FACILE AND EFFICIENT SYNTHESIS OF 1,2,4-TRIAZOLO-[4,3-*a*][1,8]NAPHTHYRIDINES USING $Hg(OAc)_2$ UNDER MICROWAVE IRRADIATION

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Abstract
A simple and efficient protocol for the transformation of aryl aldehyde 3-(*o*-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones **7** to 1-aryl-4-(*o*-chloro-phenyl)-1,2,4-triazolo[4,3-*a*][1,8]-naphthyridines **8** is reported under microwave irradiation utilizing inexpensive and easily available reagent - $Hg(OAc)_2$ with high yields. The structures of all the compounds were determined by IR, ^1H NMR and mass spectroscopy. A most probable mechanistic pathway of this transformation is also proposed.

Introduction

1,8-Naphthyridine derivatives constitute an important class of compounds possessing diverse type of biological properties including antimalarial (1), diuretic (2), antibacterial (3) and anti-inflammatory (4). 1,2,4-Triazoles and their derivatives are another class of heterocycles, which have been widely studied for their pharmacological activities (5-8). Microwave-assisted organic reactions have been recently received a great deal of attention and are quickly developing area in synthetic organic chemistry (9-12). The reactions under microwave irradiation proceeded much faster with higher yields compared to the conventional heating. In view of this and in continuation of our interest on microwave assisted organic transformations (13-17), we report herein a time and energy efficient process for the synthesis of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines using $Hg(OAc)_2$ under microwave irradiation. The synthetic approach is outlined in **Scheme 1**.

Experimental

Melting points were determined in open capillary tubes using Cintex apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra in KBr were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer, ^1H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard and mass spectra on a Finnigan MAT 8230 GC-MS spectrometer. The reactions were carried out in a domestic microwave oven (BPL-SANYO 800 G, 2450 MHz).

Condensation of 2-aminonicotinaldehyde **1** with *o*-chlorobenzyl cyanide **2** in the presence of 10% NaOH under microwave irradiation afforded 2-amino-3-(*o*-chlorophenyl)-1,8-naphthyridine **3**, which is converted into 1,2-dihydro-3-(*o*-chlorophenyl)-1,8-naphthyridin-2-one **4** on treatment with HNO_2. Compound **4** on reaction with $POCl_3$ under reflux yielded 2-chloro-3-(*o*-chlorophenyl)-1,8-naphthyridine **5**, which on hydrazinolysis with hydrazine hydrate in boiling ethanol furnished 2-hydrazino-3-(*o*-chlorophenyl)-1,8-naphthyridine **6**.

The hydrazine **6** on condensation with a variety of aromatic aldehydes in ethanol containing a catalytic amount of gl. acetic acid under microwave irradiation resulted in the formation of the corresponding aryl aldehyde 3-(*o*-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones **7** in excellent yields.

Oxidative cyclization of hydrazones **7** with $Hg(OAc)_2$ in ethanol under microwave irradiation afforded 1-aryl-4-(*o*-chlorophenyl)-1,2,4-triazolo[4,3-*a*] [1,8]naphthyridines **8** in good yields.

The reaction is fairly general, facile and efficient and is devoid of any by-products. The products that are obtained are pure and do not require purification. The experimental procedure is very simple. In a typical case, equimolar amounts of hydrazone **7b** and $Hg(OAc)_2$ in ethanol was irradiated in a microwave oven for 3 min. The hot reaction mixture was filtered and the filtrate was treated with water.

