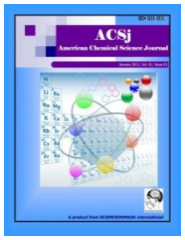

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A Facile Synthesis of 7-amino-1,3-diaryl-5-phenyl-2-thioxo-pyrano[2,3-*d*]pyrimidine-4(*5H*)-ones

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Research Article

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ABSTRACT

The reactions of arylidene derivatives such as ethylphenylmethylenemalononitrile 3a, ethylphenylmethylenecyanoacetate 3b and ethylphenylmethylenecyano-acetamide 3c with substituted thiobarbituric acids 2a-e in presence of $NaOCH_3$ and MeOH afforded 7-amino-1,3-diaryl-5-phenyl-2-thioxo-pyrano[2,3-*d*]pyrimidin-4(5H)ones 4a-e and 5e by cyclocondensation.

Keywords: Synthesis; pyranopyrimidines; thiobarbituric acids; arylidenes;

1. INTRODUCTION

Among the pyranopyrimidines one of the most important classes are the dihydro-5H-pyrano[2,3-*d*]pyrimidines**.** Compounds containing this moiety have interesting biological properties (Yun et al., 2000). For example, molecules fused to a coumarine unit exhibit antibacterial activity and are used as fungicides. In addition, compounds having a chalcone unit attached to the pyranopyrimidine ring are efficient herbicides (Antonio et al., 2006). Various novel pyrano [2,3-*d*]pyrimidines and furopyrano[2,3-*d*]pyrimidines were synthesized in 80-90% yields via a multicomponent domini Knoevenagel/ hetero Diels-Alder reaction of 1,3-dimethyl barbituric acid with an aromatic aldehyde and ethyl vinyl ether or 2,3-dihydrofuran in presence of 1 mol % of indium (III) chloride. The reaction also proceeds in aqueous media without using any catalyst, but the yield is comparatively less (65-75%). Pyrimidine derivatives continue to be of great interest due to their wide range of biological

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activities (Mazaahir et al., 2007; Ji-Feng et al., 2005). Preparation of naturally occurring complex molecules containing a uracil ring possess significant synthetic challenges. The develpoment of clinically useful anticancer (5-fluorouracil) and antiviral drugs (AZT, DDC, DDI, BVDV) has renewed interest in the synthetic manipulation of uracils (Dipak and Mukut, 2006; Jain et al., 2006; Jing and Hanqing, 2006). Furthermore, pyrano[2,3-*d*]pyrimidines also represent broad classes of annelated uracils. A number of compounds having these systems are synthesized with diverse pharmacological activity. For the preparation of these complex molecules, there has been remarkable interest in the synthetic manipulations of uracils.

Although a variety of routes for the synthesis of these compounds have been appeared in the literature, the majority of them involve a number of steps, drastic conditions, long reaction time and low yields (Ahmed et al., 2006; Rovnyak et al., 1978). Thus new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to these heterocycles and their diverse biological properties. In search of an efficient method and in continuation to our studies on fused pyrimidine derivatives (Herojit et al., 2005; Warjeet et al., 2002), we have investigated a new, simple and efficient synthesis of novel fused pyrimidines based on 1,3-diaryl thiobarbituric acids (DTBA) which were used as precursors for the synthesis of various fused heterocyclic compounds. In recent years, we have reported one-pot cyclizations of DTBA with hydrazine, hydroxylamine, guanidine, etc. (Anita et al., 1995, 1996; Brajakishor et al., 2006). In continuation of our work on the synthesis of fused heterocycles, we report in this part full details of the work and studies related to the synthesis of pyrano[2,3-*d*]pyrimidines of DTBA by reacting with various arylidenes, such as, ethylphenylmethylenemalononitrile **3a**, ethyl phenylmethylenecyanoacetate **3b** and phenylmethylenecyanoacetamide **3c**, in presence of sodium methoxide and methanol.

