Indian Journal of Chemistry
Vol. 48B, June 2009, pp. 868-872

Facile and efficient synthesis of 1,3,4-oxadiazolyl 1,8-naphthyridines under microwave irradiation

K Mogilaiah*, H Sharath Babu & R Shiva Prasad

Department of Chemistry, Kakatiya University, Warangal 506 009, India

E-mail: mogilaiah_k@yahoo.co.in

Received 1 October 2008; accepted (revised) 19 February 2009

An efficient and convenient method for the synthesis of 1-(5-aryl-[1,3,4]-oxadiazol-2-ylmethyl)-3-(3-trifluromethyl-phenyl)-1*H*-[1,8]-naphthyridin-2-ones **5**, by the oxidation of [2-oxo-3-(3-trifluoromethyl-phenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic acid arylidenehydrazides **4** with iodobenzene diacetate [$PhI(OAc)_2$] under microwave irradiation in solvent-free conditions, is described. The products are obtained in good yields and in a state of high purity. The structures of the synthesized compounds have been established on the basis of spectral and analytical data.

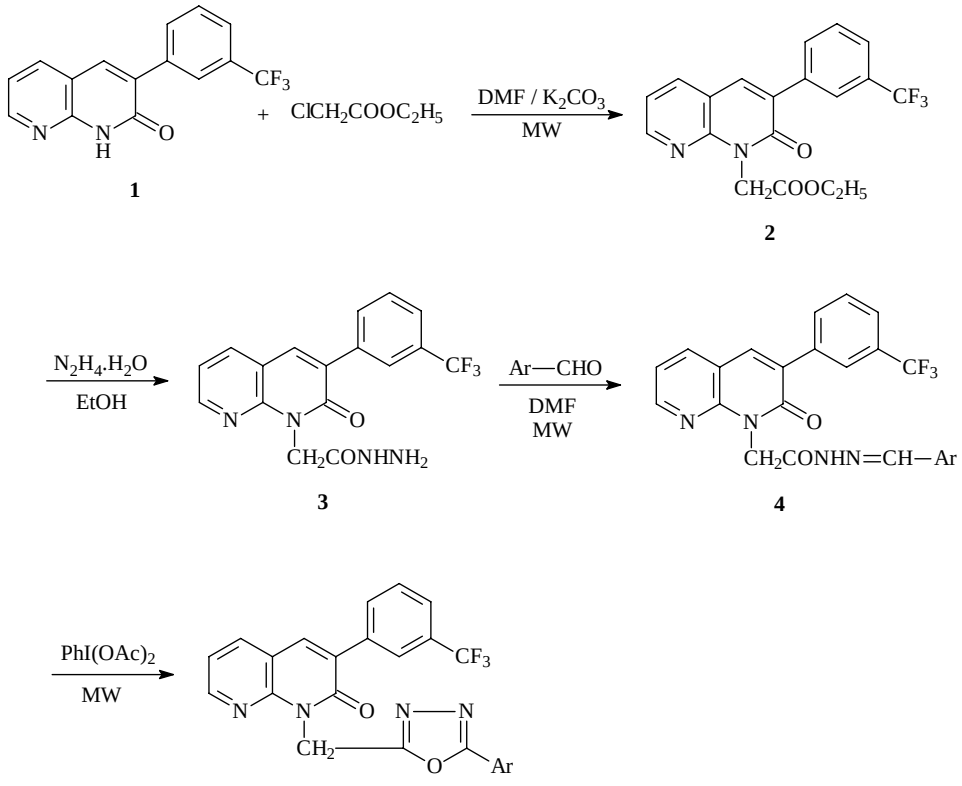
Keywords: 1,8-Naphthyridines, 1,3,4-oxadiazoles, iodobenzene diacetate [$PhI(OAc)_2$], microwave irradiation, solvent-free conditions

Derivatives of 1,3,4-oxadiazole constitute an important family of heterocyclic compounds[1-3]. There are several methods available in the literature for the synthesis of 1,3,4-oxadiazoles[4-6]. However, some of these methods suffer from disadvantages such as long reaction times, lower yields, requirement of severe conditions and using strong or toxic oxidants. Therefore, a convenient and eco-friendly method for the synthesis of 1,3,4-oxadiazoles is highly desirable. 1,8-Naphthyridines have attracted considerable attention owing to their effective biological activity[7-10]. Iodobenzene diacetate [$PhI(OAc)_2$] is a very versatile oxidizing agent and is of much importance in its synthetic utility[11-13]. Microwave irradiation has been successfully applied in organic synthesis[14-16]. Recently reaction facilitated by microwaves under solvent-free condition[15] have attracted more attention because of their enhanced selectivity, reducing reaction time and easier work-up procedure. In view of these and in continuation of the interest in the microwave-assisted organic transformations of 1,8-naphthyridine derivatives[17-21] herein is reported an efficient method for the synthesis of 1,3,4-oxadiazolyl-1,8-naphthyridines using iodobenzene diacetate[$PhI(OAc)_2$] under microwave irradiation in solvent-free conditions.

