Ultrasound-assisted one-pot synthesis of 1,3-oxazine derivatives catalysed by BF_3–SiO_2 under neat conditions

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An efficient and environment-friendly method for the synthesis of 1,3-oxazine derivatives has been developed using the ultrasound-mediated condensation of 2-naphthol with formaldehyde and primary amines under solvent-free condition at room temperature in the presence of BF_3-SiO_2 to give the desired product in good to excellent yield. This procedure provides several advantages over current methods including a simple work-up, cost effectiveness, a reusable catalyst and shorter reaction times.

Keywords: 1,3-oxazines, BF_3-SiO_2, ultrasound irradiation, green synthesis

Non-polluting synthetic procedures are being developed, because of increasing concerns of the harmful effects of organic solvents on the environment. Ultrasound-promoted reactions[1] have attracted attention during the last few years to accelerate a number of organic transformations.[2]

Ultrasound induced organic transformations offer simple experimental procedure, clean reaction, short reaction time, high yields, and improved selectivity.[3] Recently, a number of heterocycles have been synthesised under solvent-free conditions accelerated by ultrasound irradiation.[4,5]

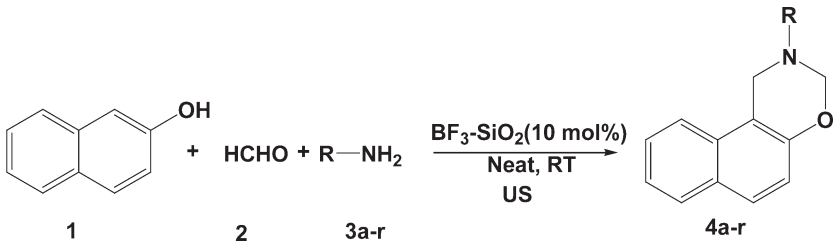
The 1,3-oxazine ring system is a core structure present in a number of biologically-active heterocycles possessing analgesic,[6] anti-cancer,[7] anti-HIV,[8] and anti–ulcer activity.[9] In addition, naphthoxine derivatives possess therapeutic potential for the treatment of Parkinson's disease.[10] The syntheses of dihydro-1,3-oxazines which have been previously reported by several investigators involve a Mannich type condensation of a phenol or naphthol with formaldehyde and a primary amine using highly inflammable organic solvents [11] and alkaline media.[12] Further, research has led to mild, solvent free, water and ionic liquid methods for the construction of these molecules.[13–15] However, many of these processes are associated with several shortcomings such as long reaction times, high reaction temperature, use of volatile and hazardous organic solvents, and occurrence of side products. Hence, the development of new and simple synthetic methods for the preparation of heterocyclic compounds containing 1,3-oxazine derivatives still remains an interesting challenge. Silica-supported boron trifluoride, BF_3–SiO_2 is a bench-top catalyst which is easy to handle, reusable, cheap, readily available, eco-friendly, versatile and efficient for promotion of many acid-catalysed organic reactions[16–18] which we have examined for the synthesis of 1,3-oxazine derivatives.

There are no reports on the synthesis of 1,3-oxazines under ultrasound irradiation in solvent-free at room temperature mediated by BF_3–SiO_2. Our main target was to develop a green organic reaction methodology which was faster and cleaner than conventional reactions as part of our ongoing research program on the development of clean protocols,[19,20] We report a facile one-pot synthesis of 1,3-oxazines by a three-component coupling of 2-naphthol, formaldehyde and aromatic/aliphatic/heterocyclic amines (**3**) in the presence of a catalytic amount (10 mol %) of BF_3–SiO_2 under solvent-free ultrasound irradiation at room temperature (Scheme 1).

Result and discussion

In order to investigate the ultrasonic effect on the three-component coupling reaction in solvent-free condition at room temperature in the presence of BF_3–SiO_2, we explored the reaction of 2-naphthol, formaldehyde and aniline as a model.

