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AN ENVIRONMENTALLY BENIGN AND SOLVENT-FREE SYNTHESIS OF 3-ARYL[1,2,4]TRIAZOLO[4,3-*a*]PYRIDINES AND 1-ARYL-5-METHYL[1,2,4]TRIAZOLO[4,3-*a*]QUINOLINES USING PHENYLIODINE BIS(TRIFLUOROACETATE) OR IODOBENZENE DIACETATE

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A simple, solvent-free and effective method for oxidative cyclization of 2-pyridyl- and 2-quinolyl-hydrazones with phenyliodine bis(trifluoroacetate) and iodobenzene diacetate to the corresponding 3-aryl[1,2,4]triazolo[4,3-a]pyridines and 1-aryl[1,2,4]triazolo[4,3-a]quinolines is described. All reactions were characterized by short reaction times and high yields at room temperature. All reactions were carried out by just grinding the reaction components.

Keywords: bridgehead triazoles, hydrazones, iodobenzene diacetate, phenyliodine bis(trifluoroacetate), grinding, oxidative cyclization, solvent-free reactions.

In the last few decades, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives have received considerable attention owing to their synthetic and biological importance [1–11]. 1,2,4-Triazole makes up the core structure of numerous biologically active compounds, including blockbuster drugs such as conazole fungicides (Fluconazole, Hexaconazole), triazolobenzodiazepines (Estazolam, Triazolam, Alprazolam), Rizatriptan, and Ribavirin, which find a wide range of applications in pharmaceutical and agrochemical industry [12]. Triazole fused with other ring systems is also found to possess diverse applications in medicine [12–18], i.e., as antitumor [12], anticancer, and antimicrobial agents [13, 15].

The principle underlying green chemistry entails testing the necessity of use of organic solvents and reducing the energy requirements. Because many organic solvents are ecologically harmful, strategies to minimize their use make up part of the developments toward environmentally benign chemical technologies. Hypervalent iodine reagents have gained much importance as oxidants in the attempts to avoid the use of toxic transition metals in oxidizing processes [19–27]. Recent literature survey shows the development of new hypervalent iodine reagents that can be used as "green" oxidants [28–29]. The poor solubility of hypervalent iodine reagents in most common organic solvents has led to the development of solvent-free reactions [30–31].

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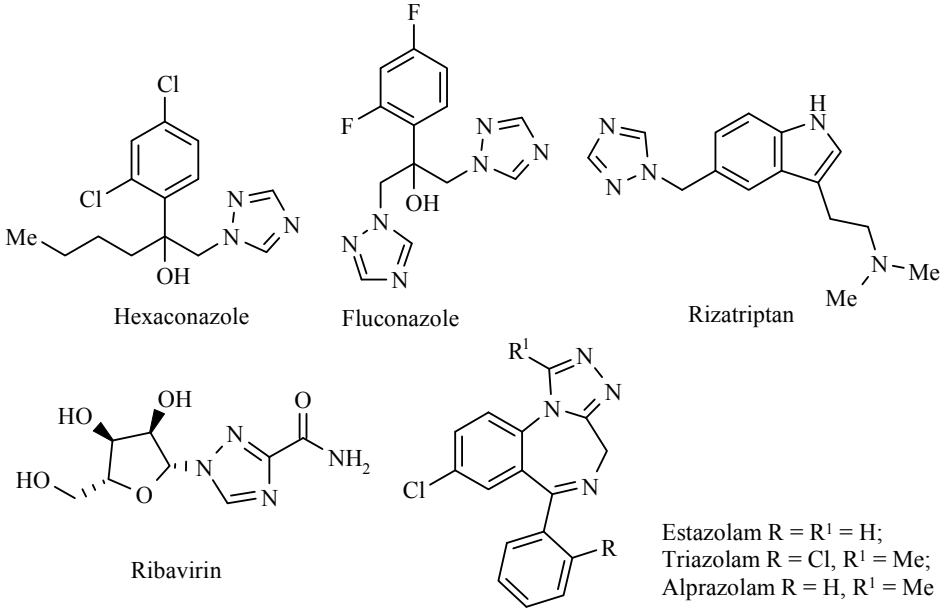
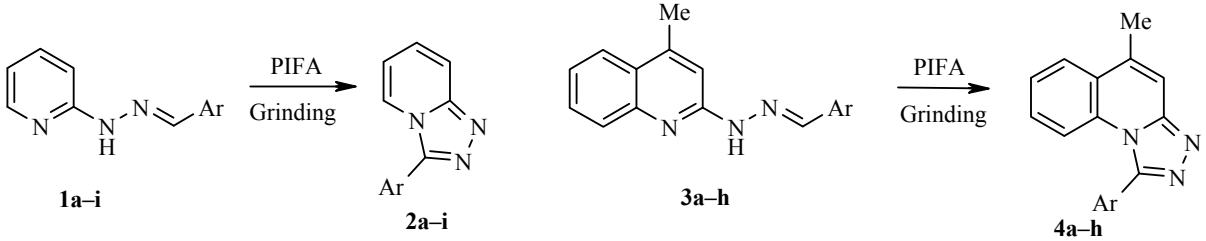
Many exothermic reactions can be accomplished by just grinding solids together in a mortar with a pestle. Reactions are initiated by the transfer of very small amounts of energy through friction. It brings advantages from the environmental point of view, as well as rate enhancement, less waste products, and higher yields [32].