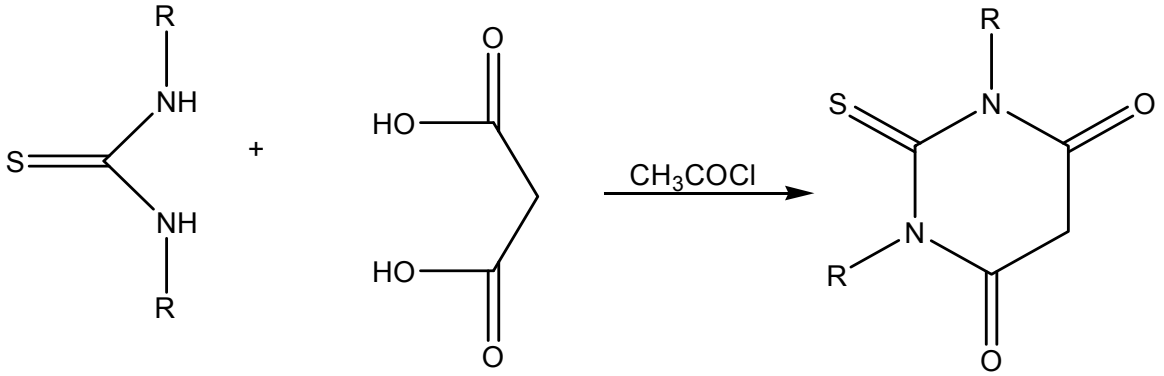
2. EXPERIMENTAL DETAILS

2.1 General

Melting points were determined by capillary tubes and are uncorrected. Infrared (IR) spectra were recorded on FTIR spectrometer and Shimazdu IR-408 spectrometer. Absorption maxima were recorded in wave numbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker AC-400 spectrometers. ^{13}Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AC-100 MHz spectrometers. Residual non-deuterated solvent was used as an internal reference and all chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS). All samples were run in deutero-chloroform ($CDCl_3$) as solvent unless otherwise stated. Mass spectra were recorded on a Kratas concept-IS mass spectrometer couples to a Mach 3 data system, or on a Jeol-D 300 mass spectrometer.

2.2 General Procedure for the Synthesis of 1,3-Diarylthiobarbituric Acids (2)

1,3-Diarylthiobarbituric acids **2** having an active methylene group can furnish several condensation products for easy cyclization to give various fused heterocyclic compounds of interest. The compounds **2** are among the simplest synthetic intermediates that can be easily prepared in a one pot reaction by treating 1,3-diaryl thioureas **1** with malonic acid in the presence of acetyl chloride. These intermediates have been extensively explored for five- and six-membered heterocycles (Das and Dutt, 1938).



1 **2**

1a, **2a**: R = 4-$CH_3C_6H_4$
1b, **2b**: R = 2-$OCH_3C_6H_4$
1c, **2c**: R = 4-ClC_6H_4
1d, **2d**: R = 2-$CH_3C_6H_4$
1e, **2e**: R = C_6H_5

Scheme 1. Synthesis of 1,3-diarylthiobarbituric acids (2a-e)

The compounds 2 were prepared by the condensation reaction of compounds 1 with malonic acid in the presence of acetyl chloride (Scheme 1).

2.2.1 Synthesis of 1,3-Diphenyl-1,3-Dihydro-2-Thioxo-*2H,5H*-Pyrimidine-4,6-Dione (2e)

1,3-Diphenylthiourea, **1e** (2.2 g, 0.01 mol), malonic acid (1.10 g, 0.01 mol) and acetylchloride (10 mL) were refluxed for 20-30 min. The reaction mixture on cooling and treatment with crushed ice solidified. The separated solid was filtered, dried and separated by column chromatography as light yellow crystals of **2e** (yield 80%), mp 245-246^{o}C (Litt, mp 245-246^{o}C).

The above method was similarly used for the synthesis of the following 1,3-diaryl-2-thiobarbituric acids **(2a**-**d**), Table 1.

2.2.2 Synthesis of 1,3-Di(4-methylphenyl)-1,3-dihydro-2-thioxo-*2H,5H*-pyrimidine-4,6-dione (2a)

The condensation of **1a** (2.98 g, 0.01 mol) with malonic acid (1.10 g, 0.01 mol) in presence of acetyl chloride (10 mL) afforded **2a** as light yellow crystals (yield 75%), mp 262-263^{o}C (Litt mp 262-263^{o}C).

2.2.3 Synthesis of 1,3-di(2-methoxyphenyl)-1,3-dihydro-2-thioxo-*2H,5H*-pyrimidine-4,6-dione (2b)

The condensation of **1b** (2.88 g, 0.01 mol) with malonic acid (1.10 g, 0.01 mol) in presence of acetyl chloride (10 mL) afforded **2b** as light yellow crystals (yield 69%), mp 203-204^{o}C (Litt mp 203-204^{o}C).

