An Efficient One-Pot Three-Component Synthesis of 4-Phenyl hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one Derivatives

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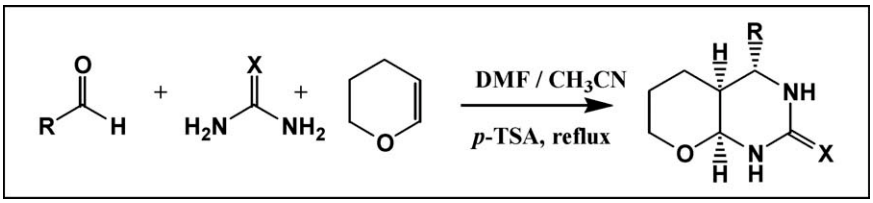
Received November 5, 2009
DOI 10.1002/jhet.379
Published online 11 May 2010 in Wiley InterScience (www.interscience.wiley.com).



An efficient method for the synthesis of a series of 4-phenylhexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one derivatives via the one-pot three-component reaction of aromatic aldehydes, urea or thiourea and 3,4-dihydro-2*H*-pyran in DMF/CH_3CN using *p*-TSA catalyst is described. Although three chiral centers are created, only one diastereomer is formed in a highly selective way. This method has several advantages such as higher yield, lower cost, and shorter reaction times.

J. Heterocyclic Chem., **47**, 687 (2010).

INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry [1]. In times, where a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses [2]. The synthesis of dihydropyrimidinones using variants of the well-established Biginelli reaction is one of the most recognized and often used MCRs for the generation of novel pyrimidine scaffolds [3]. Most notably are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors [4]. There is a widespread interest in the synthesis of pyranopyrimidinones and related fused ring pyrimidinones with diverse range of biological properties [5], such as antitumor, antibacterial, antihypertensive, vasodilator, bronchiodilator, hepatoprotective, cardiotonic, and antiallergic activities. Some of them also exhibit antimalarial, antifungal, analgesics, and herbicidal properties [6]. Recently, modified Biginelli reaction has been used in accessing fused pyrimidinones or spiro-fused pyrimidinones [3e,3f]. Recently, Wu and coworkers [7] reported a TMSCl catalyzed three-component diastereoselective reaction of 3,4-dihydro-(2*H*)-pyran with urea/thiourea and aromatic aldehydes to give respective 4-phenyl hexahydro-*1H*-pyrano[2,3-*d*] pyrimidin-2(8a*H*)-ones (thiones). In continuation of our previous work on the synthesis of heterocyclic compounds [8], we wish to report an efficient one-pot three-component method for the preparation of substituted 4-phenyl hexahydro-*1H*-pyrano[2,3-*d*] pyrimidin-2(8a*H*)-one derivatives using *p*-TSA as catalyst in DMF/CH_3CN under reflux conditions. This method not only preserved the simplicity of Biginelli type one-pot condensation but also remarkably improved the yields of the pyrimidin-2-one derivatives in shorter reaction times (5–6 h) as against the longer reaction times required for the other catalysts (e.g., TMSCl).

RESULTS AND DISCUSSION

Initially, we subjected the condensation of 4-fluoro benzaldehyde with urea and 3,4-dihydro-2*H*-pyran in the presence of various acid catalysts in different solvent systems at room temperature as well as under reflux conditions (Table 1). The best yield (95%) of product 4-(4-flurophenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8 a*H*)-one **4g** was obtained when *p*-TSA was used as catalyst in DMF/CH_3CN (1:1) under reflux conditions (entry 4, Table 1). The formation of product **4g** was confirmed by IR, ^1H, ^{13}C, and mass spectral analysis. Although theoretically three chiral centers are created, only one diastereomer was formed in a highly selective way. To access the stereochemistry of the product, we chose 4-methylbenzaldehyde as substrate and reacted with urea and 3,4-dihydro-2*H*-pyran in DMF/CH_3CN (1:1) using *p*-TSA under identical reaction conditions. NMR spectral data determined the product as 4-(4-methylphenyl)hexa hydro-*1H*-pyrano [2,3-*d*]pyrimidin-2(8a*H*)-one **4a**. The spectral data obtained was closely identical to the literature reported [7], X-ray analyzed, diasteroselective product **4a**.