Alkylation of 1,2-dihydro-3-(3-trifluoromethyl-phenyl)-1,8-naphthyridin-2-one **1** with ethyl chloroacetate in DMF in the presence of anhydrous K_2CO_3 under microwave irradiation resulted in the formation of ethyl [2-oxo-3-(3-trifluoromethylphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetate **2** in excellent yield. The ester **2** on hydrazinolysis with refluxing hydrazine hydrate in ethanol afforded [2-oxo-3-(3-trifluoromethylphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic acid hydrazide **3**. Condensation of **3** with various aromatic aldehydes in the presence of catalytic amount of DMF under microwave irradiation afforded the corresponding hydrazones, [2-oxo-3-(3-trifluoromethyl-phenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic acid arylidenehydrazides **4** in excellent yields.

Oxidative cyclization of hydrazones **4** with $PhI(OAc)_2$ under microwave irradiation in solvent-free conditions furnished the respective 1-(5-aryl-[1,3,4]-oxadiazol-2-ylmethyl)-3-(3-trifluoromethyl-phenyl)-1*H*-[1,8]naphthyridin-2-ones **5** in good yields (**Scheme I**). The oxidative transformation is very clean and rapid. The reaction conditions and work-up procedure are mild, simple and convenient. The products were obtained with high purity by this procedure. The process is environmentally benign. A plausible mechanism for the conversion of **4** to **5** is depicted in **Scheme II**.

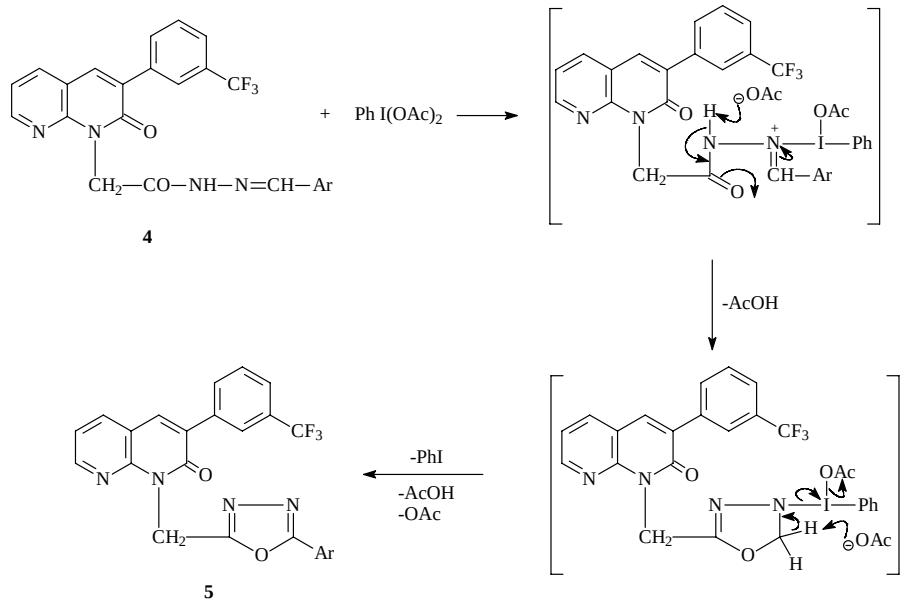
Interestingly, this reaction proceeds only to a minor extent (5-8% in 3.5-4.5 min) when conducted under conventional conditions in an oil-bath preheated to 120^{o}C (temperature measured at the end of exposure during microwave experiment) which confirms the rate increase during microwave heating.