2.2.4 Synthesis of 1,3-di(4-chlorophenyl)-1,3-dihydro-2-thioxo-*2H,5H*-pyrimidine-4,6-dione (2c)

The condensation of **1c** (2.98 g, 0.01 mol) with malonic acid (1.10 g, 0.01 mol) in presence of acetyl chloride (10 mL) afforded **2c** as light yellow crystals (yield 65%), mp 203-204^{o}C (Litt mp 206-207^{o}C).

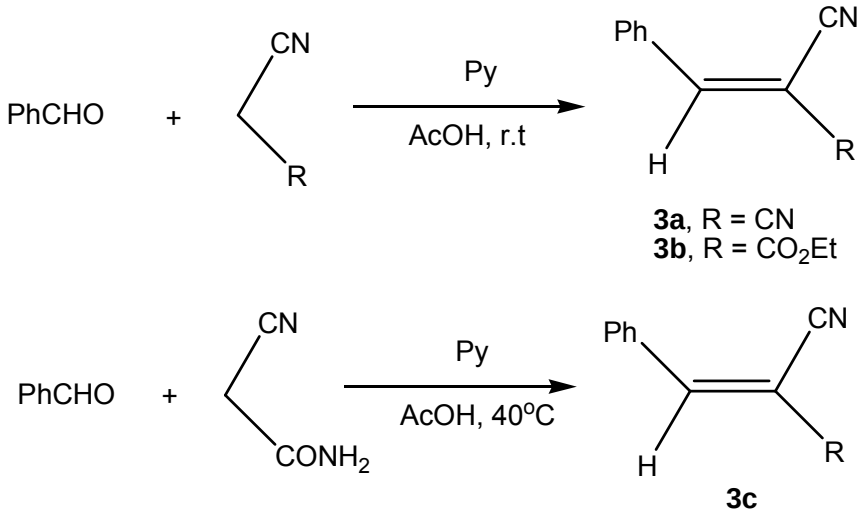
2.2.5 Synthesis of 1,3-di(2-methylphenyl)-1,3-dihydro-2-thioxo-*2H,5H*-pyrimidine-4,6-dione (2d)

The condensation of **1d** (2.98 g, 0.01 mol) with malonic acid (1.10 g, 0.01 mol) in presence of acetyl chloride (10 mL) afforded **2d** as light yellow crystals (yield 78%), mp190-192^{o}C (Litt mp191-192^{o}C).

Table 1. Characteristic data of thiobarbituric acids (2a-e)

Compounds	mp (^{o}C)	Yield (%)	Molecular formula (mol. mass)
2a	262-263	75	$C_{18}H_{16}N_2O_2S$ (324)
2b	203-204	69	$C_{18}H_{16}N_2O_4S$ (356)
2c	206-207	65	$C_{16}H_{10}N_2Cl_2O_2S$(365)
2d	190-192	78	$C_{18}H_{16}N_2O_2S$ (324)
2e	245-246	80	$C_{16}H_{12}N_2O_2S$ (296)

2.3 Synthesis of Arylidenes (3a-c)



Scheme 2. Synthesis of arylidenes (3a-c)

2.3.1 Synthesis of ethylphenylmethylene (3a)

A mixture of malononitrile (0.15 mol, 9.9 g) and benzaldehyde (0.15 mol, 15.2 mL) in glacial acetic acid (80 mL) was treated with a solution of piperidine (2 mL) in glacial acetic acid (20 mL) and allowed to stir at ambient temperature. After stirring overnight at room temperature, the reaction mixture was diluted with water (200 mL), extracted with ethyl acetate (3x200 mL), washed with water (3x200 mL) and dried (Na_2SO_4). After removal of the solvent on Rotavapor, phenylmethylenemalononitrile, **3a** was obtained as white shining crystals; mp 84-85^oC as shown in Scheme 2, Table 2; IR (KBr): 3369, 3034, 2226, 1564, 1452, 1219, 957, 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 7.91 (2H, d, *J* = 8.7 Hz, ArH), 7.79 (1H, s, CH=), 7.64 (1H, d, *J* = 8.7 Hz, ArH), 7.55 (2H, d, *J* = 8.7 Hz, ArH); ^{13}C NMR δ_C 159.66 (C=), 134.32, 130.56, 130.40, 129.50, 129.30 (ArC), 113.38 (CN), 112.22 (CN), 82.48 (CH=).