We found that there was remarkable ultrasound and catalytic effects on the one-pot in this coupling reaction. When the three-component mixture in THF was kept at room temperature for 8h, none of the product was observed. (Table 1, entry 1), Only a low yield of product was obtained when this one-pot reaction was carried out by refluxing for 3 h in the presence of $ZnCl_2$–SiO_2 without sonication (Table 1, entry 2). Instead, reasonable yield (60%) of product **4a** was obtained when the $ZnCl_2$–SiO_2-catalysed three-component reaction in THF was carried out at room temperature for 2 h under ultrasound irradiation (Table 1, entry 3). It seemed that the solvent-free one-pot coupling took place sluggishly at room temperature in 20% yield even overnight without catalyst (Table 1, entry 4). However, these methods involved a long reaction time and gave an unacceptable yield. Therefore, our efforts were focused on the search for a suitable catalyst. We examined; TiO_2–SiO_2, PPA–SiO_2 and BF_3-SiO_2 as catalysts for this reaction under solvent-free condition at 80 °C. Long reaction times and low transformation rates were in these experiments (Table 1, entries 5–7). Attempts were made to use ultrasound irradiation with the same catalysts at room temperature, in solvent-free conditions. The results are listed in Table 1. TiO_2–SiO_2 and PPA–SiO_2 were found to catalyse the reaction to give a moderate yield over a long reaction time. Surprisingly, in the case of BF_3–SiO_2 (Table 1, entry 10) the target product **4a** was obtained in 92% yields within 10 min at room temperature. Evidently, the sonochemical effect might be the significant factor to the high efficiency of the one-pot and solvent-free reactions.



Scheme 1 Synthesis of 1,3-oxazine derivatives.

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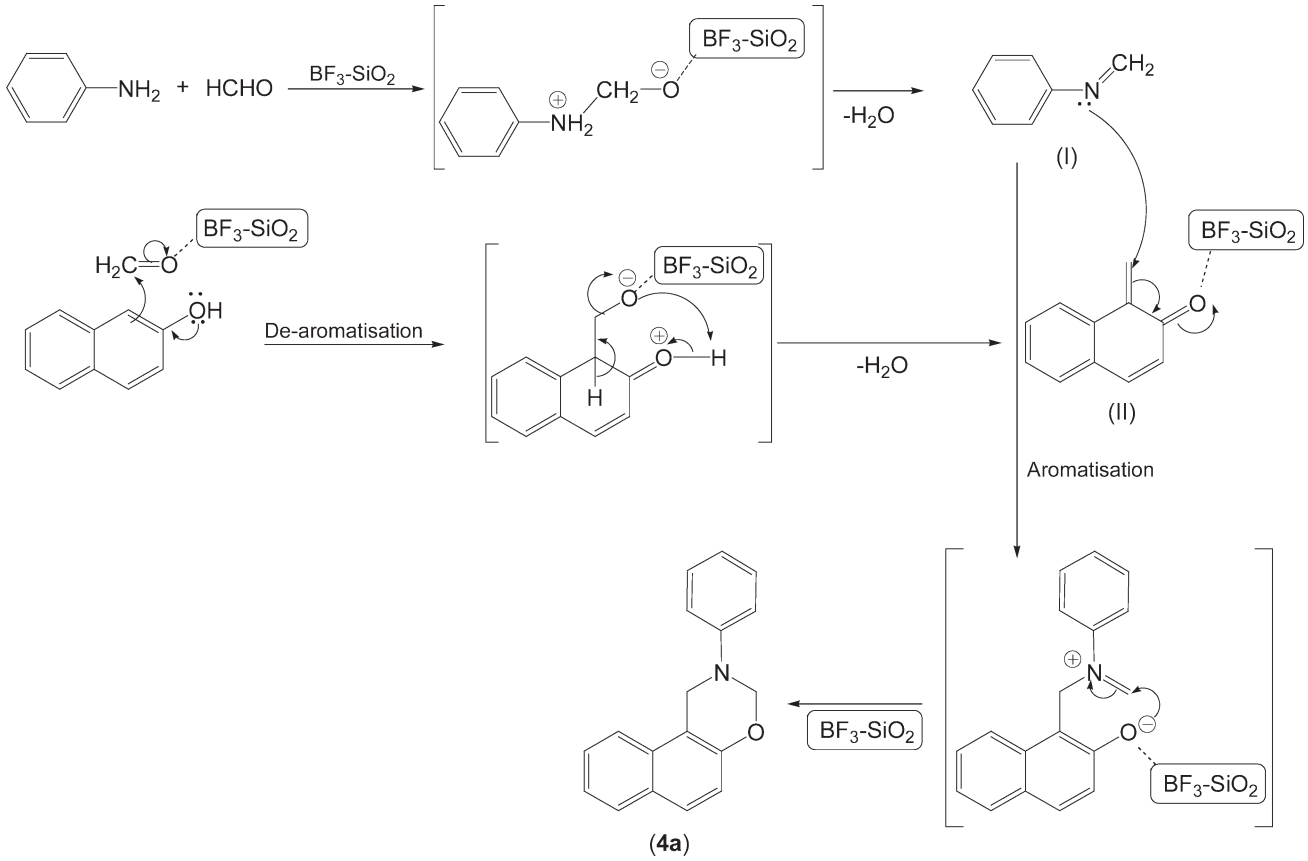
Table 1 Coupling of 2-naphthol (1 mmol), formaldehyde (2.2 mmol) and aniline (1 mmol) under different conditions