In continuation of our previous work [16, 33–37] on biologically active heterocyclic compounds and development of novel synthetic methodologies and because of the biological significance of 1,2,4-triazole, a solvent-free oxidative cyclization of 2-pyridyl- and 2-quinolylhydrazones with phenyliodine bis(trifluoroacetate) (PIFA) or iodobenzene diacetate (IBD) to the corresponding 3-aryl-[1,2,4]triazolo[4,3-*a*]pyridines and 1-aryl-5-methyl-[1,2,4]triazolo[4,3-*a*]quinolines is reported here.

Two series of 2-pyridyl- and 2-quinolylhydrazones were synthesized to study their oxidative cyclization to the analogous triazole derivatives. The reaction of 2-(2-benzylidenehydrazinyl)pyridine (**1a**) with IBD was taken as a model reaction. In a preliminary experiment, 1.0 eqv. of 2-(2-benzylidenehydrazinyl)pyridine (**1a**) was ground with 1.2 eqv. of IBD at room temperature. As expected, 3-phenyl-[1,2,4]triazolo[4,3-*a*]pyridine (**2a**) was obtained in 75% yield in 20 min. The same reaction with PIFA (1.2 eqv.) yielded compound **2a** in 89% in 6 min. However, the oxidative cyclization reaction of 2-quinolylhydrazones **3a–d** with IBD did not proceed at room temperature and required some heating (40–50°C), whereas with PIFA, the reaction occurred at room temperature. Thus the oxidative efficiency of PIFA was higher in terms of yield and time (Table 1).



1a–i **2a–i** **3a–h** **4a–h**

1–4 a Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 4-ClC_6H_4, **d** Ar = 4-$MeOC_6H_4$, **e** Ar = 5-O_2N-2-furyl,
f Ar = 2-thienyl; **1, 2 g** Ar = 4-FC_6H_4, **h** Ar = 2-$MeOC_6H_4$, **i** Ar = 2-furyl;
3, 4 g Ar = 4-$O_2NC_6H_4$, **h** Ar = 3,4-$(MeO)_2C_6H_3$

