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Enamines as a precursor for synthesized of some azoles and azines with expected biological activity

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ABSTRACT

Pyrimidinthione **(3)** and pyridinthione derivative **(4)** are obtained from the reaction of enamine **(1)** with benzoyl isothiocyanate. Condensation of compound **(3)** with ethyl acetate afforded quinoxaline derivative **(6)**. pyridinothiothiazole **(7)** was prepared by the reaction of compound **(4)** with sodium hypochloride. Alkylation of compound **(4)** with chloro acetic acid yielded thienopyridine **(9)**. Condensation of 4 with diethyl oxalate afforded pyridopyridine derivative **(11)**. heterocyclo condensation of benzylidene cyanoacetamide derivative and enamine **(1)** yielded hydroxypyridene **(12)**. Addition of benzylidene malononitrile to enamine **(1)** yielded 4H-pyridone **(13)**. Compound **(1)** was reacted with potassium isothiocyanate affording oxathiazol **(15)** and with ethyl cyano acetate afforded pyridinone derivative **(16)**. The structures of the new products were confirmed on the basis of elemental and spectral data. Some of the synthesized compounds were screened as antibacterial and antifungal.

KEYWORDS

Pyrimidinthione;
Pyridinthione;
Quinoxaline;
Pyridinothiothiazole;
Thienopyridine;
Pyridopyridine.

INTRODUCTION

β-B-Enaminone derivatives[1-9] useful synthetic precursors[10,11] and their utilisation in organic synthesis is of great interes[12,13] due to the presence of the nucleophilic character of the enamine moiety and the electrophilic character of the enone moiety.

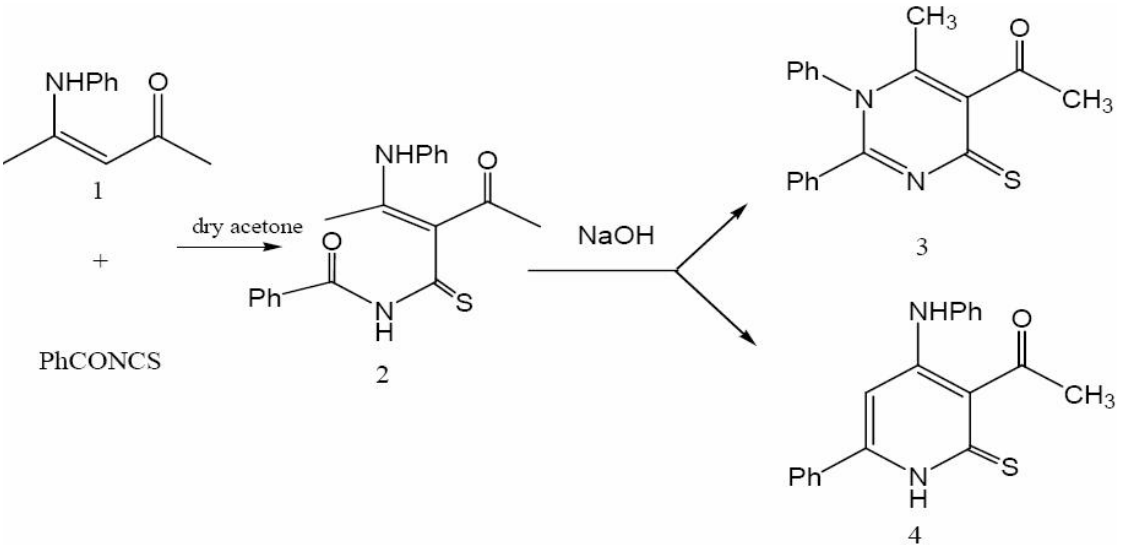
RESULTS AND DISCUSSION

When enamine **(1)** was allowed to react with benzoylisothicyanate afforded the acyclic compound **(2)**. cyclization of compound **(2)** was achieved by refluxing in alcholic sodium hydroxide to afford pyrimidinthione **(3)** via the attack of nucleophilic nitrogen to the electrophilic carbonyl group. Also pyridinthione **(4)** was also obtained via the attack of nucleophlilc enaminic carbon to the carbonyl group (scheme 1).

