SOLVENT-FREE, ONE-POT SYNTHESIS OF 2,4,6-TRIARYLPYRIDINES USING TRICHLOROISOCYANURIC ACID OR *N*-BROMOSUCCINIMIDE AS A NOVEL AND NEUTRAL CATALYST

Behrooz MALEKI[1,*], Hafezeh SALEHABADI[2], Zeinalabedin SEPEHR[3] and Mina KERMANIAN[4]

Department of Chemistry, Sabzevar Tarbiat Moallem University, 397 Sabzevar, Iran; e-mail: [1] maleki@sttu.ac.ir, [2] hafezeh_s6245@yahoo.com, [3] szeinalabedin@yahoo.com, [4] m_kermaniyan@yahoo.com

Received January 26, 2011
Accepted June 3, 2011
Published online October 30, 2011

A simple and benign protocol has been explored for the preparation of 2,4,6-triarylpyridines by a one-pot reaction between aryl aldehydes, enolizable ketones and ammonium acetate in the presence of *N*-bromosuccinimide or trichloroisocyanuric acid as green and neutral catalysts. The reactions proceed smoothly at 130 °C under solvent-free conditions to provide 2,4,6-triarylpyridines in good yields.

Keywords: 2,4,6-Triarylpyridines; Aldehydes; Ketones; Ammonium acetate; *N*-Bromosuccinimide; Trichloroisocyanuric acid; Green chemistry.

In the past few decades, the synthesis of new heterocyclic compounds has been a subject of great interest due to their wide range applicability. Heterocyclic compounds occur very widely in nature and are essential to life. Among a large variety of heterocyclic compounds, heterocycles containing the pyridine moiety receive much interest[1–3]. 2,4,6-Triarylpyridines known as Krohnke pyridines are considered as prominent building blocks in supramolecular chemistry[4]. Many naturally occurring derivatives of these compounds such as NAD nucleotides, pyridoxol (vitamin B_6), and pyridine alkaloids posses important biological properties[5]. In addition, many of these compounds have been reported in medicinal and pharmaceutical literature as antimalarial, anticonvulsant, anesthetic, antiinflammatorial, antioxidant, antibacterial, and antiparasitic agents[6–10]. Also, a number of 2,4,6-triarylpyridines are known as luminescence compounds[11].

Hence, in view of their wide range applications as pharmaceutical and industrial agents as well as in organic synthesis, a good number of methods have been developed for the synthesis of Krohnke type pyridines[12]. Tradi-

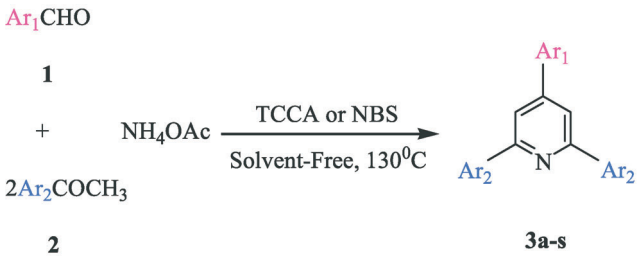
doi:10.1135/cccc2011021

tionally, Krohnke-type pyridines have been synthesized through the reaction of *N*-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate[12,13]. The same compounds have also been synthesized via condensation reaction of 1,5-diketones with formamide-ammonium formate[14] and by other synthetic procedures[12].

More recently, one-pot syntheses of 2,4,6-triarylpyridines by three-component condensation between aromatic ketones, aldehydes, and ammonium acetate have been reported[15–26]. However, many of the previously established methods are subject to certain disadvantages including multi-step procedures, use of costly and toxic catalysts, acidic media and organic solvents. To avoid such drawbacks, development of more simple, inexpensive, environmentally benign and efficient protocols are still in demand.

RESULTS AND DISCUSSION

In recent years, solvent-free organic reactions[27] have caused great interests, because they have many advantages such as high efficiency and selectivity, very facile separation and purification, mild reaction conditions, and beneficial to industry as well as for environment. In continuation of our ongoing endeavour on the application of heterogeneous and solvent-free conditions for the synthesis of organic compounds[28]. Herein, we describe a practical and simple method to prepare 2,4,6-triarylpyridines by a three-component condensation of aromatic ketones or aldehydes with ammonium acetate under solvent-free conditions at 130 °C using *N*-bromosuccinimide (NBS) or trichloroisocyanuric acid (TCCA) as catalysts (Scheme 1).