2.3.2 Synthesis of Ethylphenylmethylenecyanoacetate (3b)

A mixture of ethyl cyanoacetate (0.15 mol, 16 mL) and benzaldehyde (0.15 mol, 15.2 mL) in glacial acetic acid (5 mL) was treated with a solution of piperidine (2 mL) in glacial acetic acid (20 mL) and allowed to stir at ambient temperature. After stirring overnight at room temperature, the reaction mixture was diluted with water (200 mL), extracted with ethyl acetate (3x200 mL), washed with water (3x200 mL) and dried with a solution (Na_2SO_4). After removal of the solvent on rotavapor, ethyl phenylmethylenecyanoacetate, **3b** was obtained as white shining crystals; mp 64-65^oC; IR (KBr): 3431, 2980, 2224, 1718, 1608, 1447, 1300, 1188, 1096, 1011, 889, 851 cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 8.21 (1H, s, CH=), 7.95 (2H, d, *J* = 8.7 Hz, ArH), 7.44-7.54 (3H, m, ArH), 4.35 (2H, q, *J* = 4.6 Hz, OCH_2CH_3), 1.36 (3H, t, *J* = 4.6 Hz, OEt); ^{13}C NMR δ_C 162.55 (CO), 155.16 (C=), 133.42, 131.53, 131.17, 129.37 (ArC), 116.60 (CN), 103.05 (CH=), 62.84 (CH_2), 14.26 (CH_3).

2.3.3 Synthesis of Ethylphenylmethylenecyanoacetamide (3c)

A mixture of 2-cyanoacetamide (0.15 mol, 12.6 g) and benzaldehyde (0.15 mol, 15.2 mL) in glacial acetic acid (5 mL) was treated with a solution of piperidine (0.5 mL) in glacial acetic acid (20 mL) and allowed to stir at 40^{o}C for nearly 6 h. After stirring overnight at room temperature for 2 days, the reaction mixture was diluted with water (200 mL), extracted with ethyl acetate (3x200 mL), washed with water (3x200 mL) and dried (Na_2SO_4). Excess of the solvent was removed on rotavapor and the compound phenylmethylenecyanoacetamide, **3c** was obtained as white shining crystals; mp 119-120^{o}C; IR (KBr): 3400, 3163.4, 2220, 1693.6, 1597.1, 1373.4, 1209.4 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ_H 8.24, 7.87, 7.86, 7.48, 7.46, 7.44, 7.43, 7.41, 7.39, 6.67, 6.46.

Table 2. Characteristic data of ethylphenylmethylenearylidine (3a-c)

Compound	mp(^{o}C)	Yield (%)	Molecular formula (mol. mass)
1	84-85	95	$C_{10}H_6N_2$ (140)
3b	64-65	88	$C_{12}H_{11}NO_2$ (201)
3c	190-120	87	$C_{10}H_8N_2O$ (172)

2.4 Synthesis of Pyranopyrimidine Derivatives

2.4.1 Synthesis of 7-amino-5-phenyl-2-thioxo-1,3-di(4-methylphenyl)pyrano[2,3-*d*]pyrimidine-4(*5H*)-one (4a)

1,3-Di(4-methylphenyl)thiobarbituric acid, **2a** (0.4 g, 0.001 mol) and ethyl phenylmethylenecyanoacetate, **3b** (0.3 mL, 2.6 mol) were refluxed in the presence of NaOMe and MeOH, excess of the solvent was concentrated in a vacuum rotavapor & then purified by column chromatography using PE and EA as eluent. The product, **4a** was obtained as amorphous solid (yield = 80%, mp = 170-171^{o}C); IR (KBr): 3298, 3263, 1663, 1603, 1537, 1516, 1450, 1317, 820, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ_H 7.35 (1H, m), 7.36-7.41 (5H, m, Ar), 7.05-7.12 (3H, m, Ar), 2.36 (3H, s, Me), 2.15 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ_C 168.38, 135.32, 133.95, 129.46, 120.07, 24.50, 20.86; Mass: *m/z* 453 (Scheme 4).

The compound **4a** was also obtained by reacting 1,3-Di(4-methylphenyl) thiobarbituric acid, **2a** (0.4 g, 0.001 mol) with phenyl methylenecyanoacetamide, **3c** (0.3 mL, 2.6 mol) in the presence of NaOMe and MeOH at 120^{o}C for 6 h in an oil bath. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was concentrated in a vacuum rotavapor & then purified by column chromatography using PE and EA as eluent. The product, **4a** was obtained as amorphous solid (yield = 77%, mp = 170-171^{o}C); IR (KBr): 3298, 3263, 1663, 1603, 1537, 1516, 1450, 1317, 820, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ_H 7.35 (1H, m), 7.36-7.41 (5H, m, Ar), 7.05-7.12 (3H, m, Ar), 2.36 (3H, s, CH_3), 2.15 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ_C 168.38, 135.32, 133.95, 129.46, 120.07, 24.50, 20.86; Mass: *m/z* 453 (Scheme 5).