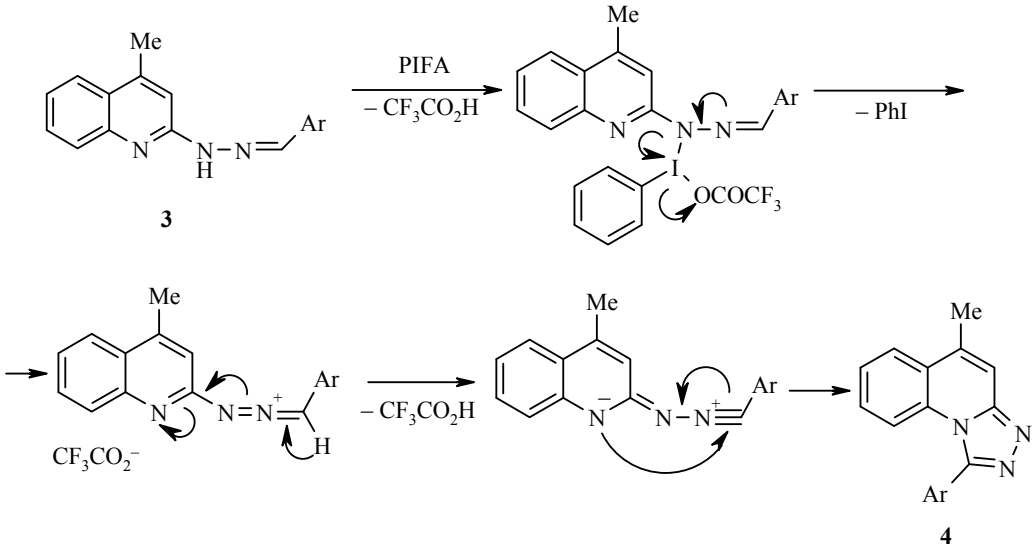
TABLE 1. Solvent-free Synthesis of 3-Aryl-[1,2,4]triazolo[4,3-*a*]pyridines **2a–i** and 1-Aryl-5-methyl-[1,2,4]triazolo[4,3-*a*]quinolines **4a–h**

Product	Grinding time, min		Yield, %	
	PIFA	IBD	PIFA	IBD
2a	6	20	89	75
2b	6	20	86	70
2c	8	25	87	68
2d	5	15	85	64
2e	8	18	90	68
2f	5	16	88	65
2g	5	20	84	64
2h	6	15	86	66
2i	7	16	85	65
4a	6	15	90	65
4b	8	15	86	64
4c	10	15	85	66
4d	5	15	85	64
4e	10	15	81	65
4f	8	15	80	61
4g	5	15	86	65
4h	7	15	85	65

TABLE 2. Characteristics of Compounds **2a–i** and **4a–h**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	lit. mp, °C [38]
		C	H	N		
2a	$C_{12}H_9N_3$	73.98 / 73.83	4.55 / 4.65	21.33 / 21.52	174-75	173-75
2b	$C_{13}H_{11}N_3$	74.56 / 74.62	5.26 / 5.30	20.22 / 20.08	155-56	154-55
2c	$C_{12}H_8ClN_3$	62.88 / 62.76	3.46 / 3.51	18.22 / 18.30	189-91	190-91
2d	$C_{13}H_{11}N_3O$	69.44 / 69.32	5.03 / 4.92	18.53 / 18.66	123-25	124-26
2e	$C_{10}H_6N_4O_3$	52.32 / 52.18	2.77 / 2.63	24.22 / 24.34	256-58	254-56
2f	$C_{10}H_7N_3S$	59.58 / 59.68	3.62 / 3.51	20.74 / 20.88	113-14	112-114
2g	$C_{12}H_8FN_3$	67.51 / 67.60	3.72 / 3.78	19.61 / 19.71	161-162	—
2h	$C_{13}H_{11}N_3O$	69.41 / 69.32	4.81 / 4.92	18.71 / 18.66	161-62	—
2i	$C_{10}H_7N_3O$	64.69 / 64.86	3.87 / 3.81	22.60 / 22.69	189-91	—
4a	$C_{17}H_{13}N_3$	78.88 / 78.74	4.99 / 5.05	16.31 / 16.20	153-55	152-153
4b	$C_{18}H_{15}N_3$	78.98 / 79.10	5.43 / 5.53	15.45 / 15.37	211-12	213-214
4c	$C_{17}H_{12}ClN_3$	69.44 / 69.51	4.15 / 4.12	14.41 / 14.30	200-02	201-202
4d	$C_{18}H_{15}N_3O$	74.59 / 74.72	5.28 / 5.23	14.45 / 14.52	160-62	162-163
4e	$C_{15}H_{10}N_4O_3$	61.26 / 61.22	3.36 / 3.43	18.97 / 19.04	183-185	182-183
4f	$C_{15}H_{11}N_3S$	68.02 / 67.90	4.05 / 4.18	15.69 / 15.84	165-166	164-165
4g	$C_{17}H_{12}N_4O_2$	66.98 / 67.10	4.05 / 3.97	18.56 / 18.41	281-282	—
4h	$C_{19}H_{17}N_3O_2$	71.27 / 71.46	5.26 / 5.37	12.99 / 13.16	224-235	—