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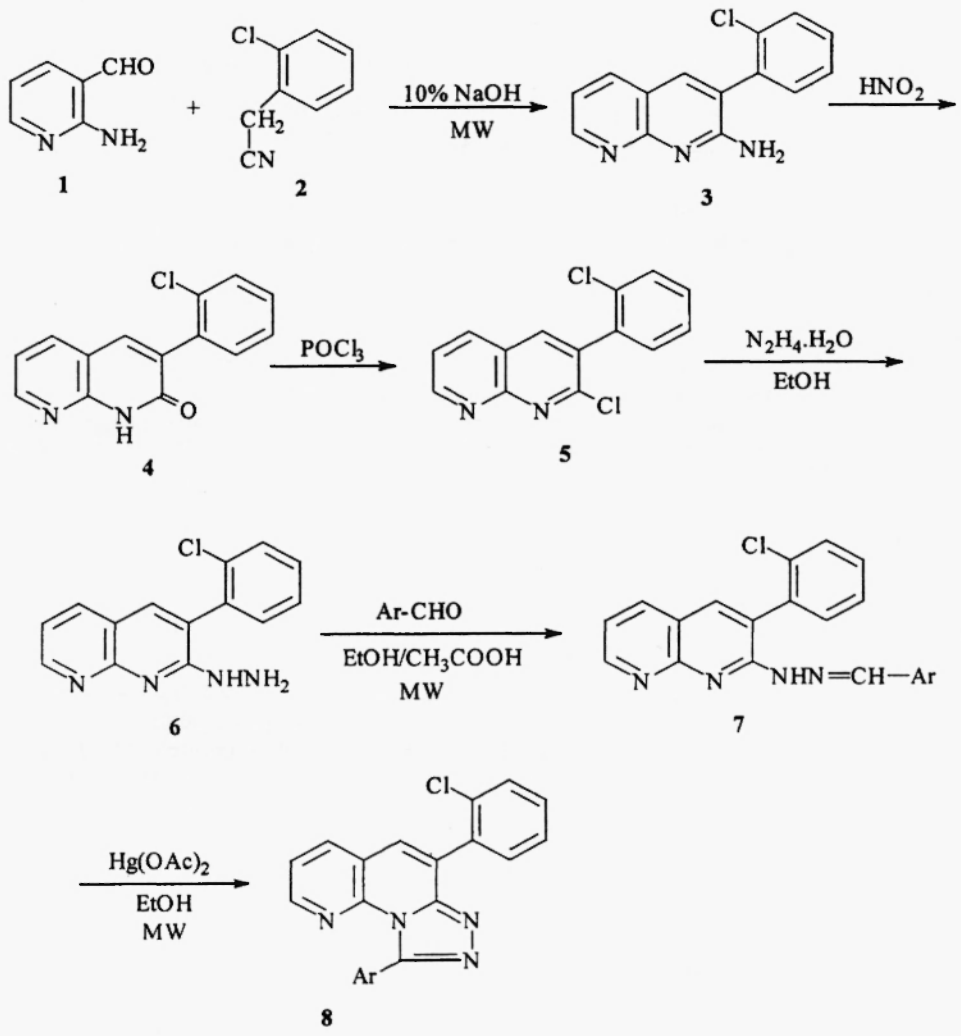
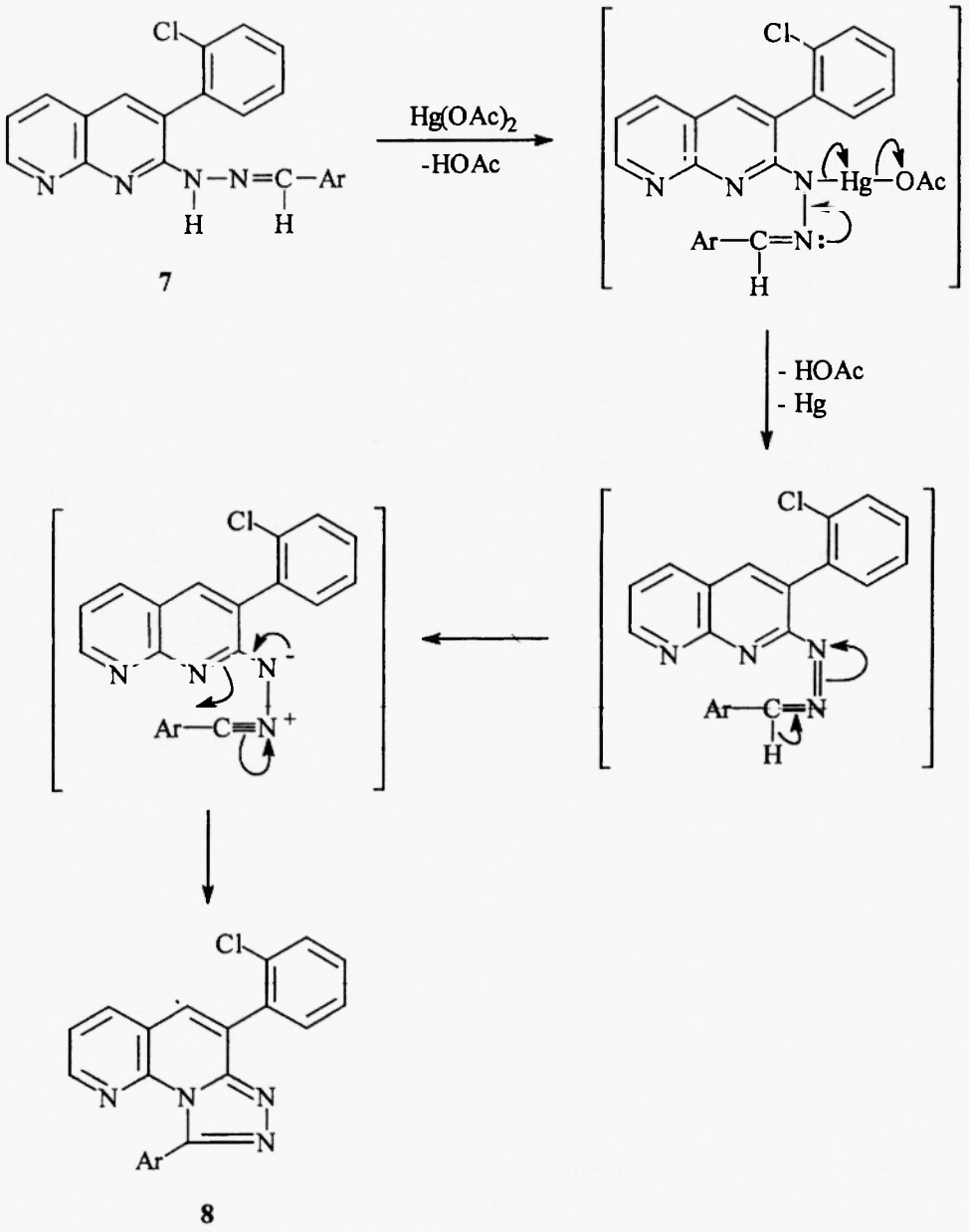