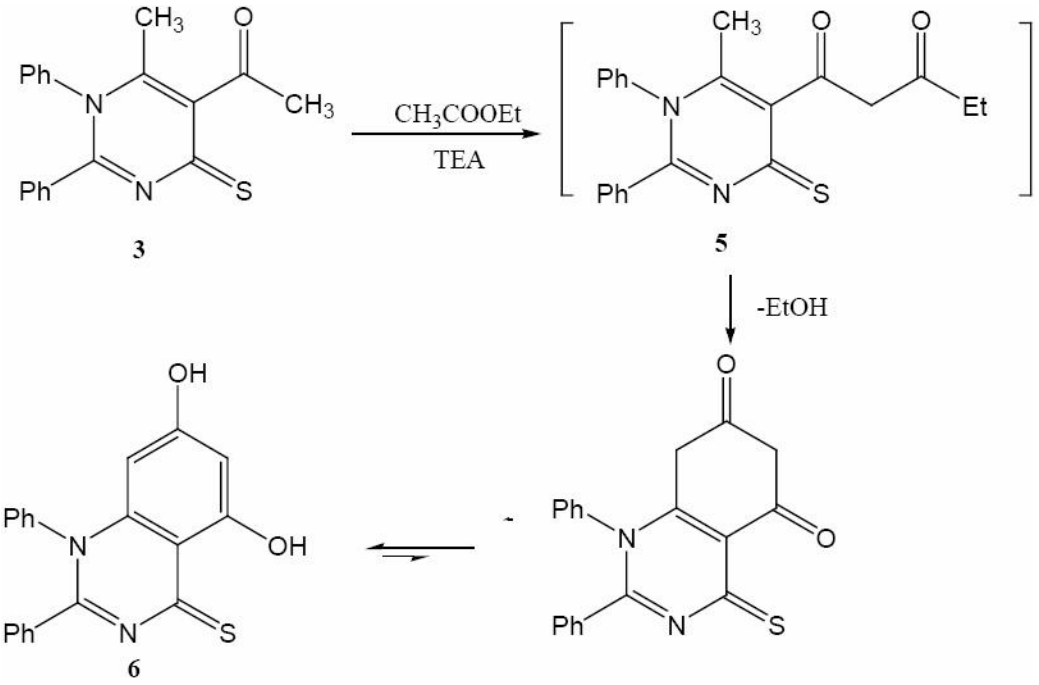
Condensation of acetylpyrimidinthione **(3)** with ethyl acetate in the presence of triethylamine (TEA) afforded quinoxaline **(6)** presumably via the formation of nonisolable ester derivative **(5)** that undergo intramolecular cyclocondensation affording **(6)**. (Scheme 2, Scheme 3 and Scheme 4)

The reaction of pyridinthione **(4)** with sodium hypo chloride NaOCl in the presence of NaOH /NH_4OH afforded thiazolopyridine derevative **(8)** presumably via the formation of nonisolable sulfenamide **(7)** followed by intermolecular cyclodehydration. Alkylation of compound **(4)** with chloroacetic acid yielded thienopyridine

derivative **(9)**. Condensation of acetylpyridine **(4)** with diethyl oxalate afforded pyridopyridine derivative **(11)** via the ester **(10)** that undergo hydrolysis followed by decarboxylation.



