Chlorotrimethylsilane-promoted synthesis of 1,2-dihydro-1-arylnaphtho [1,2-*e*] [1,3]oxazine-3-ones

Chenggang Jiang, Xin Geng, Zonglei Zhang, Hangxian Xu and Cunde Wang*

College of Chemistry and Chemical Technology, Yangzhou University, Yangzhou 225002, P. R. China

Chlorotrimethylsilane (TMSCl) is effective as a catalyst for the preparation of 1,2-dihydro-1-arylnaphtho[1,2-*e*] [1,3]oxazine-3- ones using a one-pot condensation of 2-naphthol, aromatic aldehydes and urea in DMF as solvent. The reaction times, temperature, and catalyst amounts were varied.

Keywords: 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-ones, Betti base, 2-naphthol, aromatic aldehydes, chlorotrimethylsilane

1-(α-Aminobenzyl)-2-naphthols, known as Betti bases, and their derivatives are attractive for use in asymmetric syntheses. These compounds have been employed as precursors in the preparation of chiral ligands for asymmetric catalysis. They are suitable for such purposes owing to their ease of synthesis, the ready availability of the precursors, and their potential for enantiomeric separation.[1–4] Important new applications as synthons have been found in asymmetric syntheses.[5–8] These compounds have also has been used as chiral auxiliaries in the total syntheses of natural alkaloidal products such as (2S,6R)-dihydropinidine and (2S,6R)-isosolenopsins.[9] In recent years, these oxazinone derivatives of 1-(α-aminobenzyl)-2-naphthols have attracted interest. A number of oxazinone derivatives are biologically active.[10–12] In general ,substituted Betti bases were prepared utilising the classical synthesis involving the three-component condensation of 2-naphthol, benzaldehyde and ammonia in alcoholic solution at room temperature. Subsequently, condensation reactions of substituted Betti bases with phosgene or carbonyl diimidazole gave naphthalene-condensed 1,3-oxazin-3-ones.[13,14] Recently there have been some reports of the preparation of 1-aminoalkyl-2-naphthols by the three-component reaction between 2-naphthol, aromatic aldehydes and amides or urea using different catalysts.[15–21] With the growing realization that some oxazinone derivatives of 1-(α-aminobenzyl)-2-naphthols display significant biological activities, the development of novel synthetic methods has attracted attention. All these methods required either expensive toxic or hazardous reagents or solvents. Therefore, easy-to-handle and highly efficient methods in which the reagents used are nontoxic, inexpensive and safe are still targets. Previous studies have shown that chlorotrimethylsilane (TMSCl) is a mild and efficient promoter for various organic transformations.[22–25] It has also been reported as a mild useful and inexpensive Lewis acid catalyst for one-pot multicomponent preparations of heterocyclic compounds.[26–30] In our previous work,[31–33] TMSCl was employed to carry out several unusual cyclo-condensations including one-pot synthesis of substituted quinolines and pyrroles. We selected TMSCl as the catalyst, for the preparation of 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3] oxazine-3-ones The results obtained are now reported.

Results and discussion

Although these oxazine-3-ones were prepared under microwave or thermal solvent-free conditions in the previous report,[16] the limitations of these methods it was very difficult to sythesise these oxazine-3-ones on a large scale. In order to facilitate their industrial production, we selected a convenient and efficient procedure for the preparation of oxazine-3-ones in the liquid phase. The reaction was initially studied with 2-naphthol, urea and benzaldehyde, in various solvents (Table 1).