The mechanistic pathway could include initial electrophilic attack of hypervalent iodine(III) at the hydrazone nitrogen of compound **3,** giving *N*-iodine(III) adduct, followed by reductive elimination of iodobenzene, resulting in the intermediate which on elimination of proton affords nitrile imine that undergoes intramolecular cyclization to yield the product **4**. The results in Table 1 clearly indicate the advantage of PIFA over IBD: a) time required for oxidative cyclization of 2-pyridyl- and 2-quinolylhydrazones is shorter; b) oxidative cyclization takes place at room temperature; c) yields are higher. Solvent-phase oxidative cyclization of 2-pyridyl- and 2-quinolylhydrazones using IBD in dichloromethane has already been used for this reaction [38], but the reaction time was long and yields were low.



3 **4**

In conclusion, a rapid and environmentally benign method for oxidative cyclization of 2-pyridyl- and 2-quinolylhydrazones to a triazole derivative is demonstrated. In terms of reaction time and yields, PIFA is a more efficient oxidant than IBD. The mild experimental conditions, solvent-free synthesis, operational simplicity, rapid conversions, and high yields of the product are attractive features of the present protocol. These results, therefore, could contribute to the development of sustainable methods in organic synthesis.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker Avance spectrometer (300 MHz) using TMS as internal standard. The elemental analyses were performed on a Carlo Erba 1106 instrument. Melting points were determined on a Buchi oil-heated melting apparatus and are uncorrected.

2-Pyridyl- and 2-quinolylhydrazones were prepared as reported previously [38], not additionally purified, and used directly in oxidative cyclization. All chemicals used in this study were of the highest purity available and purchased from Lancaster, Merck, and Fluka.

The Oxidative Cyclization of 2-Pyridyl- and 2-Quinolylhydrazones with PIFA (General Method). A mixture of the correspoding hydrazone (1.0 mmol) and PIFA (516 mg, 1.2 mmol) was blended thoroughly in a mortar. The resulting homogeneous mixture was ground with a pestle at room temperature for 5-10 min. The progress of reaction was monitored by TLC (benzene–acetone, 4:1). After completion of the reaction as indicated by the appearance of liquid in the reaction mixture, 20 ml of 5% solution of sodium bicarbonate was added. The reaction mixture was filtered, and the solid collected on the filter was recrystallized from ethanol to afford the respective cyclized product **3** or **4.**