Table 1

Catalyst effect on the reaction of 4-fluorobenzaldehyde, urea, and 3,4-dihydro-2*H*-pyran.

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	Montmorillonite K10	DMF/CH_3CN	Reflux	10	45
2	PPA-SiO_2	DMF/CH_3CN	Reflux	10	No reaction
3	PPA-SiO_2	Solvent free	120	10	No reaction
4	*p*-TSA	DMF/CH_3CN	Reflux	5.2	95
5	TMSCl/NaI	CH_3CN	Reflux	10	62
6	Silica sulfuric acid	DMF/CH_3CN	Reflux	10	35
7	$HCLO_4$-SIO_2	DMF/CH_3CN	Reflux	10	35
8	*p*-TSA	DMF/CH_3CN	r.t.	24	15–20
9	Montmorillonite K10	DMF/CH_3CN	r.t.	24	No reaction

Because of its great facility and easy availability of catalyst, we further proceeded to examine the scope of this catalytic transformation. The reaction of 3,4-dihydro-2*H*-pyran with a range of other aromatic, and heterocyclic aldehydes and urea/thiourea under similar conditions using *p*-TSA, furnishing the respective pyrimidin-2-one derivatives **4a–4l** (Scheme 1) in excellent yields. The optimized results are listed in Table 2. All the products were fully characterized by IR, NMR, and Mass spectroscopic analysis. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. A variety of substituted aromatic heterocyclic aldehydes carrying either electron donating or withdrawing substituents afforded high yields of products in high purity. Thiourea has also been used with similar success to provide corresponding pyrimidin-2-thione derivatives, which are also of much interest with regard to the biological activity [9].

In summary, we have developed an economically and environmentally friendly procedure for the synthesis of substituted 4-phenylhexahydro-*1H*-pyrano[2,3-*d*] pyrimidin-2(8a*H*)-ones (thiones) derivatives with excellent yields and short reaction times, which involves the use of inexpensive catalyst *p*-TSA under DMF/CH_3CN reflux conditions. Furthermore, the present procedure is readily amenable to parallel synthesis and generation of combinatorial DHPMs libraries.

EXPERIMENTAL

All reagents were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on Varian FT-200/50 MHz (Gemini) and Bruker UX NMR FT-300/75 MHz (Avance) instruments, in deuterated dimethylsulfoxide [D6]-DMSO. Chemical shifts are reported in parts per million relative to TMS as internal standard. LC-mass spectra were recorded on a LC-MSD-Trap-SL mass spectrometer. Elemental analyses were performed by Elementar analyzer Vario EL. Melting points has been recorded on an Electrothermal melting point apparatus. The IR spectra were obtained with Perkin Elmer 240-C instrument using potassium bromide pellets/neat. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on glass).

General procedure. Aromatic aldehyde (5 mmol), 3,4-dihydro-2*H*-pyran (5 mmol) and urea or thiourea (6 mmol) in anhydrous DMF/CH_3CN (1.5 mL/3 mL) were mixed in a flask and *p*-TSA (0.3 mmol) was added at room temperature. The resulting reaction mixture was stirred at reflux for 5–6 h and then poured into crushed ice with stirring. The precipitation was isolated by filtered through a Buechner funnel and washed with water followed by pet–ether, and then dried to give the desired product. All products obtained were fully characterized by spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy and have been identified by the comparison of the spectral data with those reported.

4-Phenylhexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4a. mp 252–254°C; IR (KBr, ν_{max}): 3290, 1685, 1512, 1479, 1181, 1125 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.25–1.28 (m, 1H, CH_2), 1.46–1.89(m, 4H, CH_2 and H-10), 2.30 (s, 3H, CH_3), 3.47 (t, J = 10.11 Hz, 1H, H-7), 3.97 (d, J = 9.76 Hz, 1H, H-7), 4.48(q, J = 1.92 Hz, 1H, H-9), 4.60 (d, J = 11.15 Hz, 1H, H-4), 6.68(s, 1H, NH), 7.08–7.16 (m, 5H, ArH and NH) Mass LCMS $^+$MS 247. Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.65; H, 7.86; N, 11.13.

