyrrolo-[2,3-*d*]pyrimidin-4-one (**5g**).

This compound has the following spectral properties: mp 216-218°; ir: 1664.21 (C=C-C=O), 1600.61 (C=C arom), 1280.05 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 2.41(6H, s, CH$_3$), 6.41 (1H, s, C$_5$-H), 7.20-7.64 (18 H, m, arom).

Anal. Calcd. for C$_{30}$H$_{25}$N$_3$OS: C, 75.78; H, 5.26; N, 8.84. Found: C, 75.87; H, 5.33; N, 8.75.

1,3-Di(*m*-tolyl)-7-(furan-2-yl)-6-phenyl-2-thioxo-1,2,3,7-tetra-hydropyrrolo[2,3-*d*]pyrimidin-4-one (**5h**).

This compound has the following spectral properties: mp 192-194°; ir: 1650.84 (C=C-C=O), 1599.27 (C=C arom), 1268.65 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform) δ: 2.48 (6H, s, CH$_3$), 6.52 (1H, s, C$_5$-H), 7.26-7.64 (16 H, m, arom).

Anal. Calcd. for C$_{28}$H$_{23}$N$_3$O$_2$S: C, 72.25; H, 4.94; N, 9.03. Found: C, 72.28; H, 4.99; N, 9.11.

1,3,7-Tri(*m*-tolyl)-6-phenyl-2-thioxo-1,2,3,7-tetrahydropyrrolo-[2,3-*d*]pyrimidin-4-one (**5i**).

This compound has the following spectral properties: mp 212-215°; ir: 1649.27 (C=C-C=O), 1608.84 (C=C arom), 1271.05 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 2.35 (9H, s, CH$_3$), 6.39 (1H, s, C$_5$-H), 7.28-7.59 (17 H, m, arom)

Anal. Calcd. for C$_{31}$H$_{27}$N$_3$OS: C, 76.07; H, 5.52; N, 8.58. Found: C, 76.16; H, 5.61; N, 8.64.

1,3-Bis(4-chlorophenyl)-6,7-diphenyl-2-thioxo-1,2,3,7-tetrahydro-pyrrolo[2,3-*d*]pyrimidin-4-one (**5j**).

This compound has the following spectral properties: mp 188-190°; ir: 1664.91 (C=C-C=O), 1605.62 (C=C arom), 1268.05 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 6.46 (1H, s, C$_5$-H), 7.31-7.65 (18 H, m, arom).

Anal. Calcd. for C$_{30}$H$_{19}$N$_3$OSCl$_2$: C, 66.66; H, 3.51; N, 7.77. Found: C, 66.70; H, 3.44; N, 7.67.

1,3-Bis(4-chlorophenyl)-7-(furan-2-yl)-6-phenyl-2-thioxo-1,2,3,7-tetrahydro-pyrrolo[2,3-*d*]pyrimidin-4-one (**5k**).

This compound has the following spectral properties: mp 236-238°; ir: 1652.68 (C=C-C=O), 1599.36 (C=C arom), 1290.19 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 6.41 (1H, s, C$_5$-H), 7.29-7.60 (16 H, m, arom).

Anal. Calcd. for C$_{28}$H$_{17}$N$_3$O$_2$SCl$_2$: C, 63.39; H, 3.20; N, 7.92. Found: C, 63.41; H, 3.28; N, 7.87.

1,3-Bis(4-chlorophenyl)-6-phenyl-7-(*m*-tolyl)-2-thioxo-1,2,3,7-tetrahydropyrrolo[2,3-*d*]pyrimidin-4-one (**5l**).

This compound has the following spectral properties: mp 260-262°; ir: 1647.24 (C=C-C=O), 1583.02 (C=C arom), 1274.43 (C=S) cm^{-1}; ^{1}H nmr (300 MHz, deuteriochloroform): δ 2.35 (3H, s, CH$_3$), 6.47 (1H, s, C$_5$-H), 7.34-7.69 (17 H, m, arom),.

Anal. Calcd. for C$_{31}$H$_{21}$N$_3$OSCl$_2$: C, 67.14; H, 3.79; N, 7.58. Found: C, 67.21; H, 3.83; N, 7.64.

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