Scheme 1



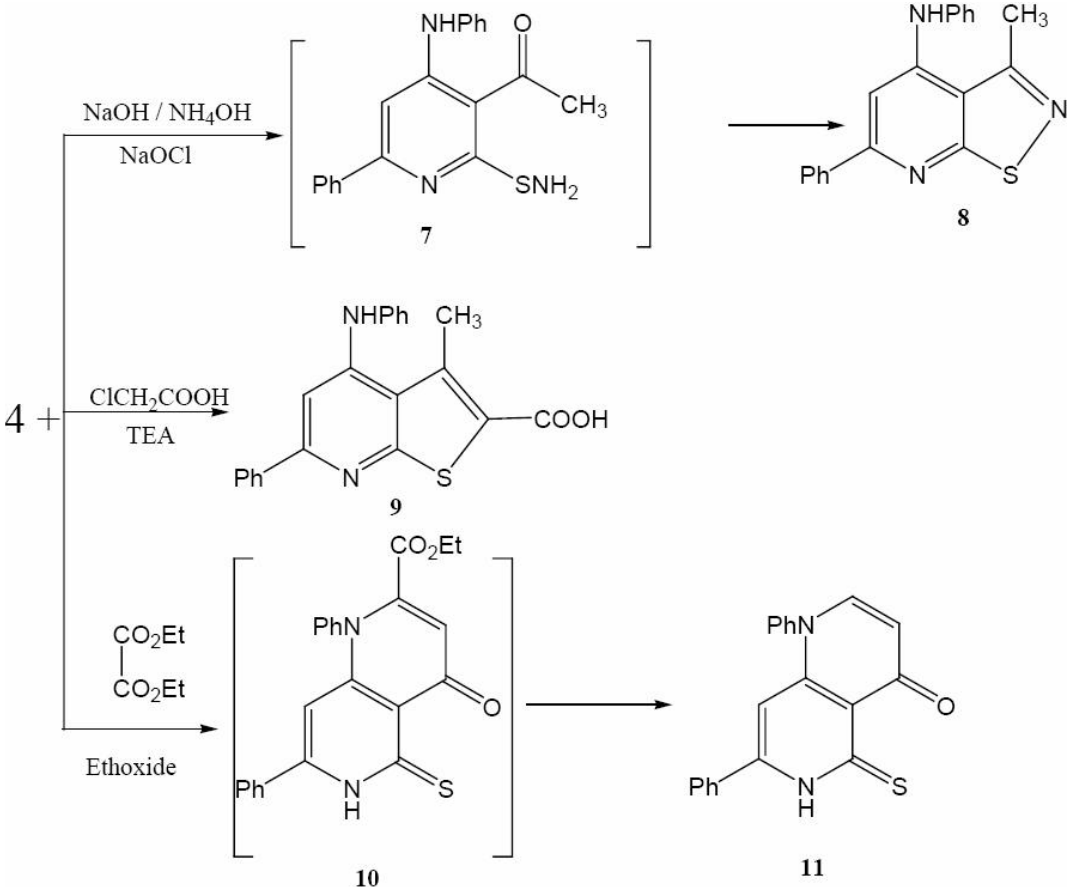
Scheme 2

Base induced heterocycloaddition of benzylidene cyano acetamide derivative and enamine **(1)** yielded hydroxypyridine 12. While addition of benzylidene malononitrile to enamine **(1)** yielded 4-H- pyridine **(13)** instead of amino cyanopyridine 14. Enamine **(1)** was reacted with potassium isothiocyanate in the presence of bromine to produce oxathiazol derivative **(15)**. Condensation of enamine **(1)** with ethyl cyanoacetate produces pyridinone **(16)**.

ANTIMICROBIAL ACTIVITY

The different synthetic compounds were dissolved at a concentration of 100 mg/ 10 ml in dimethyl foramide (DMF) in order to obtain a final concentration of 10 mg/ 1 ml. Czepak Dox media used for cultivation of fungal species. The medium was seeded with different fungal species. After solidification of media on plates,

make pores in agar with cup porer (10 mm) diameter. Then 0.1 ml of concentration (10 mg / 1 ml) of the different synthetic compounds was transferred into the well. Dimethyl foramide (DMF) was used as a control. The plates were incubated for 5 days at 30 °C. The inhibition zone formed by the tested compounds against the particular test fungal strain determined as the anti-fungal activities of the different tested compounds.