Table 1 The effect of varous **c**atalysts and solvents on the reaction[a]

Entry	Catalyst	Solvent	Yields /%[b]
1	AcOH	DMF	62[c]
2	PTSA	DMF	65[d]
3	BF_3Et_2O	DMF	67
4	$ZnCl_2$	DMF	48
5	ZnO	DMF	40
6	TMSCl	DMF	68
7	TMSCl	DMSO	66
8	TMSCl	THF	26
9	TMSCl	dioxane	43

[a]Benzaldehyde (1 mmol), urea (1.1 mmol), β-naphthol (1 mmol), catalyst (0.05 mmol), solvent (10 mL); reflux for THF and dioxane, 140 °C for DMSO and DMF; 12 h.
[b]Isolated yields.
[c]Without solvent 45% in yield.[16]
[d]Without solvent 58% in yield.[16]

At the outset, various catalysts and solvents were screened. To our delight, we observed the formation of the desired product **4a** (Table 2) when the reaction was carried out using benzaldehyde (1 mmol), urea (1.1 mmol), β-naphthol (1 mmol), DMF (10 mL) in the presence of various catalysts (0.05 mmol) under reflux for 12 h. A comparison of the method using TMSCl as a catalyst (Table 1, entry 6, 68% in yield), with other selected catalysts such as acetic acid and PTSA and other Lewis acid ($BF_3 \cdot Et_2O$, $ZnCl_2$) or ZnO (Table 1, entry 1, 62% in yield; entry 2, 65% in yield; entry 3, 67% in yield; entry 4, 48% in yield; entry 5, 40% in yield, respectively) demonstrated that the method using TMSCl as a catalyst was superior to several of the other protocols.

We then investigated the preparation of 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-ones by multi-components cyclocondensation of 2-naphthol, urea and aromatic aldehydes via a tandem reaction in the presence of TMSCl. In order to optimise the reaction conditions, solvent, time, and the amount of TMSCl were varied. Firstly the solvent used in the preparation of 1-phenyl-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (**4a**) from benzaldehyde (1 mmol), 2-naphthol (1 mmol) and urea (1.1 mmol) in the presence of TMSCl (0.05 mmol) was varied. Among the solvents tested (Table 1, entries 6–9), DMF and DMSO gave the best result. The result showed that DMF, DMSO gave the product **4a** in 68%, 66% yield, respectively. In the second set of experiments, the model reaction with benzaldehyde, 2-naphthol and urea in DMF was carried out at various temperatures. After some experimentation, it was found that the model reaction using a reaction temperature of 135–140 °C produced the product **4a** in excellent yield. Furthermore, the reaction time and the catalyst concentration could be reduced to 12 h and 10%, respectively. Thus, with these results in hand, we synthesised nine naphthoxazin-3-ones (Table 2, **4a–i**) in yields varying from 49 to 83% by the cyclo-condensation reaction of 1.0 mmol 2-naphthol

* Correspondent. E-mail: cundeyz@hotmail.com

Table 2 One-pot synthesis of 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-ones via tandem reaction promoted by TMSCl

Entry	Aldehydes(R)(**2**)	Oxazine-3-ones (**4**)[a]/%
a	H	68
b	*m*-NO_2	49
c	*m*-CH_3O	68
d	*m*-CF_3	73
e	*p*-CF_3	59
f	3,4-(OCH_2O)	83
g	*o*-NO_2	56
h	*p*-NO_2	76
i	*p*-$(CH_3)_2N$	78

[a]Isolated yields.

and 1.0 mmol of the appropriate aromatic aldehyde (**2a–i**) in 7.5 mL DMF with 1.1 mmol urea in the presence of 0.1 mmol TMSCl at 135–140 °C for 12 h (Scheme 1).

The structural and chemical data for the products (Table 2, **4a–i**) are given in the experimental section. The IR spectra of the products showed C=O stretching band at about 1740 cm^{-1}. ^1H NMR spectra, C_1–H and N–H protons of the oxazin-3-one ring were observed near 6.0 and 6.20 ppm. The protons belonging to the aromatic ring and substitutent groups were observed with the expected chemical shift values. The structures of the products were confirmed by IR, ^1H NMR, MS spectra and by comparison with authentic samples prepared according to literature methods.