1 **2** **3** **4** **5**

Ar		Ar	
a,	C_6H_5	**e,**	*p*-ClC_6H_4
b,	*p*-$CH_3C_6H_4$	**f**,	*p*-FC_6H_4
c,	*p*-$CH_3OC_6H_4$	**g,**	*m*-$NO_2C_6H_4$
d,	*o*-ClC_6H_4	**h,**	*p*-$NO_2C_6H_4$

Scheme I



4 **5**

Scheme II

Table I — IR and ^{1}H NMR spectral data of compounds **4** and **5**

Compd	Ar	IR (KBr) ν_{max} in cm^{-1}	^{1}H NMR (200 MHz, $CDCl_3$) (δ, ppm)
4a	C_6H_5	3428 (NH), 1658 (ring C=O), 1625 (CONH), 1614 (C=N)	5.80 (s, 2H, CH_2), 8.30 (m, 1H, C_6-H), 8.38 (s, 1H, C_4-H), 8.27 (m, 1H, C_5-H), 8.58 (m, 1H, C_7-H), 7.10-7.93 (m, 9H, Ar-H), 9.01 (s, 1H, N=CH), 10.18 (s, 1H, CONH)
4b	*p*-$CH_3C_6H_4$	3430 (NH), 1657 (ring C=O), 1624 (CONH), 1585 (C=N)	2.15 (s, 3H, CH_3), 5.70 (s, 2H, CH_2), 7.95 (m, 2H, C_4-H, C_6-H), 8.35 (m, 1H, C_5-H), 8.55 (m, 1H, C_7-H), 6.98-7.70 (m, 8H, Ar-H), 9.05 (s, 1H, N=CH), 10.20 (s, 1H, CONH).
4c	*p*-$CH_3OC_6H_4$	3356 (NH), 1657 (ring C=O), 1622 (CONH), 1580 (C=N)	3.80 (s, 3H, CH_3), 5.72 (s, 2H, CH_2), 7.90 (m, 2H, C_4-H, C_6-H), 8.25 (m, 1H, C_5-H), 8.48 (m, 1H, C_7-H), 6.80-7.60 (m, 8H, Ar-H), 8.80 (s, 1H, N=CH), 10.15 (s, 1H, CONH).
4d	*o*-ClC_6H_4	3402 (NH), 1660 (ring C=O), 1624 (CONH), 1591 (C=N)	5.82 (s, 2H, CH_2), 8.00 (m, 2H, C_4-H, C_6-H), 8.20 (m, 1H, C_5-H), 8.50 (m, 1H, C_7-H), 7.00-7.65 (m, 8H, Ar-H), 9.00 (s, 1H, N=CH), 10.20 (s, 1H, CONH).
4e	*p*-ClC_6H_4	3349 (NH), 1663 (ring C=O), 1625 (CONH), 1585 (C=N)	5.84 (s, 2H, CH_2), 7.85 (m, 2H, C_4-H, C_6-H), 8.45 (m, 1H, C_5-H), 8.65 (m, 1H, C_7-H), 7.00-7.80 (m, 8H, Ar-H), 8.85 (s, 1H, N=CH), 10.18 (s, 1H, CONH).
4f	*p*-FC_6H_4	3435 (NH), 1657 (ring C=O), 1625 (CONH), 1597 (C=N)	5.83 (s, 2H, CH_2), 7.87 (m, 2H, C_4-H, C_6-H), 8.32 (m, 1H, C_5-H), 8.60 (m, 1H, C_7-H), 7.00-7.82 (m, 8H, Ar-H), 8.88 (s, 1H, N=CH), 10.20 (s, 1H, CONH).