Scheme 1



Scheme 2

The precipitated solid was filtered to give 1-(*p*-methylphenyl)-4-(*o*-chlorophenyl)-1,2,4-triazolo[4,3-*a*][1,8]naphthyridine **8b**, in 90% yield. When the reaction was carried out in ethanol under reflux for the same reaction time as above (3 min) at 110°C (temperature measured at the end of exposure during microwave experiment), the product was obtained only in 8% yield.

The generality of above transformation was checked by treating other hydrazones 7 with $Hg(OAc)_2$ under microwave irradiation and in all cases respective 1-aryl-4-(*o*-chlorophenyl)-1,2,4-triazolo[4,3-*a*][1,8]naphthyridines **8** were obtained in 80-90% yields. The most probable mechanism of above transformation is depicted in **Scheme 2.**

To the best of our knowledge this is the first report on the $Hg(OAc)_2$ mediated synthesis of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines under microwave irradiation.

In summary, we have demonstrated here a facile and efficient method for the preparation of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines using $Hg(OAc)_2$ under microwave irradiation. The inexpensive and commercial availability of the reagent, simple reaction conditions, good yields and excellent purities of the products make this method valuable from a preparative point of view.

2-Amino-3-(o-chlorophenyl)-1,8-naphthyridine 3.

A mixture of 2-amino-nicotinaldehyde **1** (0.01 mole), *o*-chlorobenzyl cyanide **2** (0.01 mole) and 10% NaOH (5 drops) was subjected to microwave irradiation at 150 watts for 2 min. The reaction mixture was cooled and treated with water. The resultant product was filtered, washed with water and recrystallized from methanol to give **3**, M.p. 295°C, Yield 98%; IR (KBr) : 3457, 3273 (NH_2), 1633 (C-NH_2), 1592 cm^{-1} (C=N); ^1H NMR (DMSO-d_6) : δ 6.50 (s, 2H, NH_2), 7.91 (s, 1H, C_4-H), 8.15 (m, 1H, C_5-H), 8.74 (m, 1H, C_7-H), 7.20-7.58 (m, 5H, C_6-H, 4Ar-H); MS : m/z 255 (M^+). Anal. Calcd for $C_{14}H_{10}N_3Cl$: C, 65.75; H, 3.91; N, 16.44. Found : C, 65.91; H, 3.95; N, 16.50%.

1,2-Dihydro-3-(o-chlorophenyl)-1,8-naphthyridin-2-one 4.