Based on the above results, some larger scale reactions were carried out using the following amounts of the starting materials: benzaldehyde (5.3 g, 0.05 mol), urea (3.3 g, 0.055 mol), β-naphthol (7.2 g, 0.05 mol) and TMSCl (0.25 g, 2.5 mmol) in DMF (80 mL) at 140 °C for 12 h; benzaldehyde (10.6 g, 0.10 mol), urea (6.6 g, 0.11 mol), β-naphthol (14.4 g, 0.10 mol) and TMSCl (0.50 g, 5.0 mmol) in DMF (120 mL) at 140 °C for 12 h; benzaldehyde (21.2 g, 0.20 mol), urea (13.2 g, 0.22 mol), β-naphthol (28.8 g, 0.10 mol) and TMSCl (1.0 g, 10.0 mmol) in DMF (200 mL) at 140 °C for 12 h; the yield of product **4a** was 68, 66 and 66%, respectively. The results showed that approximately the same yields were obtained.

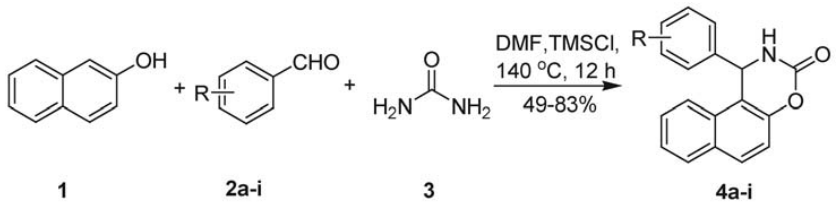
Many studies of using aldehydes for a range of condensations in the presence of chlorotrimethylsilane as promoting reagents have been recently reported. According to these results, the mechanism can be explained tentatively as in Scheme 2 for the conversion of intermediate acylimine from the aldehyde with urea, and the subsequent addition of the β-naphthol to the acylimine, followed by cyclisation in the presence of TMSCl affords the corresponding products and ammonia.

In summary, a novel, efficient and one-pot synthesis has been described for the preparation of naphthoxazine-3-ones in three-component cyclo-condensation reactions of 2-naphthol, aromatic aldehydes and urea. This involves the use of inexpensive and relatively nontoxic reagent TMSCl as a catalyst. The novelty and synthetic utility of this methodology was demonstrated in the efficient synthesis of naphthoxazinone derivatives.

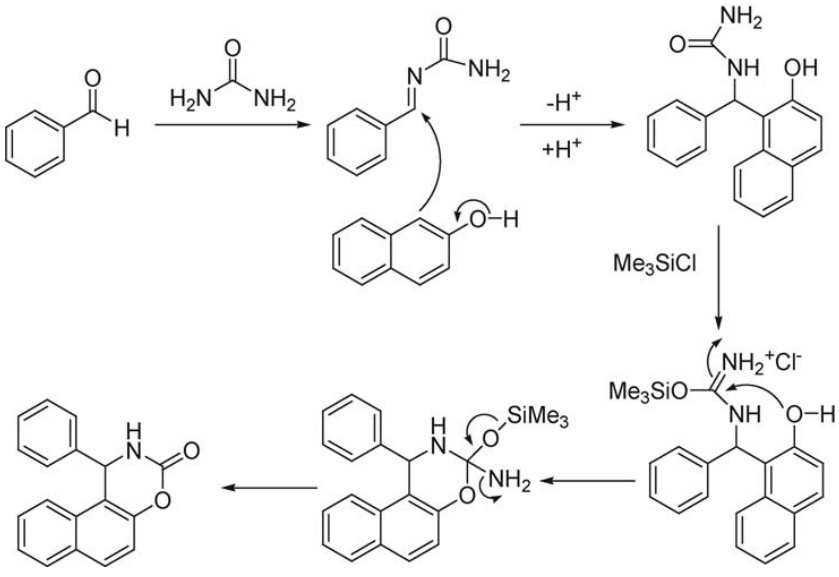
Experimental

General procedures

IR spectra were measured with a model 408 IR spectrometer; Elemental analytical data were obtained by using a model 240 elementary instrument; ^1H NMR spectra were recorded on a JNM-90Q Spectrometer by using TMS as an internal standard ($CDCl_3$ as solvent). Melting points are uncorrected; the MS spectra were obtained on a ZAB-HS mass spectrometer with 70 eV.