4g	*m*-$NO_2C_6H_4$	3430 (NH), 1647 (ring C=O), 1626 (CONH), 1591 (C=N)	5.82 (s, 2H, CH_2), 7.98 (m, 2H, C_4-H, C_6-H), 8.20 (m, 1H, C_5-H), 8.60 (m, 1H, C_7-H), 7.00-7.72 (m, 8H, Ar-H), 8.82 (s, 1H, N=CH), 10.22 (s, 1H, CONH).
4h	*p*-$NO_2C_6H_4$	3415 (NH), 1656 (ring C=O), 1625 (CONH), 1595 (C=N)	5.85 (s, 2H, CH_2), 8.00 (m, 2H, C_4-H, C_6-H), 8.34 (m, 1H, C_5-H), 8.64 (m, 1H, C_7-H), 7.15-7.84 (m, 8H, Ar-H), 8.92 (s, 1H, N=CH), 10.25 (s, 1H, CONH).
5a	C_6H_5	1639 (C=O), 1600 (C=N)	6.00 (s, 2H, CH_2), 8.10 (m, 2H, C_4-H, C_6-H), 8.30 (m, 1H, C_5-H), 8.50 (m, 1H, C_7-H), 7.15-7.85 (m, 9H, Ar-H).
5b	*p*-$CH_3C_6H_4$	1642 (C=O), 1602 (C=N)	2.40 (s, 3H, CH_3), 6.05 (s, 2H, CH_2), 7.90 (m, 2H, C_4-H, C_6-H), 8.25 (m, 1H, C_5-H), 8.48 (m, 1H, C_7-H), 7.20-7.80 (m, 8H, Ar-H).
5c	*p*-$CH_3OC_6H_4$	1640 (C=O), 1605 (C=N)	3.85 (s, 3H, OCH_3), 6.02 (s, 2H, CH_2), 7.97 (m, 2H, C_4-H, C_6-H), 8.20 (m, 1H, C_5-H), 8.52 (m, 1H, C_7-H), 7.12-7.75 (m, 8H, Ar-H).
5d	*o*-ClC_6H_4	1639 (C=O), 1600 (C=N)	6.05 (s, 2H, CH_2), 8.15 (m, 2H, C_4-H, C_6-H), 8.32 (m, 1H, C_5-H), 8.55 (m, 1H, C_7-H), 7.20-7.82 (m, 8H, Ar-H).
5e	*p*-ClC_6H_4	1644 (C=O), 1602 (C=N)	6.08 (s, 2H, CH_2), 7.98 (m, 2H, C_4-H, C_6-H), 8.40 (m, 1H, C_5-H), 8.58 (m, 1H, C_7-H), 7.20-7.83 (m, 8H, Ar-H).
5f	*p*-FC_6H_4	1650 (C=O), 1600 (C=N)	6.08 (s, 2H, CH_2), 8.00 (m, 2H, C_4-H, C_6-H), 8.35 (m, 1H, C_5-H), 8.62 (m, 1H, C_7-H), 7.22-7.86 (m, 8H, Ar-H).
5g	*m*-$NO_2C_6H_4$	1646 (C=O), 1603 (C=N)	6.10 (s, 2H, CH_2), 8.08 (m, 2H, C_4-H, C_6-H), 8.31 (m, 1H, C_5-H), 8.64 (m, 1H, C_7-H), 7.18-7.83 (m, 8H, Ar-H).
5h	*p*-$NO_2C_6H_4$	1648 (C=O), 1605 (C=N)	6.12 (s, 2H, CH_2), 8.13 (m, 2H, C_4-H, C_6-H), 8.38 (m, 1H, C_5-H), 8.70 (m, 1H, C_7-H), 7.20-7.85 (m, 8H, Ar-H).