Entry	Solvent	Catalyst/mol %	Conditions	Time/min	Yield/%[a]
1	THF	-	r.t	480	0
2	THF	ZnCl2–SiO_2(10)	Reflux	180	25
3	THF	$ZnCl_2$–SiO_2(10)	US/r.t	120	60
4	Solvent-free	-	rt	Overnight	20
5	Solvent-free	TiO_2–SiO_2(10)	80 °C	150	40
6	Solvent-free	PPA–SiO_2(10)	80 °C	190	55
7	Solvent-free	BF_3–SiO_2(10)	80 °C	60	80
8	Solvent-free	TiO_2–SiO_2(10)	US/r.t	80	65
9	Solvent-free	PPA–SiO_2(10)	US/r.t	65	72
10[b]	Solvent-free	BF_3–SiO_2 (10)	US/r.t	10	92, 91. 90
11	Solvent-free	BF_3–SiO_2 (2)	US/r.t	10	35
12	Solvent-free	BF_3–SiO_2 (5)	US/r.t	10	65
13	Solvent-free	BF_3–SiO_2 (15)	US/r.t	10	92

[a] Isolated yield.
[b] Catalyst was reused three times.
US, ultrasound.

Subsequently, catalyst loading was optimised and 10 mol% BF_3–SiO_2 provided the maximum yield in minimum time (Table 1, entry 10). A further increase in the amount of BF_3–SiO_2 did not have any significant effect on the product yield or reaction time, whereas the yield was reduced by decreasing the amount of BF_3–SiO_2 (Table 1, entries 11–13). The catalytic activity of the recycled BF_3–SiO_2 was also examined. BF_3–SiO_2 could be re-used three times in the reaction without noticeable loss of activity (Table 1, entry 10).

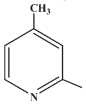
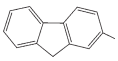
Based on the optimised reaction conditions, a group of 1,3-oxazine derivatives were synthesised by this reaction using different aromatic/aliphatic/heterocyclic amines. In all the cases, the reaction proceeded smoothly at room temperature and gave good to excellent yields. To find the specific effect of ultrasound on this reaction, all the previously mentioned reactions were carried out under the same conditions in the absence of ultrasound irradiation (Table 2). It was observed that the reaction times increased considerably and the yields of the products decreased under conventional reflux conditions. Thus, ultrasonic irradiation was found to have a beneficial effect on the synthesis of 1,3-oxazine derivatives over conventional heating and offered significant improvements in terms of simplicity and green aspects by avoiding a high temperature. In comparison with conventional methods, the main advantages of our procedure are the significant decrease of reaction time and improvement of yields. While conventional methods required 1 h at reflux, when ultrasonic irradiation is employed, the products were obtained in 10 min with better yields. Another advantage of the present method is the absence of an additional purification step.



(**4a**)

Scheme 2 Tentative mechanism for the formation of 1,3-oxazines (**4a**).