To a cold solution of **3** (0.01 mole) in 2N HCl (25 ml) was added $NaNO_2$ solution (0.015 mole in 25 ml water) and the reaction mixture was stirred at room temperature for 0.5 hrs and treated with chilled water. The solid that precipitated was filtered, washed with water and recrystallized from DMF to afford **4**, M.p. 215°C, Yield 85%; IR (KBr) : 3320 (NH), 1657 (ring C=O), 1605 cm^{-1} (C=N); ^1H NMR (DMSO-d_6) : δ 8.18 (m, 2H, C_4-H, C_5-H), 8.56 (m, 1H, C_7-H), 7.26-7.82 (m, 5H, C_6-H, 4Ar-H), 12.42 (s, 1H, NH); MS : m/z 256 (M^+). Anal. Calcd for $C_{14}H_9N_2OCl$: C, 65.50; H, 3.50; N, 10.92. Found : C, 65.68; H, 3.54; N, 10.86%.

2-Chloro-3-(o-chlorophenyl)-1,8-naphthyridine 5.

A mixture of **4** (0.01 mole) and $POCl_3$ (15 ml) was refluxed for 0.5 hrs. The reaction mixture was cooled and poured into a mixture of ice water and $NaHCO_3$. The precipitated product was filtered, washed with water, and recrystallized from methanol to furnish **5**, M.p. 194°C, Yield 90%; IR (KBr) : 1604 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : δ 8.08 (s, 1H, C_4-H), 8.23 (m, 1H, C_5-H), 9.18 (m, 1H, C_7-H), 7.22-7.60 (m, 5H, C_6-H, 4Ar-H); MS : m/z 274 (M^+). Anal. Calcd for $C_{14}H_8N_2Cl_2$: C, 61.09; H, 2.91; N, 10.18. Found : C, 61.26; H, 2.96; N, 10.25%.

2-Hydrazino-3-(o-chlorophenyl)-1,8-naphthyridine 6.

A mixture of **5** (0.01 mole) and hydrazine hydrate (0.015 mole) in ethanol (25 ml) was refluxed on a water-bath for 4 hrs and cooled. The solid thus separated was filtered and recrystallized from ethanol to give **6**, M.p. 210°C, Yield 86%; IR (KBr) : 3410, 3275 (-$NHNH_2$), 1628 (C-$NHNH_2$), 1598 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : δ 3.95 (brs, 2H, NH_2), 7.65 (s, 1H, C_4-H), 7.92 (m, 1H, C_5-H), 8.84 (m, 1H, C_7-H), 7.18-7.53 (m, 6H, C_6-H, NH, 4Ar-H); MS : m/z 270 (M^+). Anal. Calcd for $C_{14}H_{11}N_4Cl$: C, 62.10; H, 4.06; N, 20.70. Found : C, 62.27; H, 4.10; N, 20.78%.

General procedure for the synthesis of aryl aldehyde 3-(o-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones 7 under microwave irradiation.

A mixture of **6** (0.01 mole), appropriate aromatic aldehyde (0.01 mole) and ethanol (20 ml) containing a drop of gl. acetic acid was subjected to microwave irradiation at 150 watts for 1.5-2.0 min. The reaction mixture was cooled, the solid that separated was filtered and recrystallized from ethanol to furnish **7**. Physical and analytical data of compounds **7** are given in **Table 1. 7a :** IR (KBr) : 3359 (NH), 1624

Table 1 : Physical and analytical data of aryl aldehyde 3-(*o*-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones 7 and 1-aryl 4-(*o*-chlorophenyl)-1,2,4-triazolo[4,3-*a*][1,8]naphthyridines **8**.