4-(3,4,5-Trimethoxyphenyl)hexahydro-*1H*-pyrano[2,3-*d*] pyrimidin-2(8a*H*)-one 4b. mp 238–240°C; IR (KBr, ν_{max}): 3371, 3215, 1683, 1597, 1460, 1127, 1033 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.21–1.93 (m, 5H, CH_2 and H-10), 3.47–3.55 (m, 1H, H-7), 3.69 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3), 3.95–4.00 (m, 1H, H-7), 4.47–4.50 (m, 1H, H-9), 4.98 (d, J = 10.64 Hz, 1H, H-4), 6.53 (s, 1H, NH), 6.69 (s, 2H, ArH), 7.30 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.3 (CH_2), 23.0 (CH_2), 37.5 (CH), 52.9 (CH), 55.9, 60.0 (OCH_3), 65.8 (CH_2), 80.2 (CH), 104.7 (ArCH), 125.5, 128.1, 136.9, 152.8 (ArC), 154.8 (C=O); Mass LCMS $^+$MS 323. Anal. Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.71; H, 6.91; N, 8.71.

4-(4,5-Dimethoxy-2-nitrophenyl)hexahydro-*1H*-pyrano[2,3-*d*] pyrimidin-2(8a*H*)-one 4c. mp 231–233°C; IR (KBr, ν_{max}): 3223, 2931, 1687, 1523, 1274, 1175, 1098 cm^{-1}; ^{1}H NMR

Scheme 1

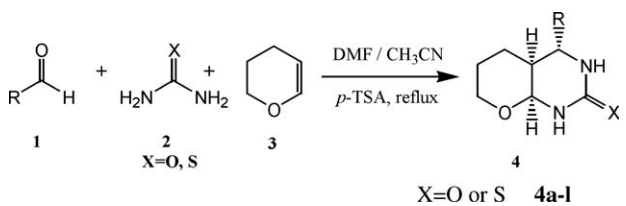


Table 2

Multicomponent reaction of 3,4-dihydro-2*H*-pyran, urea or thiourea, and aromatic aldehydes for the synthesis of **4a–4l**.

Entry	R	X	Product	Time (h)	Yield (%)	Ref.
1	4-$CH_3C_6H_4$	O	**4a**	5.5	98	7
2	3,4,5-$(OCH_3)_3C_6H_2$	O	**4b**	6.0	96	–
3	4,5-$(OCH_3)_2$-2-NO_2-C_6H_2	O	**4c**	5.5	89	–
4	4-$OCH_3C_6H_4$	O	**4d**	6.0	91	7
5	4-$OCH_3C_6H_4$	S	**4e**	6.0	88	7
6	4-BrC_6H_4	O	**4f**	5.0	97	–
7	4-FC_6H_4	O	**4g**	5.2	95	–
8		S	**4h**	6.0	88	–
9	2,4-Cl_2-C_6H_3	S	**4i**	5.0	84	–
10	3-OHC_6H_4	O	**4j**	5.5	90	–
11	2,4-Cl_2-C_6H_3	O	**4k**	5.0	97	–
12	4-FC_6H_4	S	**4l**	5.5	86	7

(200 MHz, DMSO-d_6): δ 1.22 (d, J = 10.92 Hz, 2H, CH_2), 1.42–1.65 (m, 2H, CH_2), 2.17 (d, J = 10.92 Hz, 1H, H-10), 3.40–3.52 (m, 2H, H-7), 3.87 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.47 (s, 1H, H-9), 5.16 (d, J = 10.19 Hz, 1H, H-4), 6.73 (s, 1H, NH), 7.11 (s, 1H, ArH), 7.36 (brs, 1H, NH), 7.52 (s, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (CH_2), 23.1 (CH_2), 36.9 (CH), 47.4 (CH), 56.3 (OCH_3), 65.2 (CH_2), 79.9 (CH), 107.4, 110.6 (ArCH), 129.5, 142.5, 148.0, 152.8 (ArC), 154.9 (C=O); Mass LCMS $^+$MS 338. Anal. Calcd. for $C_{15}H_{19}N_3O_6$: C, 53.41; H, 5.68; N, 12.46. Found: C, 53.49; H, 5.59; N, 12.42.