Table 2 Synthesis of 1,3-oxazine derivatives (**4a–r**) under ultrasonic irradiation.[a]

Entry	R	Product	Sonochemical method		Traditional method		M.p. /°C	
			Time/min	Yield[b]/%	Time/min	Yield[b]/%	Found	Reported
1	C_6H_5	4a	10	92	60	80	48–50	(49–51)[14]
2	4-BrC_6H_4	4b	13	90	70	78	116–117	(115–117)[14]
3	4-ClC_6H_4	4c	15	89	60	70	108–110	(109.5)[13]
4	4-FC_6H_4	4d	14	89	68	75	57–58	(56.9)[13]
5	4-$OMeC_6H_4$	4e	10	94	62	81	77–78	(78–80)[14]
6	4-MeC_6H_4	4f	11	94	65	80	89–90	(88–90)[14]
7	4-$NO_2C_6H_4$	4g	18	90	100	85	164–166	(165–167)[14]
8	2,4-$Cl_2C_6H_3$	4h	20	85	120	70	Liquid	(Liquid)[13]
9	2-MeC_6H_4	4i	14	89	80	78	55–57	(56–58)[14]
10	2-$NO_2C_6H_4$	4j	18	88	95	72	110–112	(110–112)[14]
11	4-Cl,2-OHC_6H_3	4k	17	85	115	65	103–105	–
12	2,6(CH-$(CH_3)_2)_2C_6H_3$	4l	20	85	125	60	98–100	–
13	2-OHC_6H_4	4m	14	86	100	72	98–100	–
14		4n	14	92	75	73	255–257	–
15		4o	14	91	65	79	164–166	–
16	$C_6H_5CH_2$	4p	16	90	89	72	54–56	(55–56)[12]
17	C_4H_9	4q	28	80	140	56	136–138	(138–140)[13]
18		4r	19	85	120	62	43–45	(43–44)[12]

[a] Reaction of 2-naphthol (1 mmol), formaldehyde (2.2 mmol) and amines (1 mmol) catalysed by BF_3-SiO_2(10%) under ultrasonic waves in solvent-free condition at room temperature.
[b] Isolated yield.

The reaction of aromatic/aliphatic/heterocyclic amines with formaldehyde and 2-naphthol in the presence of 10 mol % BF_3–SiO_2 under ultrasound irradiation at room temperature in solvent- free conditions resulted in the formation of the 1,3-oxazine derivatives (**4a–r**) in good to excellent yields (Table 2). It was found that there was no noticeable electron and position effects on the aromatic/heterocyclic amines containing *o-,m- and p*-electron withdrawing and donating substituents in these three-component couplings. Apart from the aromatic/heterocyclic amines, some aliphatic amines were also selected to carry out the three-component couplings. Benzylamine (Table 2, entry 16), gave the target product **4p** in reasonable yield, but only moderate yield of products were obtained from cyclohexylamine and n-butylamine (Table 2, entries 17 and 18). These results reveal that aliphatic amines were not as effective as those aromatic/heterocyclic amines for the preparation of 1,3-oxazine derivatives (**4a–r**).

The plausible mechanism is depicted in Scheme 2. Initially, BF_3–SiO_2 serves as a Lewis acid catalyst for the reaction of aniline and formaldehyde to give the imine (I). Similarly, the diene (II) was formed through de-aromatisation of the naphthol ring by reaction with formaldehyde. The diene (II) and imine (I) then undergo an aromatisation reaction in the presence of BF_3–SiO_2 to afford corresponding 1,3-oxazine (**4a**). The structures of all the synthesised compounds were established by their ^{1}H and ^{13}CNMR and ESI-MS analyses and these results are in good agreement with the reported data.

In conclusion, we have found an efficient and practical procedure for the preparation of 1,3-oxazine derivatives (**4a–r**) from 2-naphthol with formaldehyde and aromatic/aliphatic/heterocyclic amines in the presence of 10 mol% BF_3–SiO_2 under ultrasound irradiation at room temperature using solvent- free conditions. Based on those results, we have shown that compared to traditional methods (reflux method), ultrasound irradiation can speed up the reaction and is more convenient and efficient. Reusability, eco-friendly, inexpensive short reaction times, high yields and easy workup are advantages of this protocol.