Scheme 3

Aloopfull of the given bacterial strain was inoculated into 25ml of N-broth (Nutrient Broth) and incubated for 24 hrs. in an incubator at 30 °C in order to activate the bacterial strain. Apetri-dish of 15 cm diameter was filled with 100 ml of nutrient agar media. Inoculation was performed by the Pour-plate technique. 0.2 ml of the activated strain was inoculated into the media when it had reached a temperature of 40–45 °C. The complete procedure of the ditch preparation was done in a laminar airflow to maintain strict sterile and aseptic condition. The media was allowed to solidify. After solidification of the media, a pore was made in the media with the help of a cup-borer (10 mm) and then 0.1 ml of concentration (10 mg / 1 ml) of the different tested compounds was transfered into the well. Di methyl foramide (DMF) was used as a control. The plates were incubated for 24 hrs. at 30 °C. The inhibition zone formed by the synthetic compounds against the particular test bacterial strain determined the antibacterial activities of the different tested compounds[14]

It clearly observed from the obtained data in TABLE 1, compound **(7)** and **(13a)** showed higher antibacterial activity against Gram (+ve) (Bacillus subtilis) and weak activity against (Escherichia coli) Gram (-ve) using well diffusion method[14]. Compounds **(13b)**, **(15)**, **(3)**, **(12)**, **(4)**, **(9)**, **(6)**, **(10)** and **(16)** were showed weak and moderate activity against Gram (+ve) and Gram (-ve). For antifungal activity, it was observed that most of the tested compounds have no antifungal activity against (Asperigillus aryzea) and moderate activity against (Fusarium oxysporum), as shown in TABLE 1.

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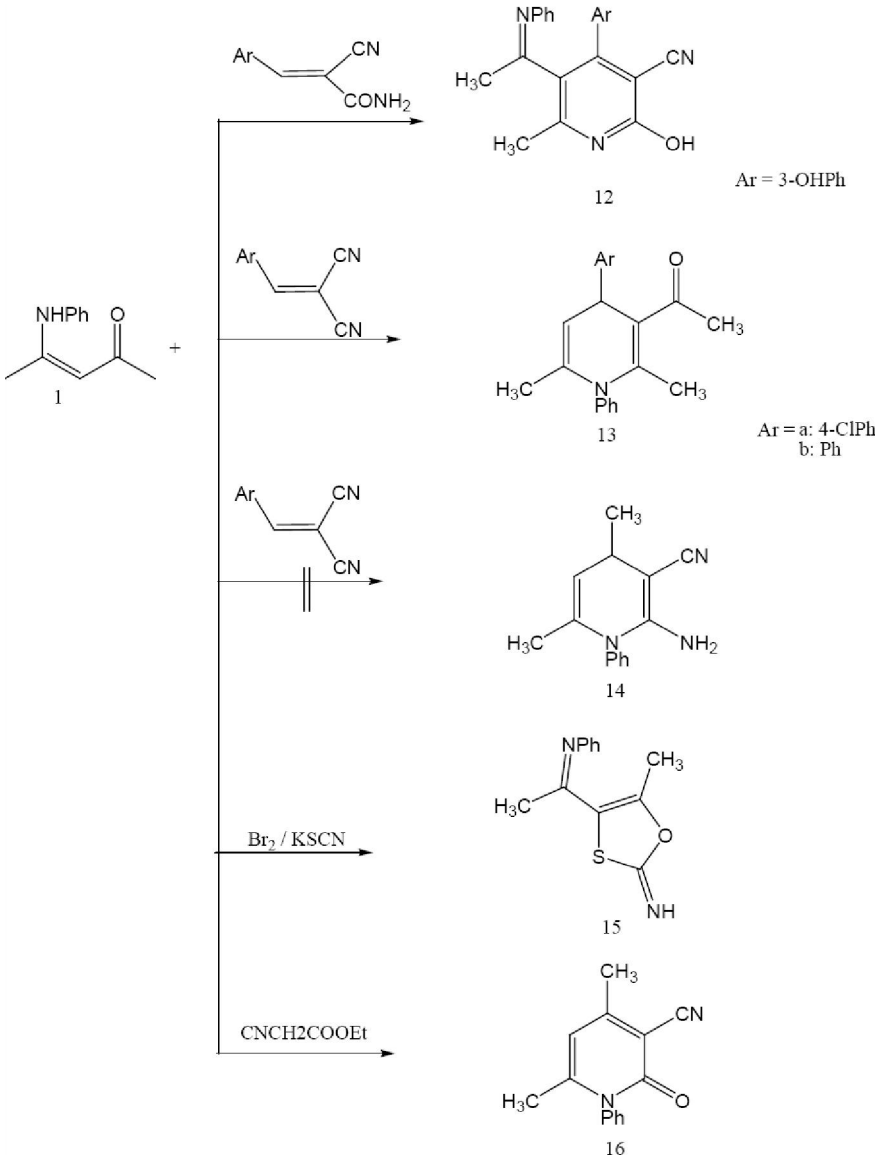

