Arabian Journal of Chemistry (2014) 7, 335–339

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Synthesis of 1,8-dioxo-decahydroacridine derivatives using sulfonic acid functionalized silica (SiO_2-Pr-SO_3H) under solvent free conditions

Ghodsi Mohammadi Ziarani [a,*], **Alireza Badiei** [b], **Malihe Hassanzadeh** [a], **Somayeh Mousavi** [a]

[a] *Department of Chemistry, Alzahra University, Tehran, Iran*
[b] *School of Chemistry, College of Science, University of Tehran, Tehran, Iran*

Received 26 November 2010; accepted 4 January 2011
Available online 26 February 2011

KEYWORDS
1,8-Dioxo-decahydroacridines;
Sulfonic acid functionlized silica (SiO_2-Pr-SO_3H);
Dimedone;
Solvent free condition

Abstract Sulfonic acid functionlized silica (SiO_2-Pr-SO_3H) was found to be an efficient and recyclable solid acid catalyst in the synthesis of 1,8-dioxo-decahydroacridine derivatives under solvent free conditions. Short reaction time, excellent yields and simple work-up are the advantages of this procedure.

1. Introduction

The 1,4-dihydropyridine (DHP) derivatives are very important compounds because of their pharmacological properties (Klusa, 1995). Many members of this family are nowadays used for the treatment of platelet antiaggregatory activity, Alzheimer's disease (Bretzel et al., 1992), tumors (Boer and Gekeler, 1995), cardiovascular diseases including hypertension (Bossert et al., 1981; Nakayama and Kasoaka, 1996) and diabetes (Godfraid et al., 1986; Sausins and Duburs, 1988; Mager et al., 1992 and Mannhold et al., 1992). These compounds can also be used as dyes (Shanmugasundaram et al., 1993, 1996; Murugan et al., 1998; Han, 1971).

Some methods are available in the literature for the synthesis of acridine derivatives containing 1,4-dihydropyridines, from dimedone, aldehyde and different nitrogen sources like urea (Bakibaev et al., 1991), methyl amine (Hua et al., 2005) and different anilines or ammonium acetate (Martin et al., 1995) via traditional heating in organic solvents, in the presence of triethylbenzylammonium chloride (TEBAC) (Wang et al., 2004), *p*-dodecylbenzenesulfonic acid (DBSA) (Jin et al., 2004), Proline (Venkatesan et al., 2009), Amberlyst-15 (Das et al., 2006), ammonium chloride or $Zn(OAc)_2{\cdot}2H_2O$ or L-proline (Balalaie et al., 2009), under microwave irradiation (Tu et al., 2002; Wang et al., 2003) and using ionic liquids (Li et al., 2005; Wang et al.,2006a,b) such as 1-methylimidazolium triflouroacetate ([Hmim]TFA) (Dabiri et al., 2008), bronsted acidic imidazolium salts containing perfluoroalkyl tails (Shen et al., 2009).

---

[*] Corresponding author. Tel./fax: +98 21 88041344.
E-mail address: gmziarani@gmail.com (G.M. Ziarani).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

1878-5352 © 2011 Production and hosting by Elsevier B.V. on behalf of King Saud University.
http://dx.doi.org/10.1016/j.arabjc.2011.01.037

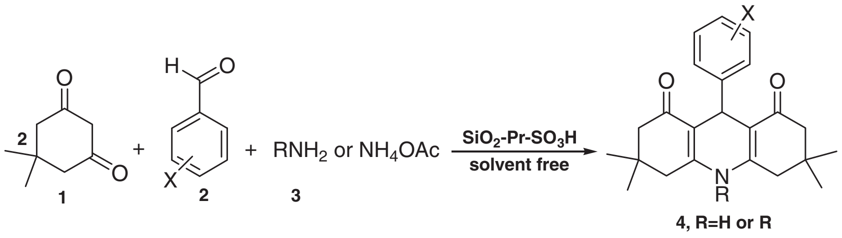
The application of heterogeneous catalysts to carry out various organic transformations has great importance in organic synthesis. These catalysts can conveniently be handled and removed from the reaction mixture, making the experimental procedure simple and ecofriendly. Therefore, the performing of an organic reaction using a simple and efficient catalyst will be an ideal methodology, if the catalyst shows high catalytical activity under solvent-free conditions. In continuation of our studies (Mohammadi Ziarani et al., 2008, 2009, 2010) on the application of heterogeneous solid catalyst in organic synthesis, we have decided to explore the catalytical activity of sulfonic acid functionalized silica (SiO_2-Pr-SO_3H) as a highly efficient heterogeneous acid catalyst toward the synthesis of 1,8-dioxo-decahydroacridine derivatives. Recently, its application has been reported in a few numbers of organic transformations (Karimi and Khalkhali, 2005; Gupta et al., 2007; Mahdavinia et al., 2009).