Experimental

Chemicals were purchased from Aldrich and Alfaaesar Chemical Companies. NMR spectra were recorded in ppm in $CDCl_3$ on a Jeol JNM ECP 400 NMR instrument using TMS as internal standard. An Elmasonic S 100 H (with a frequency of 35 kHz and a nominal power 550 W) ultrasonic bath was used for ultrasonic irradiation. It had built-in heating, and was thermostatically adjustable 30–80 °C. The reaction vessel was placed inside the ultrasonic bath containing water. Mass spectra were recorded by the Jeol JMS-700 mass spectrometer, respectively. All melting points were determined using open capillaries on an Electrothermal-9100 (Japan) instrument.

Synthesis of 1,3-oxazine derivatives; general procedure

A mixture of 2-naphthol (1 mmol), 37% aqueous formaldehyde (2.2 mmol) and the aromatic/aliphatic/heterocyclic amine (1 mmol) in the presence of BF_3–SiO_2 (10 mol%) were placed on a 25 mL beaker and exposed to ultrasonic irradiation at room temperature for appropriate time (Table 2) in solvent-free condition. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with chloroform and filtered to recover the catalyst. The filtrate was evaporated, and the crude product was recrystallised from ethanol to afford pure 1,3-oxazine derivatives in good to excellent yields.

4-Chloro-2-(1H-naphtho[1,2-e][1,3]oxazin-2(3H)-yl)phenol (**4k**): Yield; 85%; pale yellow solid; m.p. 103–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.68 (s, 2H), 5.08 (s, 2H), 6.51 (s, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 7.06 (dd, *J* = 2.3, 10.9 Hz, 1H), 7.15 (dd, *J* = 2.0, 10.9 Hz, 2H) 7.40 (t, *J* = 7.2 Hz, 1H), 7.49 (dd, *J* = 5.4, 14.2 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.7, 81.6, 112.4, 116.0, 119.7, 120.9, 124.2, 124.8, 125.4, 126.5, 127.9, 128.9, 129.5, 132.8, 137.4, 151.1. HRMS (ESI, *m/z*): Calcd for $C_{18}H_{14}ClNO_2$ ($M+H^+$) 311.0713; found: 311. 0710.

2,3-Dihydro-2-(2,6-diisopropylphenyl)-1H-naphtho[1,2-e][1,3]-oxazine (**4l**): Yield; 85%; white solid; m.p. 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 6.8 Hz, 12H), 3.27–341 (m, 2H), 4.65 (s, 2H), 5.12 (s, 2H), 7.16 (t, *J* = 7.1 Hz, 3H), 7.27 (d, *J* = 8.2Hz,

1H), 7.35 (t, *J* = 7.1 Hz, 1H), 7.42–7.46 (q, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 26.1, 29.8, 50.1, 82.2, 115.0, 120.6, 122.1, 124.7, 125.2, 127.7, 128.7, 129.1, 129.7, 130.0, 132.4, 144.0, 150.6, 153.7. HRMS (ESI, *m/z*): Calcd for $C_{24}H_{27}NO$ ($M+H^+$) 345.2093; found: 345.2095.

22-(1H-Naphtho[1,2-e][1,3]oxazin-2(3H)-yl)phenol (**4m**): Yield; 86%; white solid; m.p. 143-145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.68 (s, 2H), 5.09 (s, 2H), 6.65 (s, 1H), 6.70–6.74 (m, 1H), 6.99 (dd, *J* = 1.4, 9.5 Hz, 1H), 7.07-7.16 (m, 3H), 7.38 (t, *J* = 6.9 Hz, 1H), 7.47 (t, *J* = 6.9 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.3, 80.8, 114.8, 118.7, 120.4, 120.9, 123.9, 124.4, 126.8, 127.4, 128.5, 128.7, 129.1, 131.0, 136.1, 151.3. HRMS (ESI, *m/z*): Calcd for $C_{18}H_{15}NO_2$ ($M+H^+$) 277.1103; found: 277.1103.

2,3-Dihydro-2-(4-methylpyridin-2-yl)-1H-naphtho[1,2-e][1,3]-oxazine (**4n**): Yield; 92%; white solid; m.p. 255–257 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 5.21(s, 2H), 5.67 (s, 2H), 6.57 (d, *J* = 5.1 Hz, 1H), 6.75 (s, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.50–7.54 (m, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.78 (t, *J* = 9.1 Hz, 2H), 8.11 (d, *J* = 5.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 44.4, 75.2, 108.6, 113.0, 116.5, 118.8, 121.1, 123.7, 126.7, 128.2, 128.6, 129.0, 131.3, 147.8, 149.0, 152.3, 157.9. HRMS (ESI, *m/z*): Calcd for $C_{18}H_{16}N_2O$ ($M+H^+$) 276.1344; found: 276.1264.