Entry	Ar	M.p. (°C)	Yield (%)	Mol. Formula	Found (%) (Calcd)		
					C	H	N
7a	C_6H_5	160	92	$C_{21}H_{15}N_4Cl$	70.48 (70.29	4.22 4.18	15.68 15.62)
7b	*p*-$CH_3C_6H_4$	162	98	$C_{22}H_{17}N_4Cl$	70.99 (70.87	4.61 4.56	15.10 15.03)
7c	*p*-$CH_3OC_6H_4$	198	94	$C_{22}H_{17}N_4OCl$	67.78 (67.95	4.42 4.38	14.50 14.41)
7d	*o*-ClC_6H_4	200	93	$C_{21}H_{14}N_4Cl_2$	64.32 (64.12	3.61 3.56	14.31 14.24)
7e	*p*-ClC_6H_4	185	97	$C_{21}H_{14}N_4Cl_2$	64.31 (64.12	3.60 3.56	14.30 14.24)
7f	2,4-$Cl_2C_6H_3$	207	92	$C_{21}H_{13}N_4Cl_3$	58.75 (58.94	3.08 3.04	13.18 13.10)
7g	2,6-$Cl_2C_6H_3$	170	90	$C_{21}H_{13}N_4Cl_3$	58.77 (58.94	3.09 3.04	13.17 13.10)
7h	*o*-BrC_6H_4	196	94	$C_{21}H_{14}N_4ClBr$	57.78 (57.60	3.24 3.20	12.86 12.80)
7i	*m*-$NO_2C_6H_4$	205	90	$C_{21}H_{14}N_5O_2Cl$	62.64 (62.45	3.50 3.47	17.42 17.35)
7j	*p*-$NO_2C_6H_4$	190	92	$C_{21}H_{14}N_5O_2Cl$	62.63 (62.45	3.51 3.47	17.41 17.35)
7k	3,4-(O-CH_2-)C_6H_3	240	96	$C_{22}H_{15}N_4O_2Cl$	65.42 (65.59	3.77 3.73	13.98 13.91)
8a	C_6H_5	185	85	$C_{21}H_{13}N_4Cl$	70.87 (70.69	3.51 3.46	15.80 15.71)
8b	*p*-$CH_3C_6H_4$	245	90	$C_{22}H_{15}N_4Cl$	71.45 (71.26	4.10 4.04	15.20 15.11)
8c	*p*-$CH_3OC_6H_4$	208	86	$C_{22}H_{15}N_4OCl$	68.50 (68.31	3.92 3.88	14.56 14.49)
8d	*o*-ClC_6H_4	240	87	$C_{21}H_{12}N_4Cl_2$	64.65 (64.45	3.12 3.07	14.40 14.32)
8e	*p*-ClC_6H_4	255	88	$C_{21}H_{12}N_4Cl_2$	64.66 (64.45	3.11 3.07	14.41 14.32)
8f	2,4-$Cl_2C_6H_3$	185	84	$C_{21}H_{11}N_4Cl_3$	59.42 (59.22	2.65 2.59	13.24 13.16)
8g	2,6-$Cl_2C_6H_3$	130	82	$C_{21}H_{11}N_4Cl_3$	59.40 (59.22	2.64 2.59	13.25 13.16)
8h	*o*-BrC_6H_4	220	85	$C_{21}H_{12}N_4ClBr$	57.98 (57.86	2.80 2.76	12.94 12.86)
8i	*m*-$NO_2C_6H_4$	270	80	$C_{21}H_{12}N_5O_2Cl$	62.95 (62.76	3.04 2.99	17.51 17.43)
8j	*p*-$NO_2C_6H_4$	310	83	$C_{21}H_{12}N_5O_2Cl$	62.94 (62.76	3.03 2.99	17.52 17.43)
8k	3,4-(O-CH_2-)C_6H_3	220	86	$C_{22}H_{13}N_4O_2Cl$	65.74 (65.92	3.30 3.25	13.91 13.98)

cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : δ 7.76 (m, 3H, C_4-H, C_5-H, C_7-H), 7.13-7.48 (m, 10H, C_6-H, 9Ar-H), 8.45 (s, 1H, N=CH), 10.05 (s, 1H, NH); MS : m/z 358 (M^+); **7b :** 3345 (NH), 1623 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : δ 2.42 (s, 3H, CH_3), 7.40 (m, 2H, C_4-H, C_6-H), 7.65 (m, 2H, C_5-H, C_7-H), 6.91-7.22 (m, 8H, Ar-H), 8.30 (s, 1H, N=CH), 10.12 (s, 1H, NH); MS : m/z 372 (M^+); **7c** : IR (KBr) : 3352 (NH), 1624 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : δ3.85 (s, 3H, OCH_3), 7.40 (m, 2H, C_4-H, C_6-H), 7.65 (m, 2H, C_5-H, C_7-H), 6.88-7.12 (m, 8H, Ar-H), 8.43 (s, 1H, N=CH), 10.08 (s, 1H, NH), **7e :** IR (KBr) : 3432 (NH), 1622 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : δ 7.72 (m, 3H, C_4-H, C_5-H, C_7-H), 7.10-7.63 (m, 9H, C_6-H, 8Ar-H), 8.34 (s, 1H, N=CH), 10.15 (s, 1H, NH); **7k :** IR (KBr) : 3368 (NH), 1626 cm^{-1} (C=N) : ^1H NMR ($CDCl_3$) : δ 6.05 (s, 2H, -O-CH_2-O-), 7.44 (m, 3H, C_4-H, C_5-H, C_6-H), 7.68 (m, 1H, C_7-H), 6.82-7.15 (m, 7H, Ar-H), 8.29 (s, 1H, N=CH), 10.19 (s, 1H, NH).