SCHEME 1

We have previously examined NBS and TCCA as efficient catalysts in our various reported transformations[29]. To the best of our knowledge, the application of TCCA and NBS as catalysts in the synthesis of the title compounds has not been previously explored.

Trichloroisocyanuric acid (TCCA) is an inexpensive, eco-friendly and versatile reagent which has been used in the synthesis of various organic com-

pounds. This compound has been reported to effectively promote many transformations including the synthesis of benzimidazoles[30], oxidation of urazoles[31], synthesis of 1,8-dioxooctahydroxanthenes[32], synthesis of 2-arylbenzothiazoles and bisbenzothiazoles[33], and chemoselective dehydration of 2-imidazolines[34]. It has been also employed in the synthesis of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles[35].

In order to optimize the reaction conditions, effects of catalyst concentration and reaction temperature were investigated in the synthesis of 2,4,6-triphenylpyridine (**3a**) as the model reaction. A mixture of benzaldehyde (1 mmol), acetophenone (2 mmol) and ammonium acetate (1.3 mmol) was stirred under various reaction conditions and the resulting data are summarized in Table I. The role of TCCA as a catalyst was evaluated by conducting the reaction in the absence of TCCA and no formation of the respective product was noticed after 6 h (entry 1), while good yields were obtained in the presence of TCCA (entries 2–8). The most effective amount of TCCA to promote this reaction was found to be 2 mole %, which brings the formation of the products in highest possible yields (entry 3). The effect of temperature on the reaction was also studied by carrying out the model reaction in the presence of TCCA (2 mole %) at various temperatures such as 100, 110, 120, 130, and 140 °C. Among these, 130 °C was found to be the temperature of choice in terms of yields.

TABLE I
Optimizing the reaction conditions

Entry	Catalyst, mole%	Temperature, °C	Time, h	Yield, %[a]
1	–	120	5	–
2	1	110	4	42
3	2	110	4	64
4	5	110	4	62
5	2	100	4.5	60
6	2	120	4	70
7	2	130	4	82
8	2	140	4	74
9[b]	2	80	3	24

[a] Isolated yield. [b] The reaction was carried out under reflux in EtOH.

To develop the scope of reaction, a wide range of aldehydes and ketones was subjected to TCCA-catalyzed reaction under the optimized conditions (Table II). In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in good yields. It was founds that aromatic aldehydes

TABLE II
NBS or TCCA-catalyzed solvent-free synthesis of 2,4,6-triarylpyridines

Products[a]	Ar_1	Ar_2	Time, h **I** (**II**)[b]	Yield, %[c] **I** (**II**)	M.p., °C	
					Found	Reported[a]
3a	C_6H_5	C_6H_5	3.5 (4)	88 (82)	132–134	134–135
3b	4-ClC_6H_4	C_6H_5	4 (4.5)	82 (64)	120–122	122–124
3c	C_6H_5	4-$CH_3C_6H_4$	4 (5)	66 (52)	153–155	159–160
3d	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	4 (5)	78 (64)	178–179	176–177
3e	4-OHC_6H_4	C_6H_5	5 (6)	72 (54)	195–196	197
3f	2-$CH_3C_6H_4$	C_6H_5	3.5 (5)	82 (68)	119–120	120–122
3g	4-$MeOC_6H_4$	4-$CH_3C_6H_4$	4 (5)	86 (62)	152–154	155–157
3h	4-$N(CH_3)C_6H_4$	C_6H_5	3 (3.5)	80 (62)	136–138	138–140
3i	4-ClC_6H_4	4-$CH_3C_6H_4$	4.5 (6)	84 (72)	198–200	199–201
3j	4-ClC_6H_4	4-$MeOC_6H_4$	3.5 (5)	88 (74)	112–114	115–116
3k	4-$MeOC_6H_4$	C_6H_5	3 (4.5)	88 (70)	99–100	100–103
3l	2-Furyl	C_6H_5	4 (4.5)	74 (60)	164–165	165–166
3m	2-ClC_6H_4	C_6H_5	3.5 (4)	76 (64)	114–116	113–114
3n	2-Thienyl	C_6H_5	4 (5)	84 (62)	172–174	168–170
3o	4-BrC_6H_4	C_6H_5	4 (5)	88 (70)	164–166	166–167
3p	4-$NO_2C_6H_4$	C_6H_5	2.5 (3)	90 (76)	196–198	198–200
3q	4-$NO_2C_6H_4$	4-FC_6H_4	2 (3)	92 (82)	248–250	–
3r	4-CNC_6H_4	4-FC_6H_4	2 (3)	90 (80)	228–230	–
3s	4-BrC_6H_4	4-FC_6H_4	3 (3.5)	82 (80)	192–194	–