2. Results and discussion

In this paper, we wish to report a facile, efficient, and practical method for the preparation of 1,8-dioxo-decahydroacridines in excellent yields using silica-based sulfonic acid as a heterogeneous solid acid catalyst, which makes this reaction clean, safe and high-yielding process. The reaction was carried out under solvent free conditions at 120 °C for 2 h by taking a 1:1.2:2 mol ratio mixture of an aromatic aldehyde, an amine and 5,5-dimethyl-1,3-cyclohexanedione to give the desired products (Scheme 1). After dissolving the crude product in hot ethanol, the catalyst was removed from the reaction mixture by simple filtration and then, after cooling the filtrate, the pure products were obtained as yellow crystals. The results were shown in Table 1.

Both aromatic and aliphatic amines equally underwent the conversion well. Also electron-withdrawing or electron-donating groups present in the aromatic ring of the aldehydes have the same effect on the products. The temperature effect was studied by carrying out the reactions at different temperatures (room temperature, 50, 100 and 120 °C). By the raising of the reaction temperature, the yield of the reaction increases. Therefore, it was decided that the temperature of 120 °C is the best temperature for all reactions. The reaction mechanism is shown in Scheme 2. At first, the acid catalyst changes the aldehyde into convenient electrophil via protonation of the carbonyl group and then one molecule of dimedone condenses with the aromatic aldehyde to produce intermediate **5**. Then the active methylene group of the second molecule of dimedone reacts with **5** to give intermediate **6**. Nucleophilic attack of amine group of amonium acetate or each other amine group to carbonyl group creates intermediate **7**. In the next step, cyclization will occur by the nucleophilic attack of amine group to carbonyl group to obtain intermediate **8**. Finally, by the removal of one water molecule, the acridine derivatives **4** will be generated. The product structure was confirmed by IR, ^{1}H NMR and Gc-Mass data.

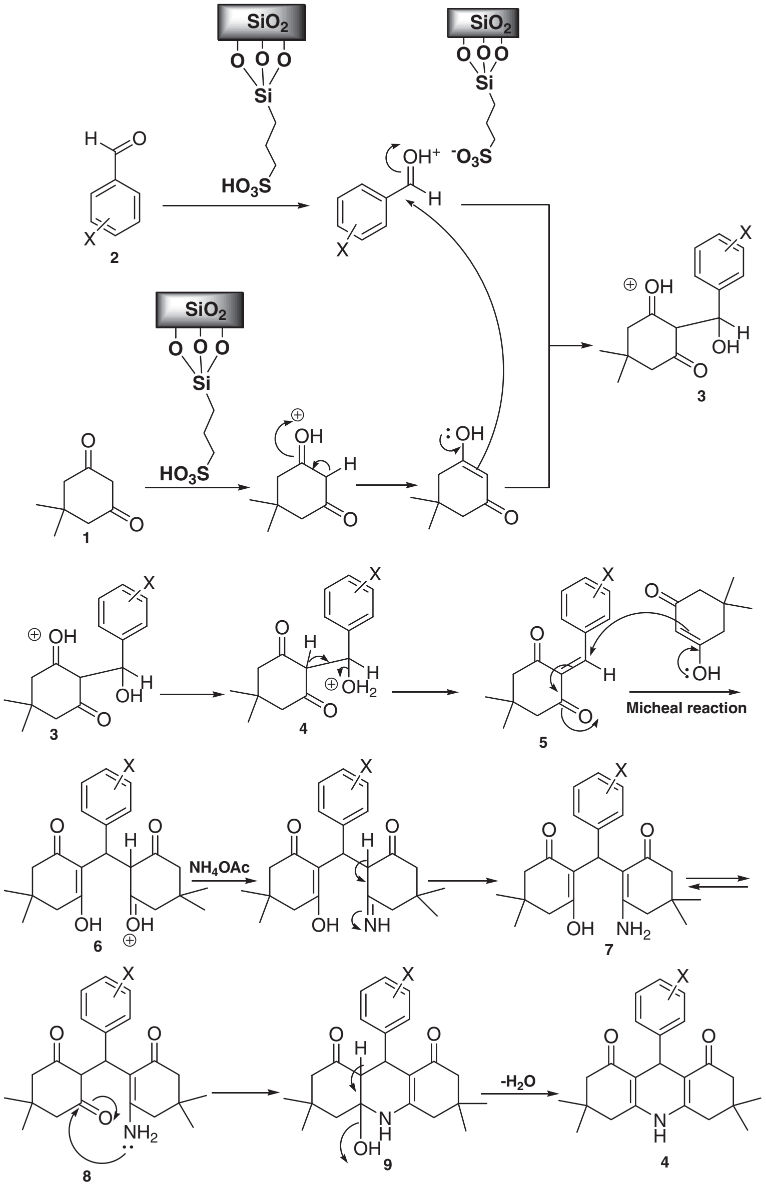
For the preparation of the catalyst, at first, the surface of silica was functionalized and grafted with (3-mercaptopropyl)trimethoxysilane (MPTS) (Lim et al., 1998; Van Rhijn et al., 1998) and then the thiol functionalities were oxidized into sulfonic acid groups by hydrogen peroxide to obtain silica based sulfonic acid (SiO_2-Pr-SO_3H) (Scheme 3). The surface of the catalyst was analyzed by different methods such as TGA,