TABLE 3. ^{1}H NMR and IR Spectra of Compounds **2a–i** and **4a–h**

Com-pound	IR, ν, cm^{-1}	^{1}H NMR ($CDCl_3$), δ, ppm (*J*, Hz)
2a	3071, 3042, 1620, 1588, 1497, 1370, 1064, 780, 750, 710	6.86-6.90 (1H, m, H Ar); 7.30 (1H, m, H Ar); 7.55-7.65 (3H, m, H Ar); 7.80-7.85 (3H, m, H Ar); 8.30 (1H, d, *J* = 7.2, H Ar)
2b	3074, 3036, 2988, 1628, 1502, 1375, 1005, 847, 744	2.43 (3H, s, CH_3); 7.23 (2H, d, *J* = 7.8, H Ar); 7.37 (1H, m, H Ar); 7.43 (2H, d, *J* = 7.8, H Ar); 7.83 (2H, m, H Ar); 8.31 (1H, m, H Ar)
2c	3033, 3022, 1631, 1475, 1406, 1367, 1312, 1090, 1060, 985, 827, 754, 741, 716	7.21 (1H, m, H Ar); 7.27-7.49 (4H, m, H Ar); 7.52 (1H, m, H Ar); 7.84 (1H, m, H Ar); 8.30 (1H, d, *J* = 7.2, H Ar)
2d	3055, 3033, 1629, 1578, 1511, 1475, 1243, 1052, 830, 755	3.89 (3H, s, OCH_3); 6.98 (2H, d, *J* = 8.1, H Ar); 7.45-7.51 (4H, m, H Ar); 7.81 (1H, m, H Ar); 8.29 (1H, d, *J* =7.2, H Ar).
2e	3098, 3067, 1631, 1598, 1533, 1490, 1341, 1101, 1023, 755	7.40-7.41 (1H, m, H Ar); 7.59-7.64 (2H, m, H Ar); 7.85-8.05 (2H, m, H Ar); 8.35 (1H, d, *J* = 7.2, H Ar)
2f	3122, 3051, 1635, 1598, 1494, 1110, 1066, 791, 752, 722	6.90-6.96 (1H, m, H Ar); 7.20-7.30 (2H, m, H Ar); 7.52 (1H, d, *J* = 3.2, H Ar); 7.65-7.80 (2H, m, H Ar); 8.38 (1H, d, *J* = 8.0, H Ar)
2g	3068, 3014, 1580, 1487, 1461, 1212, 837, 734	6.86-6.90 (1H, m, H Ar); 7.25-7.30 (3H, m, H Ar); 7.80-7.90 (3H, m, H Ar); 8.27 (1H, d, *J* = 7.2, H Ar)
2h	3066, 3016, 1605, 1556, 1502, 1457, 1233, 1025, 752, 710	3.83 (3H, s, OCH_3); 6.80-6.85 (1H, m, H Ar); 7.10-7.20 (2H, m, H Ar); 7.30-7.35 (1H, m, H Ar); 7.55-7.60 (1H, m, H Ar); 7.70-7.90 (2H, m, H Ar); 8.29 (1H, d, *J* = 7.2, H Ar)
2i	3122, 3051, 1635, 1598, 1494, 1110, 1066, 791, 752, 722	6.65-6.70 (1H, m, H Ar); 6.90-6.95 (1H, m, H Ar); 7.25-7.35 (2H, m, H Ar); 7.65-7.80 (2H, m, H Ar); 8.31 (1H, d, *J* = 7.2, H Ar)
4a	3058, 3033, 1613, 1577, 1490, 1366, 1027, 743, 713	2.59 (3H, s, CH_3); 7.28-7.82 (10H, m, H Ar).
4b	3068, 3054, 3011, 2917, 1607, 1592, 1503, 1464, 1046, 833, 782	2.48 (3H, s, CH_3); 2.60 (3H, s, CH_3); 7.14-7.85 (9H, m, H Ar)
4c	3073, 3022, 3009, 1617, 1585, 1503, 1470, 828, 785	2.60 (3H, s, CH_3); 7.31-7.92 (9H, m, H Ar)
4d	3072, 3032, 3006, 2966, 2897, 1632, 1598, 1505, 1442, 1258, 1103, 841, 744	2.61 (3H, s, CH_3); 3.85 (3H, s, OCH_3); 7.05-7.95 (9H, m, H Ar)
4e	3095, 3066, 3022, 2905, 1622, 1600, 1537, 1510, 1445, 1353, 1260, 860, 837, 722	2.62 (3H, s, CH_3); 7.27-8.00 (7H, m, H Ar)
4f	3103, 3077, 3021, 2955, 1619, 1602, 1472, 1119, 1023, 789, 747	2.60 (3H, s, CH_3); 7.31-7.98 (8H, m, H Ar)
4g*	3058, 3027, 2912, 1622, 1592, 1548, 1461, 1361, 1023, 862, 828, 739	2.68 (3H, s, CH_3); 7.32-8.42 (9H, m, H Ar)
4h	3079, 3041, 3011, 2952, 2887, 1603, 1588, 1499, 1262, 1198, 1023, 902, 852, 752	2.64 (3H, s, CH_3); 3.82 (3H, s, OCH_3); 3.95 (3H, s, OCH_3); 7.00-7.92 (8H, m, H Ar)