2.4.2 Synthesis of 7-amino-5-phenyl-2-thioxo-1,3-di(4-chlorophenyl)pyrano[*2,3-d*]pyrimidine-4(*5H*)-one (4c)

Yield : 75%; mp 232-233^{o}C; IR (KBr): 3381, 3286, 3080, 2955, 1641, 1612, 1560, 1288, 779, 704 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ_H 8.12 (1H, d, *J* = 7.6 Hz), 7.64 (1H, d, *J* = 7.6 Hz), 7.52-7.56 (5H,m, Ar), 7.34-7.49 (8H, m, Ar), 2.49 (6H, s, CH_3); ^{13}C NMR (DMSO-d_6): δ_C

195.28, 164.74, 158.51, 141.75, 132.48, 131.34, 130.36, 128.60, 128.06, 127.75, 127.39, 95.04; Mass: m/z 494.

2.4.3 Synthesis of 7-amino-5-phenyl-2-thioxo-1,3-di(2-methylphenyl)pyrano[2,3-*d*]pyrimidine-4(*5H*)-one (4d)

Yield : 75%; mp 236-237^{o}C; IR (KBr): 3381, 3286, 3080, 2955, 1641, 1612, 1560, 1288, 779, 704 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ_H 8.12 (1H, d, *J* = 7.6 Hz), 7.64 (1H, d, *J* = 7.6 Hz), 7.52-7.56 (5H,m, Ar), 7.34-7.49 (8H, m, Ar), 2.49 (6H, s, CH_3); ^{13}C NMR (DMSO-d_6): δ_C 195.28, 164.74, 158.51, 141.75, 132.48, 131.34, 130.36, 128.60, 128.06, 127.75, 127.39, 95.04; Mass: m/z 453.

2.4.4 Synthesis of 7-amino-1,3,5-triphenyl-2-thioxo-1,3-di(4-methylphenyl)pyrano[2,3-*d*]pyrimidine-4(*5H*)-one (4e)

77%; mp 185-186^{o}C; IR (KBr): 3383, 3292, 3078, 2955, 1649, 1612, 1560, 1501, 1266, 857, 777, 706 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ_H 8.14 (1H, d, *J* = 7.6 Hz), 7.65 (1H, d, *J* = 7.6 Hz), 7.54-7.61 (5H, m, Ar), 7.31-7.48 (8H, m, Ar); ^{13}C NMR (DMSO-d_6): δ_C 195.30, 164.73, 162.15, 158.52, 141.72, 132.49, 131.31, 130.38, 128.61, 128.05, 127.74, 127.40, 95.03; Mass: *m/z* 425.