Scheme 1 The synthesis of 1,8-dioxo-decahydroacridines in solvent free conditions.

Table 1 Synthesis of 1,8-dioxo-decahydroacridines in the presence of sulfonic acid functionalized silica under solvent-free conditions.

Entry	Aldehyde	Amine 3	Product	Yield (%)	mp (°C)	mp (°C)
1	4-$NO_2C_6H_4$	NH_4OAc	**4a**	92	320–322	300 (Bayer, 1971)
2	Ph	NH_4OAc	**4b**	85	277–279	272–273 (Wang et al., 2006)
3	4-$OCH_3C_6H_4$	NH_4OAc	**4c**	90	278–280	270–272 (Martin et al.,1995)
4	2,3-$(OCH_3)_2C_6H_4$	NH_4OAc	**4d**	86	324–326	–
5	3-$NO_2C_6H_4$	NH_4OAc	**4e**	87	307–310	296–297 (Wang et al., 2006)
6	4-$CH_3C_6H_4$	NH_4OAc	**4f**	86	279–281	318–320 (Fan et al., 2007)
7	4-ClC_6H_4	NH_4OAc	**4g**	95	317–320	300–302 (Bakibaev et al., 1991)
8	3-(OH)-4-$(OCH_3)C_6H_4$	NH_4OAc	**4h**	83	324–326	–
9	2-$OCH_3C_6H_4$	NH_4OAc	**4i**	88	294–296	247–249 (Pyrko, 2008)
10	4-OHC_6H_4	NH_4OAc	**4j**	85	284–286	–
11	4-$OCH_3C_6H_4$	3-$NO_2C_6H_4$	**4k**	95	276–278	276–278 (Das et al., 2006)
12	4-$OCH_3C_6H_4$	Ph	**4m**	94	218–220	220–222 (Das et al., 2006)
13	4-$OCH_3C_6H_4$	$PhCH_2$	**4n**	82	Viscous oil	Viscous oil (Das et al., 2006)
14	Ph	4-$CH_3C_6H_4$	**4o**	82	260–262	264–266 (Kumar and Sandhu, 2010)
15	Ph	Ph	**4p**	83	254–256	254–256 (Das et al., 2006)

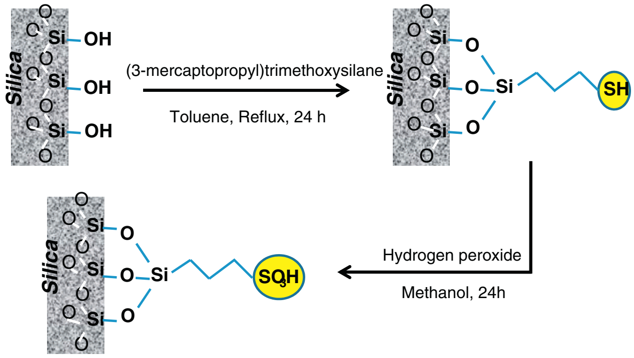


Scheme 2 The proposed mechanism.