The structural assignments of the compounds **2-5** were based on their elemental analyses and spectral (IR and ^{1}H NMR) data (**Tables I** and **II**).

In conclusion, an efficient and convenient procedure for the synthesis of 1,3,4-oxadiazoles using $PhI(OAc)_2$ under microwave irradiation in solvent-free conditions has been demonstrated. The operational simplicity, good yields of the products, short reaction times, high purity of the products environmentally benign procedure and non-toxicity of the reagent are noteworthy advantages of this method.

Experimental Section

Melting points were recorded by means of a Cintex melting point apparatus and are uncorrected. The homogeneity of the compounds was checked using precoated TLC plates (Merck, 60F-254). IR spectra were recorded in KBr on a Perkin-Elmer spectrum

Table II — Physical and analytical data of compounds **4** and **5**

Compd	Ar	Reaction time (min)	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calcd) C	H	N
4a	C_6H_5	1.5	198	94	$C_{24}H_{17}N_4O_2F_3$	64.16 (64.00	3.84 3.80	12.50 12.44)
4b	*p*-$CH_3C_6H_4$	1.0	220	98	$C_{25}H_{19}N_4O_2F_3$	64.80 (64.65	4.15 4.12	12.11 12.06)
4c	*p*-$CH_3OC_6H_4$	1.5	210	96	$C_{25}H_{19}N_4O_3F_3$	62.67 (62.50	4.04 3.99	11.72 11.66)
4d	*o*-ClC_6H_4	1.5	240	94	$C_{24}H_{16}N_4O_2F_3Cl$	59.60 (59.45	3.37 3.33	11.42 11.36)
4e	*p*-ClC_6H_4	1.0	190	97	$C_{24}H_{16}N_4O_2F_3Cl$	59.61 (59.45	3.36 3.33	11.43 11.36)
4f	*p*-FC_6H_4	1.5	180	95	$C_{24}H_{16}N_4O_2F_4$	61.71 (61.54	3.49 3.44	12.03 11.96)
4g	*m*-$NO_2C_6H_4$	1.0	270	93	$C_{24}H_{16}N_5O_4F_3$	58.38 (58.19	3.30 3.26	14.21 14.14)
4h	*p*-$NO_2C_6H_4$	1.0	252	95	$C_{24}H_{16}N_5O_4F_3$	53.37 (58.19	3.29 3.26	14.20 14.14)
5a	C_6H_5	4.5	>300	85	$C_{24}H_{15}N_4O_2F_3$	64.44 (64.29	3.40 3.37	13.05 12.49)
5b	*p*-$CH_3C_6H_4$	3.5	>300	92	$C_{25}H_{17}N_4O_2F_3$	65.08 (64.93	3.75 3.71	12.20 12.12)
5c	*p*-$CH_3OC_6H_4$	4.5	>300	87	$C_{25}H_{17}N_4O_3F_3$	62.92 (62.76	3.62 3.58	11.80 11.71)
5d	*o*-ClC_6H_4	4.0	>300	86	$C_{24}H_{14}N_4O_2F_3Cl$	59.16 (59.70	2.95 2.92	11.66 11.60)
5e	*p*-ClC_6H_4	3.5	>300	90	$C_{24}H_{14}N_4O_2F_3Cl$	59.77 (59.70	2.96 2.92	11.65 11.60)
5f	*p*-FC_6H_4	4.0	>300	88	$C_{24}H_{14}N_4O_2F_4$	61.98 (61.81	3.08 3.03	12.10 12.01)
5g	*m*-$NO_2C_6H_4$	4.5	>300	85	$C_{24}H_{14}N_5O_4F_3$	58.60 (58.42	2.90 2.86	14.25 14.19)
5h	*p*-$NO_2C_6H_4$	4.5	>300	86	$C_{24}H_{14}N_5O_4F_3$	58.58 (58.42	2.91 2.86	14.26 14.19)

BX series FT-IR spectrophotometer and ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard. Microwave irradiation was carried out in LG MG-556p domestic microwave oven.

Ethyl [2-oxo-3-(3-trifluoromethylphenyl)-2*H*-[1,8]naphthyridin-1-yl] acetate 2: A mixture of 1,2-dihydro-3-(3-trifluoromethylphenyl)-1,8-naphthyridin-2-one **1** (0.01 mole), ethyl chloroacetate (0.01 mole), anhydrous K_2CO_3 (0.01 mole) and DMF (10 mL) was subjected to microwave irradiation at 400 W intermittently at 30 sec intervals for 4.5 min. On completion of reaction, as monitored by TLC, the reaction mixture was cooled and poured onto crushed ice. The precipitates thus obtained were filtered, washed with water and purified by recrystallization from ethanol to afford **2**, m.p. 130°C, yield 95%. Anal. Calcd for $C_{19}H_{15}N_2O_3F_3$: C, 60.64; H, 4.02; N, 7.44. Found: 60.70; H, 4.06; N, 7.52%. IR (KBr): 1752 (C=O ester), 1664 (ring C=O), 1589 cm^{-1} (C=N); 1H NMR ($CDCl_3$): δ 1.55 (t, *J* = 7.0 Hz, 3H, CH_3), 4.50 (q, *J* = 7.0 Hz, 2H, CH_2), 5.60 (s, 2H, N-CH_2), 8.50 (m, 2H, C4-H, C6-H), 8.82 (m, 1H, C5-H), 9.45 (m, 1H, C7-H), 7.42-8.22 (m, 4H, Ar-H).

[2-Oxo-3-(3-trifluoromethylphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic acid hydrazide 3: A mixture of **2** (0.01 mole) and hydrazine hydrate (0.015 mole) in ethanol (25 mL) was refluxed on a water-bath for 4 hr. The reaction mixture was cooled and poured in ice-cold water with stirring. The separated solid was

filtered, washed with water and purified by recrystallization from ethanol to give **3**, m.p. 120°C, yield 92%. Anal. Calcd for $C_{17}H_{13}N_4O_2F_3$: C, 56.36; H, 3.62; N, 15.46. Found: C, 56.54; H, 3.65; N, 17.22%. IR (KBr): 3475, 3306, 3100 (-$NHNH_2$), 1664 (ring C=O), 1613 (CONH), 1565 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.45 (brs, 2H, NH_2), 5.30 (s, 2H, CH_2), 8.58 (m, 1H, C_6-H), 8.70 (m, 2H, C_4-H, C_5-H), 9.18 (m, 1H, C_7-H), 7.20-8.02 (m, 4H, Ar-H), 11.80 (s, 1H, CONH).