Scheme 4

TABLE 1 : Antimicrobial activity of the compounds considered

Compound*	** Microorganisms			
	Escherichia Coli	Bacillus Subtilis	Aspergillus Oryzae	Fusarium Oxysporum
3	4	15	-	-
4	10	20	10	16
6	5	25	-	2
7	5	26	-	16
9	5	18	15	10
10	11	10	15	8
12	18	22	-	8
13a	5	26	-	15
13b	15	18	-	11
16	8	20	4	11

EXPERIMENTAL

General

Melting points are uncorrected and were recorded on Buchi 510 apparatus. IR spectra were recorded as KBr disks on a perkin-Elmer 383 spectrometer and FTIR-spectrometer Nicolet, impact 400.^{1}H -NMR spectra was recorded on a Varian Mercury Plus-400 or Bruer-300.

1-(1, 4-Dihydro-6-methyl-1, 2-diphenyl-4-thioxo-pyrimidin-5-yl) ethanone (3)

To a mixture of compound **(1)** (0.01 mole) and

benzoylisothiocyanate (0.01 mole) in dry acetone (20 ml) is added upon stirring for two hours at room temperature. The separated solid is boiled in NaOH filtrated, dried and crystallized from acetic acid to give yellow crystals of 3. M.p. 310-312. IR ((cm^{-1}, ν): 3052, 1706, 1608, 1588, 1366 (Ar,C=O, C=C, C=N, CH_3); ^{1}H NMR (DMSO-d6, δ, ppm): 7.25-7.52(m, 10H, ArH), 2.45-2.54(2s, 6H, $2CH_3$). Anal. Calcd for ($C_{19}H_{16}N_2OS$, 320.1): C, 71.22; H, 5.03; N, 8.74. Found: C, 71.02; H, 4.96; N, 8.96.

1-(1, 2, 5, 6-Tetrahydro-6-phenyl-4-(phenylamino)-2-thioxopyridin-3-yl) ethanone (4)

To a mixture of compound **(1)** (0.01 mole) and benzoylisothiocyanate (0.01 mole) in dry acetone (20 ml) is added upon stirring for two hours at room temperature. The separated solid is boiled in NaOH filtrated, The separated solid formed upon acidification with HCl (10 ml, 20%) and dilution with water is filtered, dried and crystallized from benzene to give light yellow crystals of **(4)**. M.p.166-168. IR (cm^{-1}, ν): 3423, 3175, 1692, 1610, 1588, 1313 (NH, Ar, C=O, C=C, C=N, CH_3); ^{1}H NMR (DMSO-d6, δ, ppm): 9.62, 8.94 (2s, 2H, 2NH), 7.16-7.42 (m, 10H, ArH), 2.45-2.53 (2s, 6H, $2CH_3$). Anal. Calcd for ($C_{19}H_{18}N_2OS$, 322.4): C, 70.78; H, 5.63: N, 8.69. Found: C, 70.72: H, 5.34: N, 8.65.