Scheme 1 One-pot reaction of 2-naphthol, aromatic aldehydes and urea promoted by TMSCl.



Scheme 2 Plausible reaction mechanism.

One-pot synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones from 2-naphthol, urea and aromatic aldehydes via tandem reaction promoted by TMSCl; general procedure

To a mixture of 2-naphthol (288 mg, 2.0 mmol), aromatic aldehydes (2.0 mmol) and urea (132 mg, 2.2 mmol) in dry DMF (10 mL) was added TMSCl (10 mg, 0.1 mmol) at room temperature. The resulting mixture was stirred at 135–140 °C for 12 h. After the mixture was cooled to room temperature, 10% Na_2CO_3 (10 mL) was added to the reaction mixture and the resultant mixture was extracted with CH_2Cl_2 (2 × 15 mL), the combined organic phase was washed with water and brine, dried over Na_2SO_4. The solvent was removed and the residues were purified by column chromatography (silica gel, EtOAc/PE, 3/1) to give a product (Table 2, **4a–i**).

1-Phenyl-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one[16] (**4a**): M.p. 219–220 °C (EtOAc/Hexanes) (lit. [6b] 218–220 °C (EtOAc/Hexanes); IR (KBr, cm^{-1}) 3263, 1744, 1663, 1533, 1438, 1359, 1268; ^1H NMR ($CDCl_3$, 600 MHz, ppm) δ 5.80 (s, 1H), 6.20 (d, *J* = 2.1 Hz, 1H), 7.23–7.90 (m, 11H); MS *m/z* 275 (M+, 8). Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.28; H, 4.90; N, 5.06%.

1-(3-Nitrophenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (**4b**): M.p. 242–244 °C (EtOAc); IR (KBr, cm^{-1}) 3242, 3141, 1738, 1630, 1522, 1389, 1346; ^1H NMR ($CDCl_3$, 600 MHz, ppm) δ 5.82 (s, 1H), 6.22 (s, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.34–7.48 (m, 3H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 4.8 Hz, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.22 (s, 1H); MS *m/z* 320 (M+, 10). Anal. Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.25; H, 3.92; N, 8.46%.

1-(3-Methoxyphenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (**4c**): M.p. 195–198 °C (EtOAc); IR (KBr, cm^{-1}) 3130, 2960, 1747, 1594, 1389, 1326, 1256, 1220; ^1H NMR ($CDCl_3$, 600 MHz, ppm) δ 3.74 (s, 3H), 5.69 (s, 1H), 6.03 (s, 1H), 6.79 (s, 1H), 6.82 (dd, *J* = 1.8 and 8.4 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.42 (m, 2H), 7.58 (m, 1H), 7.84 (m, 1H), 7.84 (m, 1H), 7.90 (d, *J* = 8.4 Hz, 1H); MS *m/z* 275 (M+, 8); MS *m/z* 305 (M+, 15). Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.46; H, 4.94; N, 4.32%.

1-(3-Trifluoromethylphenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (**4d**): M.p. 229–232 °C (EtOAc/CH_2Cl_2); IR (KBr, cm^{-1}) 3252, 2923, 2853, 1752, 1669, 1323, 1223, 1172, 1116; ^1H NMR ($CDCl_3$, 600 MHz, ppm) δ 6.10 (s, 1H), 6.14 (s, 1H), 6.61 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.46 (m, 2H), 7.57 (m, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.80 (m, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.08 (m, 1H); MS *m/z* 343 (M+, 52). Anal. Calcd for $C_{19}H_{12}F_3NO_2$: C, 66.47; H, 3.52; N, 4.08. Found: C, 66.22; H, 3.80; N, 4.14%.