[a] All isolated products were characterized on the basis of their physical properties and IR, 1H NMR spectral analysis and by direct comparision with authentic materials. [b] The reaction time and yields obtained by trichloroisocyanuric acid are given in parentheses. [c] Isolated yields. [d] Literature data: **3a–3e**[10], **3f–3n**[5], **3o**[12], **3p**[24].

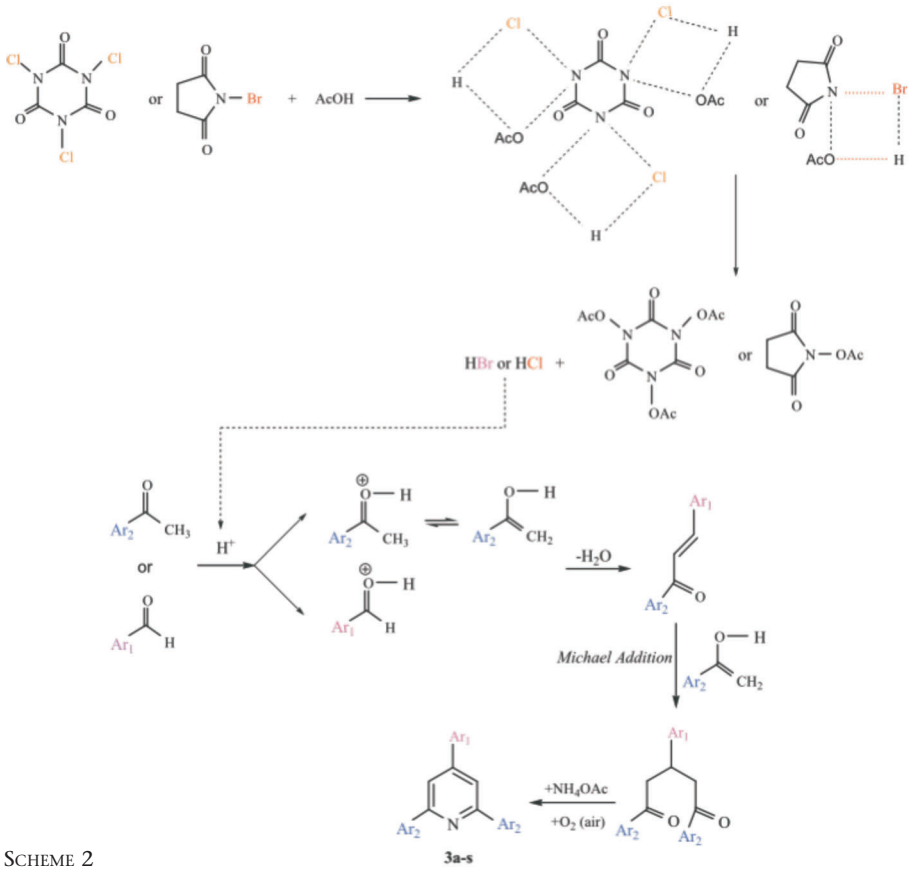
with electron-withdrawing groups reacted faster than those with electron-donating groups, as would be expected.

However, despite many advantages allocated to TCCA as a catalyst, the reactions proceeded with longer times and low yields. In view of these drawbacks, we were prompted to examine the catalytic capacity of NBS in the synthesis of 2,4,6-triarylpyridines owing to its previously reported successful applications in various organic reactions[36].

In our ongoing research on the use of NBS in various transformations[29c,29d], it was found to efficiently catalyze the one-pot synthesis of 2,4,6-triarylpyridines from aldehydes and ketones. We first studied a reaction between benzaldehyde (1 mmol), acetophenone (2 mmol), and ammonium acetate (1.3 mmol) by screening the reaction conditions. In order to determine the optimum conditions, we examined the influence of reaction temperature, reaction time, and amount of the catalyst. We noticed that the best result was obtained with 10 mole % of NBS at 130 °C. Following optimizing the conditions, we examined generality of these conditions to other substrates using several aldehydes and ketones (Table II).