5, 7-Dihydroxy-1,2-diphenylquinazoline-4(1H)-thione (6)

To a mixture of compound 3 (0.01 mole), ethyl acetate (0.01 mole) and TEA (3 drop) is fused for one hour at 120 ^{0}C. The solid obtained is crystallized from acetic acid to give brown crystals **(6)**. M.p. >360. IR ((cm^{-1}, ν): 3343, 3052, 1655, 1599, 1366 (OH, Ar, C-O, C=C, C=N, CH_3); ^{1}H NMR (DMSO-d6, δ, ppm): 12.00 (2s, 2H, 2OH), 7.26-7.54 (m, 10H, ArH), 4.3 (s, 1H, CH). Anal. Calcd for ($C_{20}H_{14}N_2O_2S$, 346.4): C, 69.35: H, 4.07: N, 8.09. Found: C, 69.53: H, 4.21: N, 8.15.

3-Methyl-N-6-diphenylisothiazolo [5,4-b] pyridin-4-amine (8)

To a mixture of compound **(4)** (0.01 mole) and NaOCl (0.01 mole) in NH_4OH / NaOH (20 ml) is added upon stirring for four hours at room temperature. The separated solid formed upon acidification with hydrochloric acid (10 ml, 20%) and dilution with water is filtered, dried and crystallized from acetic acid to give brown crystals of **(8)**. M.p. >360 IR (cm^{-1}, ν): 3424, 3052, 1610, 1565, 1493(NH, Ar, C=C, C=N, CH_3); ^{1}H NMR (DMSO-d6, δ, ppm): 9.74 (s, 1H, NH), 7.24-7.52 (m, 10H, ArH), 2.43 (s, 3H, CH_3). Anal. Calcd for ($C_{19}H_{15}N_3S$, 317.14): C, 71.90; H, 4.76; N, 13.24. Found: C, 71.86; H, 4.73; N, 13.23.

5 , 6-Dihydro-3-methyl-6-phenyl-4-(phenylamino)-thieno[2,3-b]pyridine-2-carboxylic acid (9)

A mixture of compound **(4)** (0.01 mole), chloro acetic acid (0.01 mole) and ethoxide (0.01 mole) in ethanol (20 ml) is refluxed for six hours. The separated solid formed upon acidification with HCl (10 ml, 20%) and dilution with water (20 ml) is filtered, dried and crystallized from acetic acid to give brown crystals of **(9)** M.p. 204-206. IR (cm^{-1}, ν) : 3424,3274, 3052, 1680,1605,1568, 1402 (OH, NH, Ar, C=O, C=C, C=N, CH_3); ^{1}H NMR (DMSO-d6, δ, ppm) : 11.72 (s, 1H, OH), 11.14(s, 1H, NH), 7.25-7.54 (m, 10H, ArH), 4.32 (s,1H,CH), 2.41 (s, 3H, CH_3). Anal. Calcd for ($C_{21}H_{11}N_2OS$, 360.4): C, 72.70; H, 4.27; N, 8.48. Found: C, 72.73; H, 4.02; N, 8.51.