BET and CHN methods which demonstrated that the organic groups (propyl sulfonic acid) were immobilized into the pores. Pore volume and average pore diameter of SiO_2-Pr-SO_3H are smaller than SiO_2 due to the immobilization of organic groups (propyl sulfonic acid) into the pores (Mohammadi Ziarani et al., 2009).

3. Experimental section: general information

All chemicals were obtained from Merck. Gc-Mass analysis was performed on a Gc-Mass model: 5973 network mass selective detector, Gc 6890 Agilent. IR spectra were recorded from KBr disk using an FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The ^1H NMR (250 MHz) was run on a Bruker DPX, 250 MHz. SiO_2 was purchased from Merck and its particle size, surface area, and average pore diameter are, respectively, 2–5 mm, 499 m^2/g, and 6.4 nm.



Scheme 3 The preparation of silica based sulfonic acid.

3.1. Preparation of catalyst: synthesis of 3-mercaptopropylsilica (MPS) and its oxidation

To 20 g of SiO_2 in dry toluene, 25 ml of (3-mercaptopropyl)trimethoxysilane was added, and the mixture of the reaction was refluxed for 24 h. After this period, the mixture was filtered to obtain 3-mercaptopropylsilica (MPS) which was washed with acetone and dried. 3-Mercaptopropylsilica (MPS) was oxidized with H_2O_2 (excess) and 2–3 drops of H_2SO_4 (conc) in methanol (20 ml) for 24 h at rt and then the mixture was filtered and washed with H_2O, and then acetone to obtain SiO_2-Pr-SO_3H catalyst. The modified SiO_2-Pr-SO_3H was dried and used as a solid acid catalyst in the organic synthesis.

3.2. General procedure for the preparation of 1,8-dioxo-decahydroacridine derivatives

Sulfonic acid functionalized silica (0.02 g) was activated in vacuum at 100 °C and then after cooling to room temperature, aromatic aldehyde (1 mmol), amine (1.2 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (2 mmol) were added to it. The mixture was stirred at 120 °C for 2 h under solvent free conditions. After completion of the reaction which was monitored by TLC (*n*-hexan/EtOAc, 3/1), the crude product was dissolved in hot ethanol and then the catalyst was removed by filtration. The pure product was obtained by cooling of the filtrate. The products are known compounds and were characterized by IR and NMR spectroscopy data for new compounds. Their melting points are compared with reported values in the literature. The catalyst was washed subsequently with diluted acid solution, distilled water and then acetone, dried under vacuum and re-used for several times without loss of significant activity.

*3.2.1. 3,3,6,6-Tetramethyl-9-(4-methoxyphenyl)-1,8-dioxo-decahydroacridine (**4c**)*

IR (KBr): υ_{max} = 3205, 1644, 1607, 1482, 1366, 1223 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.947 (S, 6H), 1.056 (S, 6H), 2.09–2.16 (dd, 4H), 2.19–2.28 (dd, 4H), 3.66 (S, 3H), 5.04 (S, 1H), 6.69–6.73 (d, 2H), 7.23, 7.26 (d, 2H), 8.22 (S, 1H) ppm. Mass (*m*/*e*): 379, 377.

*3.2.2. 3,3,6,6-Tetramethyl-9-(2,3-dimethoxyphenyl)-1,8-dioxo-decahydroacridine (**4d**)*

IR (KBr): υ_{max} = 3449, 1614, 1487, 1365, 1225 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ = 0.84 (S, 6H), 0.96 (S, 6H), 1.87–2.22 (dd, 4H), 2.29–2.48 (dd, 4H), 3.69 (S, 3H), 3.81 (S, 3H), 5.03 (S, 1H), 6.64–6.78 (m, 3H), 9.19 (S, 1H) ppm. Mass (*m*/*e*): 409, 407, 376.

*3.2.3. 3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-1,8-dioxo-decahydroacridine (**4g**)*

IR (KBr): υ_{max} = 3174, 1651, 1609, 1491, 1365, 1221 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ = 0.95 (S, 6H); 1.07 (S, 6H); 2.11–2.18 (dd, 4H); 2.22–2.33 (dd, 4H); 5.0 (S, 1H); 7.14–7.18 (d, 2H); 7.27–7.30 (d, 2H); 7.46 (S, 1H) ppm. Mass: 383, 381, 310, 282, 41.