1-(4-Trifluoromethylphenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (**4e**): M.p. 218–220 °C (EtOAc); IR (KBr, cm^{-1}) 3238, 3152, 1756, 1626, 1590, 1516, 1325, 1223; ^1H NMR ($CDCl_3$, 600 MHz, ppm) δ 6.14 (s, 1H), 7.20 (s, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 7.35 (m, 1H), 7.39 (m, 1H), 7.43–7.47 (m, 2H), 7.49 (m, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.84–7.86 (m, 1H), 7.89 (d, *J* = 9.0 Hz, 1H); MS *m/z* 343 (M+, 40). Anal. Calcd for $C_{19}H_{12}F_3NO_2$: C, 66.47; H, 3.52; N, 4.08. Found: C, 66.10; H, 3.56; N, 4.04%.

1-(2-Nitrophenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (**4f**): M.p. 211–214 °C (EtOAc-CH_2Cl_2); IR (KBr, cm^{-1}) 3242, 3146, 1748, 1627, 1486, 1397, 1225; ^1H NMR ($CDCl_3$, 600 MHz, ppm) δ 6.50 (s, 1H), 6.53 (s, 1H), 6.85 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 7.30–7.41 (m, 5H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 1H); MS *m/z* 320 (M+, 16). Anal. Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.42; H, 3.68; N, 8.52%.

1-(Benzo[d][1,3]dioxol-5-yl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (**4g**): M.p. 212–214 °C (EtOAc-CH_2Cl_2); IR (KBr, cm^{-1}) 3267, 1724, 1634, 1586, 1523, 1381, 1224; ^1H NMR ($CDCl_3$, 600 MHz, ppm) δ 5.83 (d, *J* = 20.8 Hz, 2H), 5.93 (s, 1H), 5.96 (s, 1H), 6.58 (s, 1H), 6.69 (d, *J* = 7.2 Hz, 1H), 6.76 (m, 1H), 7.26 (m, 1H), 7.36 (m, 2H), 7.50 (m, 1H), 7.55 (m, 2H); MS *m/z* 319 (M+, 20). Anal. Calcd for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10; N, 4.39. Found: C, 71.32; H, 4.00; N, 4.32%.

1-(4-(Dimethylamino)phenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (**4i**): M.p. 223–225 °C (EtOAc-CH_2Cl_2); IR (KBr, cm^{-1}) 3149, 1736, 1610, 1518, 1224; ^1H NMR ($CDCl_3$, 600 MHz, ppm) δ 2.92 (s, 2XCH_3, 6H), 5.88 (s, 1H), 6.01 (d, *J* = 2.4 Hz, 1H), 6.74 (s, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.40 (t, *J* = 3.6 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.84 7.16 (d, *J* = 9.0 Hz, 2H); MS *m/z* 318 (M+, 10). Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.40; H, 5.48; N, 8.62%.

We are grateful to the Natural Science Foundation of Jiangsu Education Ministry of China for financial support. (Grant 07KJB150135).

Received 13 October 2009; accepted 10 December 2009
Paper 090825 *doi: 10.3184/030823409X12615635710356*
Published online: 20 January 2010