We compared results of NBS with TCCA in the synthesis of 2,4,6-triarylpyridines. As shown in Table II, NBS can act as an effective catalyst for the mentioned transformation.

Since NBS or TCCA contain Br^+ or Cl^+ atoms which are attached to nitrogen atoms, it is very probable that these reagents release Br^+ and Cl^+, respectively, *in situ* which can act preparation of an electrophilic species[29–35]. However, we do not believe that traces of Br^+ or Cl^+ are catalyzing the reaction[36f]. One explanation for this process is that TCCA or NBS probably generates small quantities of HBr or HCl *in situ*, which may be the actual catalyst for the synthesis of 2,4,6-triarylpyridines reaction (as a protic acid). This explanation is supported based on our observations that: (i) When the reaction of benzaldehyde (1 mmol) with acetophenone (2 mmol) and ammonium acetate (1.3 mmol) was conducted in the presence of a catalytic amount of saturated HBr instead of NBS, the reaction rate considerably increased and the reaction was completed within 4.5 h giving 42% yield. This could be due to the presence of larger amount of HBr in the reaction compared with the small amount of HBr generated from NBS when used as the catalyst. (ii) In an attempt to synthesis of 2,4,6-triphenylpyridine from this reaction using TCCA as the catalyst in the presence of Br_2, only trace amount of the product was obtained after 6 h. (iii) The pH of reaction was



SCHEME 2

measured to be 2.5 proving the presence of an acid. In view of these observations, we suggest a mechanism for this reaction as shown in Scheme 2.

CONCLUSION

In conclusion, we have developed an efficient and benign procedure for the synthesis of 2,4,6-triarylpyridines from a one-pot reaction of aldehydes or ketones, with ammonium acetate in the presence of NBS or TCCA as catalysts. This protocol may be considered as environmentally friendly since no solvent has been necessarily used in these reactions and the catalysts employed are regarded as non-polluting reagents.

EXPERIMENTAL

Solvents, reagents, and chemical materials were obtained from Aldrich (USA), Merck (Germany) and Fluka (Switzerland) chemical companies and purified prior to use. Melting points were determined in open capillary tubes in a BI Branstead Electrothermal Cat No. IA9200 apparatus and are uncorrected. ^{1}H NMR spectra (δ, ppm) were recorded on Jeol FT NMR 90 MHz using tetramethylsilane (TMS) as an internal standard. IR spectra (ν, cm^{-1}) were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets).

Synthesis of 2,4,6-Triarylpyridines. General Procedure

To a stirred mixture of the aldehyde **1a–1o** (1 mmol), ketone (2 mmol), and ammonium acetate (1.3 mmol) TCCA (2 mole %) was added at room temperature. The mixture was heated to 130 °C and the progress of the reaction was followed by TLC. After completion of the reaction (3–6 h), 96% EtOH (5 ml) was added to the reaction mixture. The mixture was filtered to remove the resulting precipitate, the filtrate was evaporated and the residue was recrystallized from 96% EtOH (2 × 5 ml) to afford pure 2,4,6-triarylpyridines. In a separate set of experiments, these reactions were all repeated using NBS (10 mole %) at 130 °C (Table II).

Spectral Data for New Target Compounds

4-(4-Nitrophenyl)-2,6-bis(4-fluorophenyl)pyridine (**3q**). A brown solid, m.p. 248–250 °C. IR (KBr): 3010, 1600, 1582, 1330, 1220, 1160, 1120, 840. ^{1}H NMR (90 MHz, DMSO-d_6): 8.72–8.64 (m, 4 H, ArH), 8.52 (s, 2 H, pyridine-H), 8.32–8.14 (m, 5 H, ArH), 7.42–7.26 (m, 3 H, ArH). For $C_{23}H_{14}F_2N_2O_2$ (388.37) calculated: 71.13% C, 3.63% H, 7.21% N; found: 71.40% C, 3.54% H, 7.24% N.