4-(4-Methoxyphenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4d. mp 220–222°C; IR (KBr, ν_{max}): 3265, 1682, 1611, 1512, 1274, 1253, 1172, 1030 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.26–1.94 (m, 5H, CH_2 and H-10), 3.45 (t, J = 11.65 Hz, 1H, H-7), 3.79 (s, 3H, OCH_3), 4.03 (d, J = 8.73 Hz, 1H, H-7), 4.51 (s, 1H, H-9), 4.65 (d, J = 10.92 Hz, 1H, H-4), 6.79 (s, 1H, NH), 6.86 (d, J = 8.01 Hz, 2H, ArH),7.24 (d, J = 8.73 Hz, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0, 23.3, 38.0, 53.2, 56.3, 65.9, 80.9, 115.1, 129.5, 129.9, 135.0, 155.2, 158.9; Mass LCMS $^+$MS 263. Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.02; H, 6.98; N, 10.68.

4-(4-Methoxyphenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-thione 4e. mp 243–245°C; IR (KBr, ν_{max}): 3267, 2935, 2857, 1683, 1611, 1512, 1463, 1254, 1031 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.31–1.95 (m, 5H, CH_2 and H-10), 3.58 (t, J = 11.33 Hz, 1H, H-7), 3.79 (s, 3H, OCH_3), 3.99 (d, J = 10.98 Hz, 1H, H-7), 4.50 (m, 1H, H-9), 4.57 (d, J = 10.57 Hz, 1H, H-4), 6.88 (d, J = 9.06 Hz, 2H, ArH), 7.22 (d, J = 8.30 Hz, 2H, ArH) 7.36(brs 1H, NH) 8.47(brs, 1H, NH); Mass LCMS $^+$MS 279. Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.40; H, 6.52; N, 10.06. Found: C, 60.38; H, 6.51; N, 10.08.

4-(4-Bromophenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4f. mp 253–256°C; IR (KBr, ν_{max}): 3303, 3208, 1700, 1489, 1297, 1179, 1028 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19–1.84 (m, 5H, CH_2 and H-10), 3.47 (t, J = 11.14 Hz, 1H, H-7), 3.90 (d, J = 11.14 Hz, 1H, H-7), 4.43 (m, 1H, H-9), 4.53 (d, J = 10.76 Hz, 1H, H-4), 6.52 (s, 1H, NH), 7.20 (s, 1H, NH), 7.30 (d, J = 7.93 Hz, 2H, ArH), 7.52 (d, J = 7.93 Hz, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_2), 22.7 (CH_2), 37.5 (CH), 52.0 (CH), 65.6 (CH_2), 80.1 (CH), 120.5, 129.6 (ArCH), 131.1, 140.8 (Arc), 154.5 (C=O); mass LCMS $^+$MS 311. Anal. Calcd. for $C_{13}H_{15}BrN_2O_2$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.20; H, 4.98; N, 8.96.

4-(4-Fluorophenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4g. mp 218–220°C; IR (KBr, ν_{max}): 3301, 3245, 1692, 1508, 1220, 1183, 1027 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.28–1.93 (m, 5H, CH_2 and H-10), 3.53 (t, J = 11.58 Hz, 1H, H-7), 3.97–4.00 (m, 1H, H-7), 4.49 (m, 1H, H-9), 4.63 (d, J = 10.76 Hz, 1H, H-4), 6.92 (s, 1H, NH), 7.00–7.09 (m, 2H, ArH), 7.29–7.36 (m, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2 (CH_2), 22.8 (CH_2), 37.7 (CH), 51.9 (CH), 65.8 (CH_2), 80.2 (CH), 114.9, 115.2, 129.4 (ArCH), 129.5, 137.5 (ArC), 154.7 (C=O); Mass LCMS $^+$MS 251. Anal. Calcd. for $C_{13}H_{15}FN_2O_2$: C, 62.39; H, 6.04; N, 11.19. Found: C, 62.32; H, 5.98; N, 11.25.

4-Furan-2-yl-hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-thione 4h. mp >300°C; IR (KBr, ν_{max}): 3196, 2929, 2858, 1619, 1525, 1177, 1029 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.25–1.83 (m, 5H, CH_2 and H-10), 3.58–3.62 (m, 1H, H-7), 3.96 (d, J = 10.97 Hz, 1H, H-7), 4.54 (m, 1H, H-9), 4.68 (d, J = 9.50 Hz, 1H, H-4), 6.34 (s, 1H, NH), 7.14 (d, J = 7.31 Hz, 1H, ArH), 7.40–7.42 (m, 1H, ArH), 7.63 (d, J = 7.31 Hz, 1H, ArH), 8.48 (s, 1H, NH); Mass LCMS $^+$MS 239. Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: C, 53.44; H, 5.92; N, 11.76. Found: C, 53.32; H, 5.82; N, 11.75.