References

1 I. Szatmári andF. Fülöp, *Curr. Org. Synth*., 2004, **1**, 155.
2 C. Cardellicchio, G. Ciccarella, F. Naso, F. Perna and P. Tortorella, *Tetrahedron*, 1999, **55**, 14685.
3 J. Lu, X. Xu, C. Wang, J. He, Y. Hu and H. Hu, *Tetrahedron Lett*., 2002, **43**, 8367.
4 K. Li, Z. Zhou, L. Wang, Q. Zhou and C. Tang, *Main Group Met. Chem*., 2002, **25**, 663.
5 X. Xu, J. Lu, R. Li, Z. Ge, Y. Dong and Y. Hu, *Synlett*, 2004, 122.
6 X. Xu, J. Lu, Y. Dong, R. Li, Z. Ge and Y. Hu, *Tetrahedron: Asymmetry*, 2004, **15**, 475.
7 J. Lu, X. Xu, S. Wang, C. Wang, Y. Hu and H. Hu, *J. Chem. Soc., Perkin Trans. 1* 2002, **24**, 2900.
8 Y. Dong, J. Sun, X. Wang, X. Xu, L. Cao and Y. Hu, *Tetrahedron: Asymmetry*, 2004, **15**, 1667.
9 X. Wang, Y. Dong, J. Sun, X. Xu, R. Li and Y. Hu, *J. Org. Chem.,* 2005, **70**, 1897.
10 L. Waxman and P. L. Darke, *Antiviral Chem. Chemother*., 2000, **11**, 1.
11 A. S. Girgis, *Pharmazie,* 2000, 466.
12 N. Latif, N. Mishriky and F. M. Assad, *Aust. J. Chem*., 1982, **35**, 1037.
13 I. Szatmari, A. Hetenyi, L. Lazar and F. Fulop, *J. Heterocyclic Chem*., 2004, **41**, 367.
14 C. Cimarelli, G. Palmieri and E. Volpini, *Can. J. Chem*., 2004, **82**, 1314.
15 M. M. Khodaei, A. R. Khosropour and H. Moghanian, *Synlett*, 2006, 916.
16 M. Dabiri, A. S. Delbari and A. Bazgir, *Synlett*, 2007, 821.
17 B. P. Sachin, R. S. Pankajkumar, P. S. Mandar and D. S. Shriniwas, *Ultrason. Sonochem.*, 2007, **14**, 515.
18 B. P. Sachin, R. S. Pankajkumar, P. S. Mandar and D. S. Shriniwas, *Synth. Commun.*, 2007, **37**, 1659.
19 D. Biswanath, K. Laxminarayana, B. Ravikanth and R. B. Rama, *J. Mol. Cat. A: Chemical*., 2007, **261**, 180.
20 M. Anary-Abbasinejad, A. Hassanabadi, M. Kamali-Gharamaleki, A. Saidipoor and H. Anaraki-Ardakani, *J. Chem. Res*., 2007, 644.
21 J. M. Wen, C. P. Lin and J. H. Li, *J. Chem. Res*., 2008, 3.
22 B. Sreedhar, M. A. Reddy and P. S. Reddy, *Synlett*, 2008, **13**, 1949.
23 K. Kobayashi, A. Takanohashi, K. Hashimoto, O. Morikawa and H. Konishi, *Tetrahedron*, 2006, **62**, 3158.
24 G. Sabitha, GSKK. Reddy, K. B. Reddy and J. S. Yadav, *Synthesis*, 2004, 263.
25 H. Mao, J. Wan and Y. Pan, *Tetrahedron*, 2009, **65**, 1026.
26 S. V. Ryabukhin, A. S. Plaskon, E. N. Ostapchuk, D. M. Volochnyuk and A. A. Tolmachev, *Synthesis*, 2007, 417.
27 A. S. Degtyarenko, A. A. Tolmachev, Y. M. Volovenko and A. V. Tverdokhlebov, *Synthesis*, 2007, 3891.
28 S. Goncalves, A. Wagner, C. Mioskowski and R. Baati, *Tetrahedron Lett*., 2009, **50**, 274.
29 J. Wan, J. Zhou, H. Mao, Y. Pan and A. Wu, *Tetrahedron*, 2008, **64**, 11115.
30 V. Kysil, S. Tkachenko, A. Khvat, C. Williams, S. Tsirulnikov, M. Churakovab and A. Ivachtchenko, *Tetrahedron Lett*., 2007, **48**, 6239.
31 X. Bian, H. Liu, X. Geng, Z. Xie, S. Li and C. Wang, *J. Chem. Res*., 2009, 81.
32 Z. Xie, X. Bian, X. Geng, S. Li and C. Wang, *J. Chem. Res*., 2008, 52.
33 X. Geng, S. Li, X. Bian, Z. Xie and C. Wang, *ARKIVOC*, 2008, (**xiv**), 50.