2.4.5 Synthesis of 7-amino-1,3,5-triphenyl-2-thioxo-pyrano[2,3-*d*]pyrimidine-4(*1H*)-one (5e)

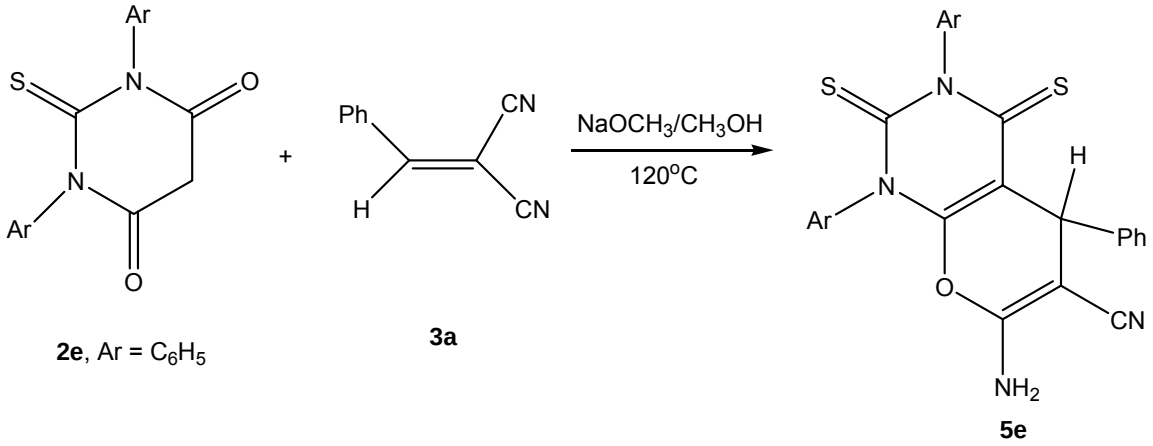
A mixture of 1,3-diphenylthiobarbituric acid (**2e**) was stirred with NaOMe in presence of methanol (1:2 mol). After stirring for ~ 15 min, phenylmethylenemalononitrile, **3a** was added to it and reflux it for 6 h at 120^{o}C in an oil bath (monitor by TLC). The crude product was extracted with $CHCl_3$ and then concentrated in a vacuum rotavapor. The crude product was then column chromatograph using PE and EA as eluent. The product, **4e** was obtained as yellow amorphous solid (yield = 78%, mp = 207-208^{o}C); IR (KBr): 3325, 3225, 2230, 1628, 1549, 1467, 1375, 1211, 989, 766 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ_H 8.14 (1H,m, 6-H), 7.52-7.65 (8H, m, Ar), 7.24-7.38 (7H, m, Ar), 4.02 (1H,m, 5-H); ^{13}C NMR (DMSO-d_6): δ_C 165.72, 160.12, 160.73, 158.91, 147.66, 142.71, 135.18, 134.01, 130.39, 130.28, 129.09, 128.64, 128.28, 128.04, 127.74, 127.67, 127.41, 126.89, 126.53, 115.42, 115.02, 83.33, 83.14, 54.73; Mass: *m/z* 450.

Table 3. Characteristic data of pyrano[2,3-*d*]pyrimidine (4a-e and 5e)

Compounds	m.p. (^{o}C)	Yield (%)	Molecular formula (mol. mass)
4a	170-171	80	$C_{27}H_{23}N_3O_2S$ (453)
4c	232-233	75	$C_{25}H_{17}N_3O_2SCl_2$ (494)
4d	236-237	75	$C_{27}H_{23}N_3O_2S$ (453)
4e	185-186	77	$C_{25}H_{19}N_3O_2S$ (425)
5e	207-208	78	$C_{26}H_{18}N_4O_2S$ (450)

3. RESULTS AND DISCUSSION

The reaction of 1,3-diarylthiobarbituric acids **2** with arylidene **3** and sodium methoxide in presence of methanol by refluxing for 6 h afforded pyrano[2,3-*d*]pyrimidines **4** and **5** in 70-82% overall yields (Scheme 3-5, Table 3).



2e, Ar = C_6H_5 **3a** **5e**

Scheme 3. Synthesis of 7-amino-1,3,5-triphenyl-2-thioxo-pyrano[2,3-*d*]pyrimidine-4(*1H*)-one (5e)

The proposed reaction mechanism for the formation of pyranopyrimidine **5** is shown in figure 1.

When **2e** was treated with phenylmethylenemalononitrile at 120°C in presence of sodium methoxide and methanol, the substituted pyrano[2,3-*d*]pyrimidine **5e** was obtained as yellow amorphous solid with 78% yield (Scheme 3). The reaction was also effective when potassium hydroxide in presence of ethanol and piperidine was used but gave lower yields. The IR spectrum of **5e** showed peaks at 3325, 3225 cm^{-1} due to NH_2 stretching frequency at 2230 and 1628 cm^{-1} due to CN and CO stretching frequencies, respectively. Its ^1H NMR spectrum displayed signals at δ_H 8.14 (1H), 4.02 (NH_2) and aromatic protons as multiplets at δ_H 7.52-7.65 and 7.24-7.38.

The reaction of **2e** with phenylmethylenecyanoacetamide, **3c** at 120°C in presence of sodium acetate and methanol afforded **4e** as yellow amorphous solid with 77% yield (Scheme 5). The IR spectrum of **4e** showed peaks at 3383, 3292 cm^{-1} due to NH_2 and 1649 cm^{-1} due to carbonyl stretching frequencies, respectively. Its ^1H NMR spectrum displayed signals at δ_H 8.14 (1H, d), 7.65 (1H, d) and aromatic protons as multiplets at δ_H 7.54-7.61 and 7.31-7.48.

Similarly, when **2a** was treated with phenyl methylenecyanoacetamide**, 3c** at 120°C in presence of sodium methoxide and methanol, **4a** was obtained as amorphous solid with 77% yield, the product was found to be same as obtained by the reaction of **2a** with ethyl phenylmethylene cyanoacetate, **3b**. And the reaction of **2d** with phenylmethylenecyanoacetamide, **3c** under similar reaction conditions gave **4d** in 75% yield (**Scheme 5**).