5, 6-Dihydro-1,7-diphenyl-5-thioxo-1,6-naphthyridin-4(1H)-one (11)

A mixture of compound **(4)** (0.01 mole), diethyl oxalate (0.01 mole) and ethoxide (0.01 mole) in ethanol (20 ml) is refluxed for six hours. The separated solid formed upon acidification with HCl (10 ml, 20%) and dilution with water (20 ml) is filtered, dried and crystallized from acetic acid to give brown crystals of **(11)**. M.p. IR (cm^{-1}, ν) : 3190, 3052, 1692, 1637, 1593, 1366 (NH, Ar, C=O, C=C, C=N, CH_3); ^{1}H-NMR (DMSO-d6, δ, ppm): 8.71 (s,1H, NH), 7.12-7.35 (m, 10H, ArH's), 4.84 (2s,2H, CH=CH), 4.12 (s,1H, CH). Anal. Calcd for ($C_{20}H_{14}N_2OS$; 330.4): C, 72.70; H, 4.27; N, 8.84. Found: C, 72.69; H, 4.13; N, 8.76.

2-Hydroxy-4-(3-hydroxyphenyl)-6-methyl-5-(1-(phenylimino) ethyl)pyridine-3-carbonitrile (12)

A mixture of compound **(1)** (0.01 mole) and (E)-2-cyano-3-(3-hydroxyphenyl) acrylamide (0.01 mole) in ethanol (20 ml) is refluxed for six hours. The separated solid formed upon dilution with water (20 ml) is filtered, dried and crystallized from ethanol to give brown

crystals of **(12)**. M.p.210-212. IR (cm^{-1}, ν): 3340, 3080, 2213, 1610, 1569, 1453(OH, Ar, CºN, C=C, C=N, CH_3; ^1H NMR (DMSO-d6, δ, ppm): 9.14 (2s, 2H, 2OH), 7.21-7.54 (m, 10H, ArH), 2.41-2.52 (2s, 6H, $2CH_3$). Anal. Calcd for ($C_{21}H_{17}N_3O_2$, 343.38):C, 73.45; H, 4.99; N, 12.24. Found: C, 73.33; H, 4.92; N, 12.16.

1-(1, 4-dihydro-2,6-dimethyl-1,4-diphenylpyridin-3-yl)ethanone (13a)

A mixture of compound **(1)** (0.01mole) and 2-benzylidene-malononitrile (0.01 mole) in ethanol (20 ml) is refluxed for six hours. The separated solid formed upon dilution with water (20 ml) is filtered, dried and crystallized from ethanol to give red crystals of **(13a)**. M.p. 218-223. IR (cm^{-1}, δ): 3052, 1699, 1615, 1575, 1455 (Ar, C=O, C=C, C=N, CH_3); ^1H NMR (DMSO-d6, δ, ppm): 7.21-7.42 (m, 10H, ArH's), 5.24 (s, 4H, CH_2 pyridene), 2.41-2.52 (2s, 6H, $2CH_3$). Anal. Calcd for ($C_{21}H_{21}NO$, 303.4): C, 83.13; H, 6.98; N, 4.62. Found: C, 83.06; H, 6.91; N, 4.53.

1-(4-(4-chlorophenyl)-1, 4-dihydro-2, 6-dimethyl-1-phenylpyridin-3-yl)ethanone (13b)

A mixture of compound **(1)** (0.01mole) and 2-(4-chlorobenzylidene) malononitrile (0.01 mole) in ethanol (20 ml) is refluxed for six hours. The separated solid formed upon dilution with water (20 ml) is filtered, dried and crystallized from ethanol to give red crystals of **(13b)**. M.p. 234-236. IR (cm^{-1}, ν):3052, 1699, 1651, 1548, 1455 (Ar, C=O, C=C, C=N, CH_3); ^1H NMR (DMSO-d6, δ, ppm): 7.21-7.54 (m, 10H, ArH's), 5.25 (s, 2H, CH_2), 2.42-2.51 (2s, 6H, $2CH_3$). Anal. Calcd for ($C_{21}H_{20}NClO$, 337.12): C, 74.60; H, 5.97; N, 4.15. Found: C, 74.53; H, 5.94; N, 4.23.