General procedure for the synthesis of [2-oxo-3-(3-trifluoromethyl-phenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic acid arylidenehydrazides 4: A mixture of **3** (0.01 mole), aromatic aldehyde (0.01 mole) and DMF (5 drops) was subjected to microwave irradiation at 200 W intermittently at 30 sec intervals for specified time (**Table II**). On completion of reaction, as monitored by TLC, the reaction-mixture was cooled and treated with ice-cold water. The resulting solid product was filtered, washed with water and purified by recrystallization from ethanol to furnish **4** (**Table II**).

General procedure for the synthesis of 1-(5-Aryl-[1,3,4]oxadiazol-2-ylmethyl)-3-(3-trifluoro-methylphenyl)-1*H*-[1,8]naphthyridin-2-ones 5: The appropriate hydrazone **4** (0.01 mole) and $PhI(OAc)_2$ are mixed thoroughly and exposed to microwaves at 400 W intermittently at 30 sec intervals for specified time (**Table II**). After complete conversion as indicated by TLC, the reaction-mixture was cooled treated with methanol and digested with cold water. The solid thus obtained was filtered, washed with water and purified by recrystallization from methanol to give **5** (**Table II**).

References

1 Dubey A K & Sangwan N K, *Indian J Chem*, 33B, **1994**, 1043.
2 Omar F A, Mahfouz N M & Rahman M A, *Eur J Med Chem Chim Ther*, 31, **1996**, 819.
3 Kalsi R, Pande K & Barthwal J P, *Indian J Chem*, 27B, **1998**, 197.
4 Baltazzi E & Wysocki A, *J Chem Ind* (*London*), **1963**, 1080.
5 Chiba T & Mitsuhiro O, *J Org Chem*, 57, **1992,** 1375.
6 Shah V R, Vadodaria M & Parikh A R, *Indian J Chem*, 36B, **1997**, 101.
7 Bouzard D, DiCesare P, Essiz M, Jacquet J P, Ledoussal B, Remuzon P, Kessler R E & Fung Tome J, *J Med Chem*, 35, **1992**, 518.
8 Zhang S X, Bastow K F, Tachibana Y, Kuo S C, Hamel E, Mauger A, Narayanan V L & Lew K H, *J Med Chem*, 42, **1999**, 4081.
9 Badawneh M, Ferrarini P L, Calderone V, Manera C, Martinotti E, Mari C, Saccomanni G & Testai L, *J Med Chem*, 36, **2001**, 925.
10 Roma G, Braccio M D, Grassi G, Mattioh F & Ghai M, *J Med Chem*, 35, **2000**, 1021.
11 Prakash O, Saini N & Sharma P K, *Synlet (Account)*, **1994**, 221.
12 Stang P T & Zhdankin V V, *Chem Rev*, 96, **1996**, 1123.
13 Moriarty R M & Prakash O, *Adv Het Chem*, 69, **1998**, 1.
14 Caddick S, *Tetrahedron*, 51, **1995**, 10403.
15 Loupy A, Petit A, Hamelin J, Texiert-Boullet F, Jacquault P & Mathe D, *Synthesis*, **1998**, 1213.
16 Lidstrom P, Tierney J, Wathey B & Westman J, *Tetrahedron*, 57, **2001**, 9225.
17 Mogilaiah K & Reddy N V, *Synth Commun*, 33, **2003**, 1067.
18 Mogilaiah K, Reddy G R & Reddy Ch S, *J Chem Res*, **2004**, 832.
19 Mogilaiah K & Reddy Ch S, *Heterocycl Commun*, 10, **2004**, 363.
20 Mogilaiah K, Prashanthi M, Kavitha S & Reddy N V, *J Chem Res*, **2005**, 523.
21 Mogilaiah K, Prashanthi M, Kavitha S & Sharath Babu H, *J Heterocycl Chem*, 44, **2007**, 1161.