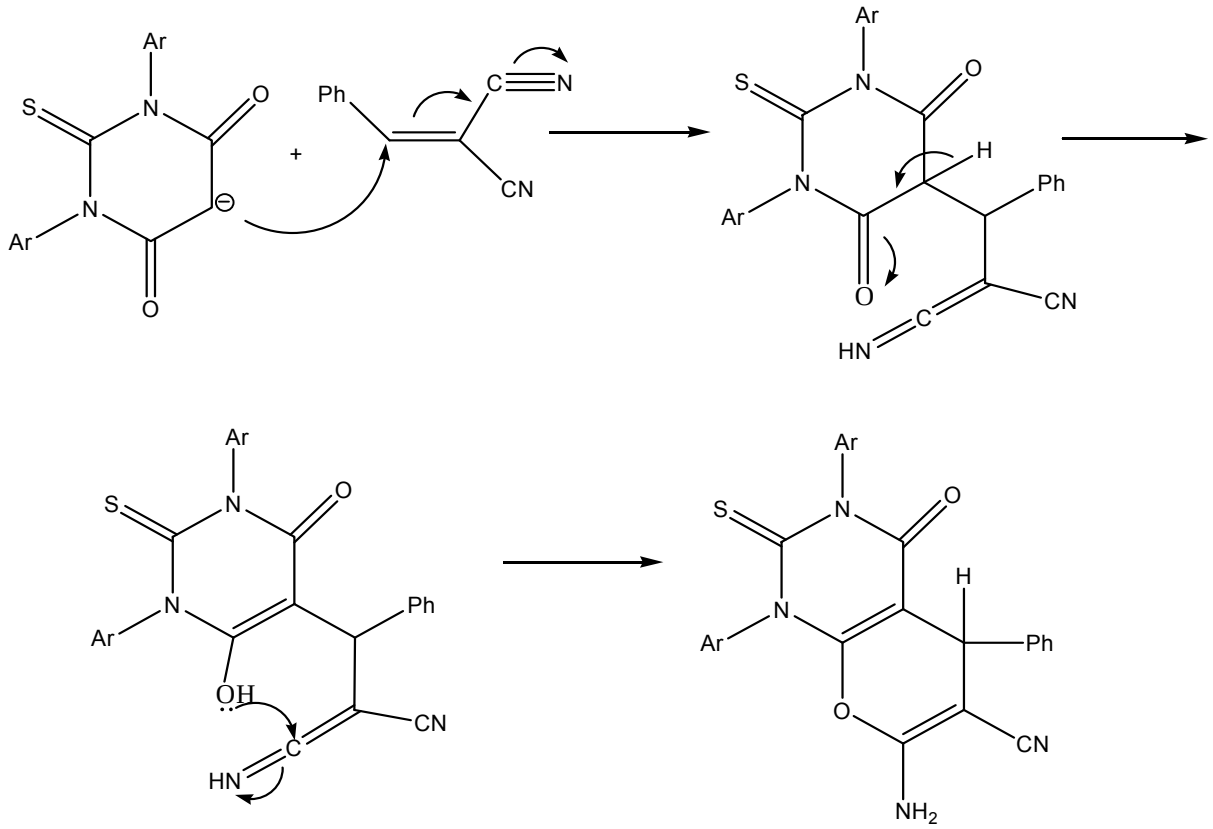
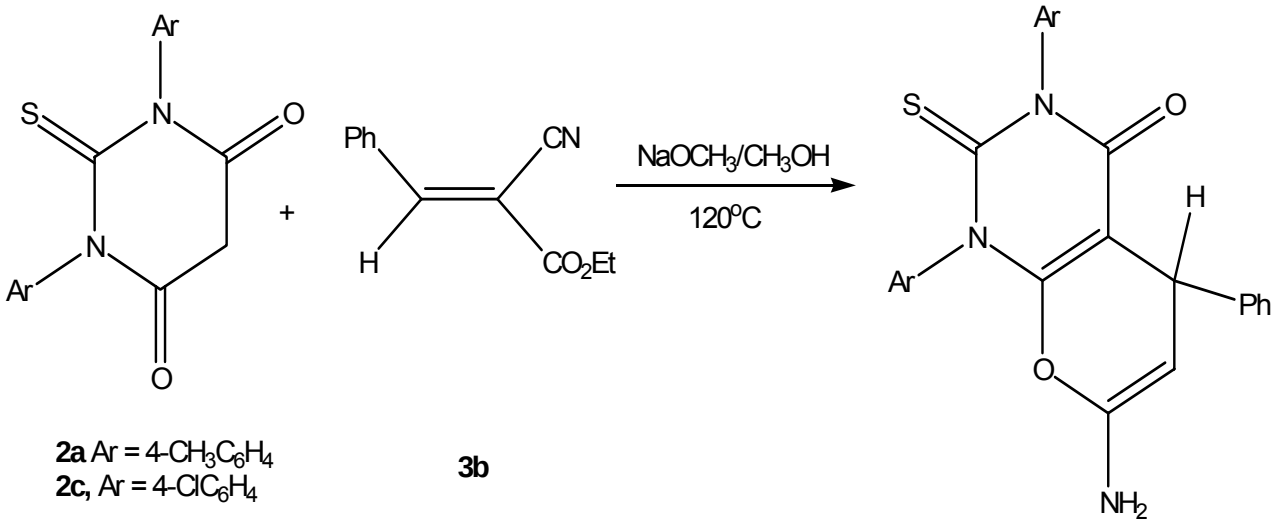