N-(1-(2-Imino-5-methyl-1, 3-oxathiol-4-yl)ethylidene)benzenamine (15)

A mixture of compound **(1)** (0.0l mole), potassium thiocyanate (0.01 mole) and Br_2 in ethanol (20 ml) is stirred for four hours at room temperature and refluxing for 1 hour. The separated solid diluted with water (40 ml) is filtered, dried and crystallized from butanol to give brown crystals of **(15)**. M.p. 170-172. IR (cm^{-1}, ν): 3292, 3052, 1680, 1610, 1597, 1455 (NH, Ar, C=O, C=C, C=N, CH_3); ^1H NMR (DMSO-d6, δ, ppm): 7.21-8, 00 (m, 6H, ArH+ NH), 2.41-2.52 (2s, 6H, $2CH_3$). Anal. Calcd for ($C_{12}H_{12}N_2OS$, 232.3): C, 62.24; H, 5.21; N, 12.06. Found: C, 62.36; H, 5.29; N, 12.29.

1,2-Dihydro-4, 6-dimethyl-2-oxo-1-phenylpyridine-3-carbonitrile (16)

To a mixture of compound **(1)** (0.01 mole), ethyl cyano acetate (0.01 mole) and TEA (3 drop) is fused for one hour at 120 ^{0}C. The solid obtained is crystallized from ethanl to give brown crystals **(16)**. M.p.154-156. IR (cm^{-1}, ν): 3445, 3052, 2218, 1732, 1634, 1575, 1435(Ar, C=N, C=O, C=C, C=N, CH_3); 1H-NMR (DMSO-d6, δ, ppm): 7.21-7.52 (m, 5H, ArH), 2.41-2.52 (2s, 6H, $2CH_3$). Anal. Calcd for ($C_{14}H_{12}N_2O$, 224.26): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.93; H, 5.21; N, 12.13.

REFERANCES

[1] X.Chen, J.She, Z.C.Shang, J.Wu, P.Z.Zhang; Synth.Commun., **39**, 947 **(2009)**.

[2] M.R.Mohammadizadeh, A.Hasaninejad, M.Bahramzadeh, Z.S.Khanjarlou; Synth.Commun., **39**, 1152 **(2009)**.

[3] J.X.Chen, X.L.Yang, M.C.Liu, H.Y.Wu, J.C.Ding, W.K.Su; Synth.Commun., **39**, 4180 **(2009)**.

[4] B.Giuseppe, B.Marcella, L.Manuela, M.Enrico, M. Paolo, S.Letizia; Synlett., 239 **(2004)**.

[5] B.Datta, M.B.M.Reddy, M.A.Pasha; Synth. Commun., **41**, 2331 **(2011)**.

[6] M.K.Samantaray, C.Dash, M.M.Shaikh, K.L.Pang, R.J.Butcher, P.Ghosh; Inorg.Chem., **50**, 1840 **(2011)**.

[7] Z.H.Zhang, T.S.Li, J.J. Li; Catal.Commun., **8**, 1615 **(2007)**.

[8] Z.H.Zhang, Z.C.Ma, L.P.Mo; Indian J.Chem., **46**, 535 **(2007)**.

[9] Z.H.Zhang, J.Y.Hu; J.Braz.Chem.Soc., **17**, 1447 **(2006)**.

[10] Z.H.Zhang, L.M.Song; J.Chem.Res., 817 **(2005)**.

[11] A.Z.A.Elassar, A.A.El-Khair; Tetrahedron, **59**, 8463 **(2003)**.

[12] B.Stanovnik, J.Svete; Chem.Rev., **104**, 2433 **(2004)**.

[13] C.Reidlinger, R.Dworczak, H.Junk; Monatsh. Chem., **129**, 1207 **(1998)**.

[14] W.F.Bow, A.K.Basak, D.A.Vicic, M.A.Tius; Org.Lett., **12**, 440 **(2010)**.

[15] Y.Vaghasiya, R.Nair, S.Chanda; J.Phamacol., **3**, 400-405 **(2007)**.