2-(9H-Fluoren-7-yl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (**4o**): Yield; 91%; pale yellow solid; m.p. 164–166 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81(s, 2H), 5.00(s, 2H), 5.47 (s, 2H), 7.06 (d, *J* = 9.1 Hz, 1H), 7.15-7.22 (m, 2H), 7.29–7.39 (m, 3H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.64 (dd, *J* = 5.1, 13.1 Hz, 3H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.8, 48.5, 80.4, 112.1, 115.4, 117.7, 119.1, 120.9, 123.6, 124.8, 126.6, 128.2, 131.1, 135.2, 141.5, 143.1, 144.6, 148.4, 150.2, 152.4. HRMS (ESI, *m/z*): Calcd for $C_{25}H_{19}NO$ ($M+H^+$) 349.1467; found: 349.1469.

This research work was supported by the second stage of BK21 Program.

Received 6 April 2012; accepted 16 April 2012
Paper 1201217 doi: 10.3184/174751912X13371662613770
Published online: 26 June 2012

References

1 G. Cravotto and P. Cintas, *Chem. Soc. Rev.*, 2006, **35**, 180.
2 A. Arcadi, M. Alfonsi and F. Mannelli, *Tetrahedron Lett*., 2009, **50**, 2060.
3 L.C. Bretanha, V.E. Teixeira, M. Ritter, G.M. Siqueira, W. Cunico, C.M.P. Pereira and R.A. Freitag, *Ultrason Sonochem*., 2011, **18**, 704.
4 S.X. Wang, Z.Y. Li, J.C. Zhang and J.T. Li, *Ultrason Sonochem*., 2008, **15**, 677.
5 Q. Wang and W. Pei, *J. Iran. Chem. Soc*., 2010, **7**, 318.
6 M. Adib, E. Sheibani and M. Mostofi, *Tetrahedron*, 2006, **62**, 3435.
7 H.V. Poel, G. Guilaumet and M. Viaud-Massuard, *Tetrahedron Lett*., 2002, **43**, 1205.
8 B.O. Buckman, R. Mohan and S. Koovakkat, *Bioorg. Med. Chem. Lett*., 1998, **8**, 2235.
9 Y. Katsura, S. Nishino and H. Takasugi, *Chem. Pharm. Bull.*, 1991, **11**, 2937.
10 J.N. Joyce, S. Presgraves and L. Renish, *Exp. Neurol.*, 2003, **184**, 393.
11 C.S. Higham, D.P. Dowling, J.L. Shaw, A. Cetin, C.J. Ziegler and J.R. Farrell, *Tetrahedron Lett*., 2006, **47**, 4419.
12 W.J. Burke, E.L.M. Glennie and C. Weatherbee, *J. Org. Chem*., 1964, **29**, 909.
13 P.M. Bijoy, K. Awanit, S. Satyasheel, P.K. Shukla and N. Mahendra, *Eur. J. Med. Chem.*, 2010, **45**, 1502.
14 P.M. Bijoy and N. Mahendra, *J. Heterocyclic Chem*., 2009, **46**, 1003.
15 B.S. Suryakant, F.S. Kiran, B.S. Bapurao and S.S. Murlidhar, *J. Korean Chem. Soci*., 2010, **54**, 437.
16 B. Sadeghi, B.F. Mirjalili and M.M. Hashemi, *Tetrahedron Lett.*, 2008, **49**, 2575.
17 R. Ramachandran, S. Jayanthi and Y.T. Jeong, *Tetrahedron*, 2011, **68**, 363.
18 S.D. Dindulkar, P. Paramasivam and Y.T. Jeong, *Monatsh Chem*., 2011, **143**, 113.
19 M. Veeranarayana Reddy, S.D. Dindulkar and Y.T. Jeong, *Tetrahedron Lett*., 2011, **52**, 4764.
20 M. Veeranarayana Reddy, K. Jongsik and Y.T. Jeong *J. Fluorine Chem*., 2012, **135**, 155.

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