*3.2.4. 3,3,6,6-Tetramethyl-9-(3-hydroxy-4-methoxyphenyl)-1,8-dioxo-decahydroacridine (**4h**)*

IR (KBr): υ_{max} = 3187, 1651, 1491, 1365, 1221 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ = 0.96 (S, 6H), 1.0 (S, 6H), 2.04–2.2 (dd, 4H), 2.3–2.5 (dd, 4H), 3.7 (S, 3H), 4.8 (S, 1H), 6.62–6.79 (d, 2H), 6.8 (S, 1H), 7.6–7.7 (S, 1H), 8.7 (S, 1H) ppm.

*3.2.5. 3,3,6,6-Tetramethyl-9-(2-methoxyphenyl)-1,8-dioxo-decahydroacridine (**4i**)*

IR (KBr): υ_{max} = 3031, 1638, 1486, 1366, 1224 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ = 0.92 (S, 6H),1.04 (S, 6H), 2.04–2.11 (dd, 4H), 2.16–2.30 (dd, 4H), 3.80 (S, 1H), 5.24 (S, 1H), 6.76–7.0 (m, 4H), 7.29 (S, 1H) ppm. Mass (*m*/*e*): 379, 377, 346 ppm.

*3.2.6. 3,3,6,6-Tetramethyl-9-(4-hydroxyphenyl)-1,8-dioxo-decahydroacridine (**4j**)*

IR (KBr): υ_{max} = 3200. 1614, 1511, 1472, 1371, 1222 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ = 0.96 (S, 6H), 1.09 (S, 6H), 2.04–2.21 (dd, 4H), 2.27–2.42 (dd, 4H), 4.6 (s, 1H), 3.33 (S, 1H), 6.50–6.59 (d, 2H), 6.8–6.9 (d, 2H) ppm.

*3.2.7. 3,3,6,6-Tetramethyl-9-phenyl-10-(4-methylphenyl)-1,8-dioxo-decahydroacridine (**4o**)*

IR (KBr): υ_{max} = 2961, 1593, 1372, 1300, 1248 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ = 1.10 (S, 6H), 1.23 (S, 6H), 2.27–2.40 (dd, 4H), 2.43–2.51 (dd, 4H), 3.7 (d, 1H), 5.54 (S, 3H), 7.08–7.19 (m, 5H), 7.24–7.26 (d, 2H), 7.27–7.30 (d, 2H) ppm.

4. Conclusion

In conclusion, we have developed a method using sulfonic acid functionalized silica as an efficient solid acid catalyst in the synthesis of 1,8-dioxo-decahydroacridines from aromatic aldehydes, an amine and a dimedone under solvent free conditions. The reasonable reaction times, very good yields, simple work-up procedure, and environmentally friendly conditions are the main merits of this method.

Acknowledgments

We gratefully acknowledge the financial support from the Research Council of Alzahra University and the University of Tehran.

References

Bakibaev, A.A., Fillimonov, V.D., Nevgodova, E.S., 1991. Zh. Org. Khim. 27, 1519.

Balalaie, S., Chadegan, F., Darviche, F., Bijanzadeh, H.R., 2009. Chin. J. Chem. 27, 1953.

Bayer, A.G., Patent: DE2003148, 1971; Chem. Abstr. 75, 98459.

Boer, R., Gekeler, V., 1995. Drugs Future 20, 499.

Bossert, F., Meyer, H., Wehinger, E., 1981. Angew. Chem. Int. Ed. Engl. 20, 762.

Bretzel, R.G., Bollen, C.C., Maeser, E., Federlin, K.F., 1992. Drugs Future 17, 465.

Dabiri, M., Baghbanzadeh, M., Arzroomchilar, E., 2008. Catal. Commun. 9, 939.

Das, B., Thirupathi, P., Mahender, I., Reddy, V.S., Rao, Y.K., 2006. J. Mol. Catal. A: Chem. 247, 233.

Fan, X., Li, Y., Zhang, X., Qu, G., Wang, J., 2007. Heteroatom. Chem. 18, 786.

Godfraid, T., Miller, R., Wibo, M., 1986. Pharmacol. Rev. 38, 321.