4-(4-Cyanophenyl)-2,6-bis(4-fluorophenyl)pyridine (**3r**). A white solid, m.p. 228–230°C. IR (KBr): 3020, 2225, 1602, 1530, 1490, 1420, 1390, 1225, 1110, 838. ^{1}H NMR (90 MHz, $CDCl_3$): 8.61–8.52 (m, 4 H, ArH), 8.44 (s, 2 H, pyridine-H), 8.30–8.09 (m, 5 H, ArH), 7.31–7.01 (m, 4 H, ArH). For $C_{24}H_{14}F_2N_2$ (368.38) calculated: 78.25 % C, 3.83% H, 7.60% N; found: 78.18% C, 3.87% H, 7.68% N.

4-(4-Bromophenyl)-2,6-bis(4-fluorophenyl)pyridine (**3s**). A white solid, m.p. 192–194°C. IR (KBr): 3030, 1602, 1525, 1492, 1437, 1372, 1220, 828. ^{1}H NMR (90 MHz, $CDCl_3$): 8.41–8.37 (m, 2 H, ArH), 8.24 (s, 2 H, pyridine-H), 8.13–7.78 (m, 6 H, ArH), 7.32–7.06 (m, 5 H, ArH). For $C_{23}H_{14}BrF_2N$ (422.27) calculated: 65.42% C, 3.34% H, 3.32% N; found: 65.51% C, 3.36% H, 3.33% N.

Authors wish to thank the University of Sabzevar Tarbiat Moallem in Sabzevar for financial support to carry out this research. We also thank Ms. N. Rahiminezhad for her assistance.

REFERENCES

1. Lhoták P., Kurfürst A.: *Collect. Czech. Chem. Commun.* **1992**, *57*, 1937.
2. Elnagdi M. H., Elmoghayar M. R. H., Elghandour A. H. H., Sadek K. U.: *Collect. Czech. Chem. Commun.* **1990**, *55*, 745.
3. Pareek M. P. K., Chippa H., Ojha R. K. G.: *Collect. Czech. Chem. Commun.* **2010**, *75*, 275.