Fig. 1. Proposed reaction mechanism for the formation of 7-amino-1,3,5-triphenyl-2-thioxo-pyrano[2,3-*d*]pyrimidine-4(*1H*)-one (5)

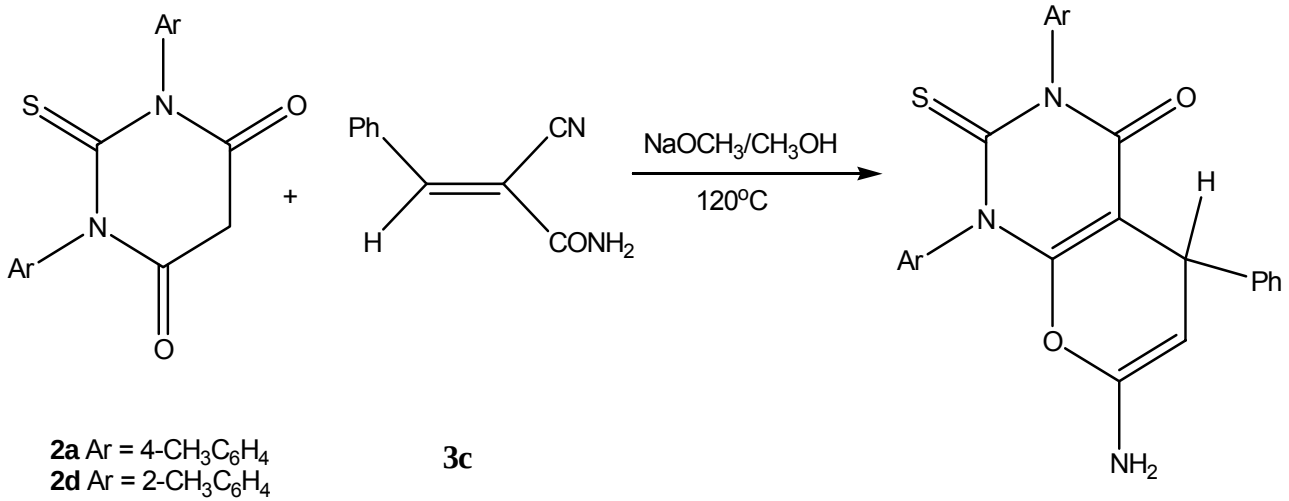


2a Ar = 4-$CH_3C_6H_4$
2c, Ar = 4-ClC_6H_4

3b

4a Ar = 4-$CH_3C_6H_4$
4c, Ar = 4-ClC_6H_4

Scheme 4. Synthesis of pyranopyrimidine derivatives (4a and c)



2a Ar = 4-$CH_3C_6H_4$
2d Ar = 2-$CH_3C_6H_4$
2e Ar = C_6H_5

3c

4a Ar = 4-$CH_3C_6H_4$
4d Ar = 2-$CH_3C_6H_4$
4e Ar = C_6H_5

Scheme 5. Synthesis of pyranopyrimidine derivatives (4a, d and e)

4. CONCLUSION

In the cyclocondensation of thiobarbituric acids having active methylene compounds under the catalytic system with arylidenes, a new conversion to form pyrano[2,3-*d*]pyrimidine takes place.

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