General procedure for the synthesis of 1-aryl-4-(o-chlorophenyl)-1,2,4-triazolo[4,3-a]|1,8|naphthyridines 8 under microwave irradiation.

To a solution of hydrazones 7 (0.01 mole) in ethanol (20 ml) was added $Hg(OAc)_2$ (0.01 mole) and reaction mixture was subjected to microwave irradiation at 150 watts for 4.0-6.0 min. The hot reaction mixture was filtered and filtrate was then digested with cold water. The solid obtained was filtered and recrystallized from methanol to give **8**. Physical and analytical data of compounds **8** are given in **Table 1**. **8a :** IR (KBr) : 1615 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : δ 7.85 (m, 2H, C_5-H, C_7-H), 8.18 (m, 1H, C_6-H), 8.50 (m, 1H, C_8-H), 7.35-7.74 (m, 9H, Ar-H); MS : m/z 356 (M^+); **8b :** IR (KBr) : 1617 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : 2.48 (s, 3H, CH_3), 7.79 (m, 2H, C_5-H, C_7-H), 8.18 (m, 1H, C_6-H), 8.52 (m, 1H, C_8-H), 7.25-7.62 (m, 8H, Ar-H) ; MS : m/z 370 (M^+); **8c :** IR (KBr) : 1615 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : δ 3.88 (s, 3H, OCH_3), 7.83 (m, 2H, C_5-H, C_7-H), 8.12 (m, 1H, C_6-H), 8.50 (m, 1H, C_8-H), 6.99-7.71 (m, 8H, Ar-H); **8e :** IR (KBr) : 1612 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : δ 7.92 (m, 2H, C_5-H, C_7-H), 8.18 (m, 1H, C_6-H), 8.48 (m, 1H, C_8-H), 7.40-7.79 (m, 8H, Ar-H); **8k :** IR (KBr) : 1615 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) : δ 6.02 (s, 2H, -O-CH_2-O-), 7.79 (m, 2H, C_5-H, C_7-H), 8.16 (m, 1H, C_6-H), 8.43 (m, 1H, C_8-H), 7.38-7.67 (m, 7H, Ar-H).

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References

1 G.B. Balin and W.L. Tan, Aust. J. Chem., **37**, 1065 (1984).
2 D.K.J. Gorecki and E.M. Hawes, J. Med. Chem., **20**, 124 (1977).
3 C.S. Cooper, P.L. Klock, D.T.W. Chu, D.J. Hardy, R.N. Swanson and J.J. Pattner, J. Med. Chem., **35**, 1392 (1992).
4 T. Kuroda, F. Suzuki, T. Tamura, K. Ohmori and H. Hosie, J. Med. Chem., **35**, 1130 (1992).
5 H. Emilsson, K. Luthaman and H. Selander, Eur. J. Med. Chem. Chim. Ther., **21**, 235 (1986).
6 R.H. Bradbury and J.E. Rivett, J. Med. Chem., **34**, 151 (1991).
7 H. Yuksek, A. Demirbas, A. Ikizler, C.B. Johanson, C. Celik and A.A. Ikizler, Arzneim-Forsch. / Drug Res., **47**, (1997).
8 S. Silva, B. Olga, R. Angelo and Bondavalli, Farmaco., **53**, 586 (1998).
9 S. Caddick, Tetrahedron, **51**, 10403 (1995).
10 A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathe, Synthesis, 1213 (1998).
11 R.S. Varma, Green Chem., **1**, 43 (1999).
12 P. Lidstrom, J. Tierney, B. Wathey and J. Westman, Tetrahedron, **57**, 9225 (2001).
13 K. Mogilaiah and N.V. Reddy, Indian J. Chem., **41B**, 2002, 215.
14 K. Mogilaiah, D.S. Chowdary and P.R. Reddy, Synth. Commun., **32**, 857 (2002).
15 K. Mogilaiah and N.V. Reddy, Synth. Commun., **33**, 73 (2003).
16 K. Mogilaiah and N.V. Reddy, Synth. Commun., **33**, 1067 (2003).
17 K. Mogilaiah, M. Prashanthi and G.R. Reddy, Synth. Commun., **33** 3741 (2003).

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