*^{1}H NMR spectra were recorded in DMSO-d_6.

The Oxidative Cyclization of 2-Pyridyl- and 2-Quinolylhydrazones with IBD (General Method). A mixture of a 2-pyridyl- (**1**) or 2-quinolylhydrazone (**3**) (1.0 mmol) and IBD (1.2 mmol) was blended thoroughly with a pestle in a mortar. The resulting homogeneous mixture was ground at room temperature for 15-25 min. In the case of the oxidative cyclization of 2-quinolylhydrazones, the reaction mass was first kept in the oven for 4-5 min at 40-50°C to initiate the reaction and then ground for 15 min. The progress of the reaction was monitored by TLC (benzene–acetone, 4:1). After completion of the reaction as indicated by the appearance of

liquid in the reaction mixture, 20 ml of 5% solution of sodium bicarbonate was added. The reaction mixture was filtered, and the solid collected on the filter was recrystallized from ethanol to afford the respective cyclized product **3** or **4**.

REFERENCES

1. L. J. Guetzoyan, R. A. Spooner, J. M. Lord, L. M. Roberts, and G. J. Clarkson, *Eur. J. Med. Chem.*, **45**, 275 (2010).
2. S. Rollas, N. Kalyoncuoglu, D. Sur-Altiner, and Y. Yegenoglu, *Pharmazie*, **48**, 308 (1993).
3. J. F. Chollet, J. L. Bonnemain, L. Miginiac, and O. J. Rohr, *Pestic. Sci.*, **29**, 427 (1990).
4. A. S. Shawali, H. M. Hassaneen, and N. K. Shurrab, *Tetrahedron*, **64**, 10339 (2008).
5. N. Demirbas, S. A. Karaoglu, A. Demirbas, and K. Sancak, *Eur. J. Med. Chem.*, **39**, 793 (2004).
6. N. Gulerman, S. Rollas, M. Kiraz, A. C. Ekinci, and A. Vidin, *Farmaco*, **52**, 691 (1997).
7. J. M. Kane, B. M. Baron, M. W. Dudley, S. M. Sorensen, M. A. Staeger, and F. P. Miller, *J. Med. Chem.*, **33**, 2772 (1990).
8. O. Bekircan, M. Küxük, B. Kahveci, and S. Kolaylı, *Arch. Pharm. Chem. Life Sci.*, **338**, 365 (2005).
9. B. S. Holla, B. Veerendra, M. K. Shivananada, and B. Poojari, *Eur. J. Med. Chem.*, **38**, 759 (2003).
10. Z. G. Turan-Zitouni, M. Sıvacı, F. S. Kılıç, and K. Erol, *Eur. J. Med. Chem.*, **36**, 685 (2001).
11. B. Modzelewska and J. Kalabun, *Pharmazie*, **54**, 503 (1999).
12. K. S. Bhat, B. Poojary, D. J. Prasad, P. Naik, and B. S. Holla, *Eur. J. Med. Chem.*, **44**, 5066 (2009).
13. B. S. Holla, S. B. Rao, B. K. Sarojini, P. M. Akberali, and N. S. Kumari, *Eur. J. Med. Chem.*, **41**, 657 (2006).