Gupta, R., Paul, S., Gupta, R., 2007. J. Mol. Catal. A: Chem. 266, 50.

Han, M.V.C.R., 1971. Seances. Acad. Sci. Ser. B 273, 777.

Hua, G.P., Zhang, X.J., Shi, F., Tu, S.J., Xu, J.N., Wang, Q., Zhu, X.T., Zhang, J.P., JI, S.J., 2005. Chin. J. Chem. 23, 1646.

Jin, T.S., Zhang, J.S., Guo, T.T., Wang, A.Q., Li, T.S., 2004. Synthesis, 2001.

Karimi, B., Khalkhali, M., 2005. J. Mol. Catal. A: Chem. 232, 113.

Klusa, V., 1995. Drugs Future 20, 135.

Kumar, D., Sandhu, J.S., 2010. Synth. Commun. 40, 510.

Li, Y.L., Zhang, M.M., Wang, X.S., Shi, D.Q., Tu, S.J., Wei, X.Y., Zong, Z.M., 2005. J. Chem. Res. (S), 600.

Lim, M.H., Blanford, C.F., Stein, A., 1998. Chem. Mater. 10, 467.

Mager, P.P., Coburn, R.A., Solo, A.J., Triggle, D.J., Rothe, H., 1992. Drug Des. Discov. 8, 273.

Mahdavinia, G.H., Bigdeli, M.A., Hayeniaz, Y.S., 2009. Chin. Chem. Lett. 20, 539.

Mannhold, R., Jablonka, B., Voigt, W., Schönafinger, K., Schraven, E., 1992. Eur. J. Med. Chem. 27, 229.

Martin, N., Quinteiro, M., Seoane, C., Soto, J.L., Mora, A., Suárez, M., Morales, A., Ochoa, E., Bosque, J.D., 1995. J. Heterocycl. Chem. 32, 235.

Mohammadi Ziarani, G., Badiei, A., Abbasi, A., Farahani, Z., 2009. Chin. J. Chem. 27, 1537.

Mohammadi Ziarani, G., Badiei, A., Khaniania, Y., Haddadpour, M., 2010. Iran. J. Chem. Chem. Eng. 29, 1.

Mohammadi Ziarani, G., Badiei, A., Miralami, A., 2008. Bull. Korean Chem. Soc. 29, 47.

Murugan, P., Shanmugasundaram, P., Ramakrishnan, V.T., Venkatachalapathy, B., Srividya, N., Ramamurthy, P., Gunasekharan, K., Velmurugan, D., 1998. J. Chem. Soc., Perkin Trans. 2, 999.

Nakayama, H., Kasoaka, Y., 1996. Heterocycles 42, 901.

Pyrko, A.N., 2008. Russ. J. Org. Chem. 44, 1215.

Sausins, A., Duburs, G., 1988. Heterocycles 27, 269.

Shanmugasundaram, P., Murugan, P., Ramakrishnan, V.T., 1996. Heteroat. Chem. 7, 17.

Shanmugasundaram, P., Prabahar, K.J., Ramakrishnan, V.T., 1993. J. Heterocycl. Chem. 30, 1003.

Shen, W., Wang, L.M., Tian, H., Tang, J., Yu, J.J., 2009. J. Fluorine Chem. 130, 522.

Tu, S.J., Miao, C.B., Gao, Y., Feng, Y.J., Feng, J.C., 2002. Chin. J. Org. Chem. 20, 703.

Van Rhijn, W.M., De Vos, D., Sels, B.F., Bossaert, W.D., Jacobs, P.A., 1998. Chem. Commun., 317.

Venkatesan, K., Pujari, S.S., Srinivasan, K.V., 2009. Synth. Commun. 39, 228.

Wang, G.W., Xia, J.J., Miao, C.B., Wu, X.L., 2006. Bull. Chem. Soc. Jpn. 79, 454.

Wang, X.S., Shi, D.Q., Wang, S.H., Tu, S.J., 2003. Chin. J. Org. Chem. 23, 1291.

Wang, X.S., Zhang, M.M., Jiang, H., Shi, D.Q., Tu, S.J., Wei, X.Y., Zong, Z.M., 2006b. Synthesis, 4187.

Wang, X.S., Shi, D.Q., Zhang, Y.F., Wang, S.H., Tu, S.J., 2004. Chin. J. Org. Chem. 24, 430.