4. Cave G. W. V., Hardie M. J., Roberts B. A., Raston C. L.: *Eur. J. Org. Chem.* **2001**, 3227.
5. Balasubramanian M., Keay J. G. in: *Comprehensive Heterocyclic Chemistry II* (A. R. Katritzky, C. W. Rees and E. V. F. Scriven, Eds), Vol. 5, Chap. 6, pp. 245–300. Pergamon Press, London 1996.
6. Kim B. Y., Ahn J. B., Lee H. W., Kang S. K., Lee J. H., Shin J. S., Ahn S. K., Hong C. I., Yoon S. S.: *Eur. J. Med. Chem.* **2004**, *39*, 433.
7. Klimešová V., Svoboda M., Waisser K., Pour M., Kaustová J.: *Farmaco* **1999**, *54*, 666.
8. Adib M., Tahermansouri H., Koloogani S. A., Mohammadi B., Bijanzadeh H. R.: *Tetrahedron Lett.* **2006**, *47*, 5957.
9. Kumar A., Koul S., Razdan T. K., Kapoor K. K.: *Tetrahedron Lett.* **2006**, *47*, 837.
10. Abdel-Monem M. I.: *Collect. Czech. Chem. Commun.* **1994**, *59*, 978.
11. Kurfürst A., Lhoták P., Petrů M., Kuthan J.: *Collect. Czech. Chem. Commun.* **1989**, *54*, 462.
12. Krohnke F.: *Synthesis* **1976**, 1.
13. Krohnke F., Zecher W.: *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 626.
14. Chubb F., Hay A. S., Sandin R. B.: *J. Am. Chem. Soc.* **1953**, *75*, 6042.
15. Heravi M. M., Bakhtiari K., Daroogheha Z., Bamoharram F. F.: *Catal. Commun.* **2007**, *8*, 1991.
16. Tu S., Li T., Shi F., Fang F., Zhu S., Wei X., Zong Z.: *Chem. Lett.* **2005**, *35*, 732.
17. Nagarapu L., Peddiraju A. R., Apuri S.: *Catal. Commun.* **2007**, *8*, 1973.
18. Tu S., Jia R., Jiang B., Zhang J., Zhang Y., Yao C., Ji S.: *Tetrahedron* **2007**, *63*, 381.
19. Tu S., Li T., Shi F., Wang Q., Zhang J., Xu J., Zhu X., Zhang X., Zhun S., Shi D.: *Synthesis* **2005**, 3045.
20. Ren Y. M., Cai C.: *Monatsh. Chem.* **2009**, *140*, 49.
21. Borthakur M., Dutta M., Gogoi S., Boruah R. C.: *Synlett* **2008**, 3125.
22. Huang X. Q., Li H. X., Wang J. X., Jia X. F.: *Chin. Chem. Lett.* **2005**, *16*, 607.
23. Ingole P. G., Jadhav S. V., Bajaj H. C.: *Int. J. Chem. Tech. Res.* **2010**, *2*, 289.
24. Davoodnia A., Bakavoli M., Moloudi R., Tavakoli-Hoseini N., Khashi M.: *Monatsh. Chem.* **2010**, *141*, 867.
25. He Q., Wang J., Feng R.: *Lett. Org. Chem.* **2010**, *7*, 172.
26. Khosropour A. R., Mohammadpoor-Baltork I., Kiani F.: *Compt. Rend. Chim.* **2011**, *14*, 441.
27. a) Cihelník S., Stibor I., Lhoták P.: *Collect. Czech. Chem. Commun.* **2002**, *67*, 1779; b) Hosseini-Sarvari M.: *J. Iran. Chem. Soc.* **2011**, *8*, S119; c) Ghorbani-Vaghei R., Malaekehpoor S. M.: *J. Iran. Chem. Soc.* **2010**, *7*, 957.
28. a) Hojati S. F., Mohammadpoor-Baltork I., Maleki B., Gholizadeh M., Shafiezadeh F., Haghdoust M.: *Can. J. Chem.* **2010**, *88*, 135; b) Maleki B., Salehabadi H., Khodaverdian-Moghadam M.: *Acta Chim. Slov.* **2010**, *57*, 741; c) Maleki B.: *Collect. Czech. Chem. Commun.* **2011**, *76*, 27; d) Maleki B., Azarifar D., Veisi H., Hojati S. F., Salehabadi H., Nejat-Yami R.: *Chin. Chem. Lett.* **2010**, *21*, 1346; e) Hojati S. F., Maleki B., Beykzadeh Z.: *Monatsh. Chem.* **2011**, *142*, 87.
29. a) Azarifar D., Maleki B.: *J. Chin. Chem. Soc.* **2005**, *52*, 1215; b) Zolfigol M. A., Azarifar D., Maleki B.: *Tetrahedron Lett.* **2004**, *45*, 2181; c) Azarifar D., Maleki B.: *Heterocycles* **2005**, *65*, 865; d) Maleki B., Azarifar D., Ghorbani-Vaghei R., Veisi H., Hojati S. F., Gholizadeh M., Salehabadi H., Khodaverdian-Moghadam M.: *Monatsh. Chem.* **2009**, *140*, 1485.
30. Bigdeli M. A., Dostmohammadi H., Mahdavinia G. H., Nemati F.: *J. Heterocycl. Chem.* **2008**, *45*, 1203.

31. Zolfigol M. A., Madrakian E., Ghaemi E., Mallakpour S.: *Synlett* **2002**, 1633.
32. Bigdeli M., Nemati F., Mahdavinia G. H., Dostmohammadi H.: *Chin. Chem. Lett.* **2009**, *20*, 1275.
33. Xiao H. L., Chen J. X., Liu M. C., Zhu D. J., Ding J. C., Wu H. Y.: *Chem. Lett.* **2009**, *38*, 170.
34. Mohhamadpoor-Baltork I., Zolfigol M. A., Abdollahi-Alibeik M.: *Synlett* **2004**, 2803.
35. Pore D. M., Mahadik S. M., Desai U. V.: *Synth. Commun.* **2008**, *38*, 3121.
36. a) Karimi B., Zareyee D.: *J. Iran. Chem. Soc.* **2008**, *5*, S103; b) Park H. S., Choi H. J., Shin H. S., Lee S. K., Park M. S.: *Bull. Korean Chem. Soc.* **2007**, *28*, 751; c) Nozoe T., Shindo K., Wakabayashi H., Kurihara T., Ishikawa S.: *Collect. Czech. Chem. Commun.* **1991**, *56*, 991; d) Salama T. A., Lackner B., Falk H.: *Monatsh. Chem.* **2003**, *134*, 1113; e) Desvard O. E., Rozas M. F., Mirifico M. V.: *Collect. Czech. Chem. Commun.* **1989**, *54*, 2176; f) Khazaei A., Rostami A., Raiatzadeh A.: *J. Chin. Chem. Soc.* **2007**, *54*, 1029.