14. N. U. Güzeldemirci and O. Küçükbasmacı, *Eur. J. Med. Chem.*, **45**, 63 (2010).
15. T. Karabasanagouda, A. V. Adhikari, and N. S. Shetty, *Eur. J. Med. Chem.*, **42**, 521 (2007).
16. P. Kumar, J. Mohan, and J. K. Makrandi, *Indian J. Chem.*, **46B**, 1883 (2007).
17. S. Shelke, N. Salunkhe, S. Sangale, S. Bhalerao, N. Naik, G. Mhaske, R. Jadhav, and B. Karale, *J. Korean Chem. Soc.*, **54**, 59 (2010).
18. R. H. Udupi, Sudheendra, Bheemachari, N. Srinivasulu, R. Varnekar, and P. Purushottamachar, *Bull. Korean Chem. Soc.*, **28**, 2235 (2007).
19. R. M. Moriarty, S. C. Gupta, H. Hu, D. R. Berenschot, and K. B. White, *J. Am. Chem. Soc.*, **103**, 686 (1981).
20. R. M. Moriarty, O. Prakash, M. P. Duncan, R. K. Vaid, and N. Rani, *J. Chem. Res. Synopses*, **9**, 432 (1996).
21. H. Tohma, S. Takizawa, H. Watanabe, and Y. Kita, *Tetrahedron Lett.*, **39**, 4547 (1998).
22. R. M. Moriarty, R. K. Vaid, M. P. Duncan, M. Ochiai, M. Inenaga, and Y. Nagao, *Tetrahedron Lett.*, **29**, 6913 (1988).
23. H. Tohma, S. Takizawa, H. Watanabe, Y. Fukuoka, T. Maegawa, and Y. Kita, *J. Org. Chem.*, **64**, 3519 (1999).
24. V. V. Zhdankin and P. J. Stang, *Chem. Re*v., **108**, 5299 (2008).
25. T. Dohi, N. Takenaga, A. Goto, H. Fujioka, and Y. Kita, *J. Org. Chem.*, **73**, 7365 (2008).
26. P. Fontaine, A. Chiaroni, G. Masson, and J. Zhu, *Org. Lett.*, **10**, 1509 (2008).
27. N. Chatterjee, P. Pandit, S. Halder, A. Patra, and D. K. Maiti, *J. Org. Chem.*, **73**, 7775 (2008).
28. A. Varvoglis, *Tetrahedron*, **53**, 1179 (1997).
29. M. Bielawski and B. Olofsson, *Org. Synth.*, **86**, 308 (2009).
30. M. S. Yusubov and T. Wirth, *Org. Lett.*, **7**, 519 (2005).
31. P. Kumar, *Chin. J. Chem.*, **27**, 1487 (2009).
32. R. Gupta, A. Jain, M. Jain, and R. Joshi, *Bull. Korean Chem. Soc.,* **31**, 3180 (2010).

33. P. Kumar, *J. Heterocycl. Chem.*, **47**, 1429 (2010).
34. P. Kumar, *Chin. J. Chem.*, **28**, 250 (2010).
35. A. Kumar, A. Chawala, S. Jain, P. Kumar, and S. Kumar, *Med. Chem. Res.*, **20**, 678 (2010).
36. P. Kumar and A. Kumar, *Bull. Korean Chem. Soc.*, **31**, 2299 (2010).
37. P. Kumar and A. Kumar, *Chin. Chem. Lett.,* **22**, 2011, 37.
38. A. K. Sadana, Y. Mirza, R. K. Aneja, and O. Prakash, *Eur. J. Med. Chem.*, **38**, 533 (2003).