4-(2,4-Dichlorophenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-thione 4i. mp 232–234°C; IR (KBr, ν_{max}): 3208, 2924, 1614, 1452, 1258, 1011 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38–2.06 (m, 5H, CH_2 and H-10), 3.50 (m, 1H, H-7), 3.82 (d, J = 10.93 Hz, 1H, H-7), 4.50 (m, 1H, H-9), 4.93 (d, J = 8.59 Hz, 1H, H-4), 7.37–7.46 (m, 3H, ArH), 8.39 (s, 1H, NH), 8.80 (brs, 1H, NH); Mass LCMS $^+$MS 317. Anal. Calcd. for $C_{13}H_{14}Cl_2N_2OS$: C, 49.22; H, 4.45; N, 8.83. Found: C, 49.24; H, 4.46; N, 8.81.

4-(3-Hydroxyphenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4j. mp 244–248°C; IR (KBr, ν_{max}): 3305, 3228, 1685, 1604, 1508, 1279, 1033 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.18–1.76 (m, 5H, CH_2 and H-10), 3.40–3.42 (m, 1H, H-7), 3.90 (d, J = 11.89 Hz, 1H, H-7), 4.40–4.45 (m, 2H, H-9 and H-4), 6.49 (s, 1H, NH), 6.66–6.75 (m, 3H, ArH), 7.16 (t, J = 8.30 Hz, 1H, ArH) 7.22 (s, 1H, NH); ^{13}C

NMR (75 MHz, DMSO-d_6): δ 20.3 (CH_2), 22.8 (CH_2), 37.7 (CH), 52.6 (CH), 65.6 (CH_2), 80.1 (CH), 113.9, 114.5, 118.1, 129.2 (ArCH), 142.9, 154.6 (ArC), 157.3 (C=O); Mass LCMS $^+$MS 249. Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.95; H, 6.52; N, 11.23.

4-(2,4-Dichlorophenyl)hexahydro-*1H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one 4k. mp 258–260°C; IR (KBr, ν_{max}): 3306, 2924, 1698, 1452, 1268, 1028 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13–1.92 (m, 5H, CH_2 and H-10), 3.45–3.49 (m, 1H, H-7), 3.80 (d, J = 9.89 Hz, 1H, H-7), 4.40–4.52 (m, 1H, H-9), 4.92 (d, J = 8.92 Hz, 1H,H-4), 6.62 (s, 1H, NH), 7.34–7.65 (m, 4H, ArH and NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (CH_2), 22.6 (CH_2), 37.0 (CH), 53.0 (CH), 65.2 (CH_2), 79.9 (CH), 127.9, 131.0 (ArCH), 136.8, 147.2, 150.3 (ArC), 154.3 (C=O); Mass LCMS $^+$MS 301. Anal. Calcd. for $C_{13}H_{14}Cl_2N_2O_2$: C, 51.84; H, 4.69; N, 9.30. Found: C, 51.86; H, 4.72; N, 9.42.

4-(4-Fluoro-phenyl)-hexahydro-*1H*-pyrano[2,3-*d*]pyrimidine-2(8a*H*)-thione 4l. mp 256–258°C; IR (KBr, ν_{max}): 3185, 2972, 2875, 1608, 1555, 1512, 1490, 1012 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.24–1.88 (m, 5H, CH_2 and H-10), 3.52 (t, J = 10.98 Hz, 1H, H-7), 3.92 (d, J = 11.10 Hz, 1H, H-7), 4.42 (m, 1H, H-9), 4.48 (d, J = 10.11 Hz, 1H, H-4), 7.20–7.42 (m, 4H, ArH), 8.40 (s, 1H, NH); Mass LCMS $^+$MS 267. Anal. Calcd. for $C_{13}H_{15}FN_2OS$: C, 58.62; H, 5.68; N, 10.52. Found: C, 58.54; H, 5.67; N, 10.54.

Acknowledgments. The authors thank Dr. J. S. Yadav, Director, IICT, and Dr. V. V. Narayan Reddy Head, Organic Chemistry Division-II, IICT, Hyderabad for their constant encouragement and support.

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