Journal of Fluorine Chemistry 132 (2011) 306–309

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Switching reaction pathways of trifluoromethylated thiobenzanilides by choice of different oxidative systems

Jiangtao Zhu [a], Haibo Xie [a], Shan Li [a], Zixian Chen [b], Yongming Wu [a,*]

[a] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China
[b] Department Chemistry, Huazhong University of Science and Technology, Wuhan, Hubei 430074, China

ARTICLE INFO

Article history:
Received 14 January 2011
Received in revised form 15 February 2011
Accepted 15 February 2011
Available online 22 February 2011

Keywords:
Trifluoromethyl
Benzothiazoles
Disulfides
CAN
PIDA

ABSTRACT

Trifluoromethylated thiobenzanilides are efficiently converted to 2-trifluoromethylbenzothiazoles via intramolecular oxidative cyclization under CAN/$NaHCO_3$ oxidation, while the dimerized products with "–S–S–" bond linkage are obtained when PIDA is used as an oxidant.

1. Introduction

2-Substituted benzothiazoles are of great interest nowadays due to their potent pharmacological activities such as anti-tumor, antimicrobial, antiviral, and antiparasitic [1]. Traditional methods for their syntheses involve the condensation of *o*-aminothiophenols with substituted carboxylic acids, aldehydes, nitriles, or esters, but such methods suffer from difficulties in the preparation of readily oxidizable *o*-aminothiophenol precursors [2]. Alternatively, oxidative cyclization of thiobenzanilides has been the most frequently used route to synthesize benzothiazoles with various oxidants such as potassium ferricyanide(III) [3], cerium(IV) ammonium nitrate (CAN) [4], hypervalent iodine reagents (DMP, PIFA) [5], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [6], and manganese(III) triacetate [7]. Recently, palladium or copper catalyzed coupling reactions to construct benzothiazoles via C–S bond formation from *ortho*-haloanilides have been developed [8]. To overcome the limited diversity of the *ortho*-halogen substituted anilines, palladium-catalyzed cyclization of thiobenzanilides leading to 2-substituted benzothiazoles (2-aryl by Doi and co-workers [9], 2-amino by Joyce and Batey [10], 2-trifluoromethyl by Wu and co-workers [11]) has been explored through an intramolecular C–H bond functionalization/C–S bond formation sequence. As our ongoing research on fluorinated heterocycle synthesis [12], we now report a facile synthesis of 2-trifluoromethylbenzothiazoles from corresponding trifluoromethylated thiobenzanilides using CAN as the oxidant, whereas the other oxidant phenyliodine(III) diacetate (PIDA) results in disulfides by intermolecular dimerization.

2. Results and discussion

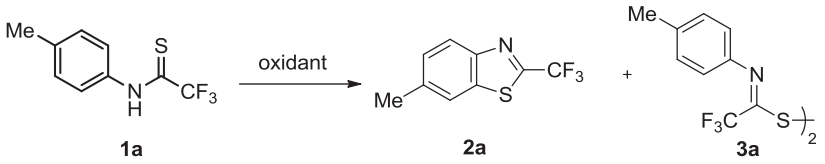
During our investigation for the synthesis of 2-trifluoromethylbenzothiazoles by palladium-catalyzed cyclization of the trifluoromethylated thiobenzanilides, we found that 2-trifluoromethylbenzothiazoles could be obtained in good yields using CAN as oxidant. To identify an optimal oxidative reagent for this transformation, 2,2,2-trifluoro-*N*-*p*-tolylethanethioamide **1a**, which was chosen as a model substrate, was treated with several different oxidants. As listed in Table 1, 2 equiv. of CAN was found essential for the complete conversion of the substrate **1a** and the desired product **2a** was obtained in 93% yield. However, when **1a** was treated with 1 equiv. of PIDA in CH_2Cl_2 for 5 min, disulfide **3a** was unexpectedly produced as the major product even with 2 equiv. of PIDA in CH_3CN at 80 °C. Utilization of $FeCl_3$ gave **2a** in lower yield, whereas other oxidants such as DDQ, I_2 were not capable of above conversion as the starting material **1a** was recovered after the reaction.

With the optimized reaction conditions in hand, we examined a series of substituted trifluoromethylated thiobenzanilides **1** to establish the scope and limitations of this process under different

* Corresponding author. Tel.: +86 21 54925190; fax: +86 21 64166128.
E-mail address: ymwu@sioc.ac.cn (Y. Wu).

0022-1139/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2011.02.010

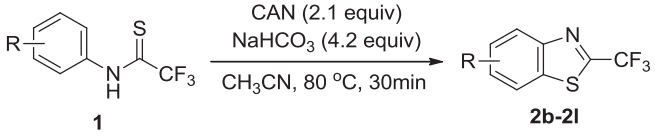
Table 1
Optimization of reaction conditions[a].



Entry	Oxidant (equiv.)	Solvent	Temp. (°C)	Time	Yield (%)[b]
1	CAN/2	CH_3CN	80	10 min	**2a**/93
2	CAN/1	CH_3CN	80	10 min	**2a**/46
3	CAN/2	CH_3CN	r.t.	7 h	**2a**/78
4	PIDA/1	CH_2Cl_2	r.t.	5 min	**3a**/86
5	PIDA/2	CH_3CN	80	30 min	**3a**/80
6	DDQ/1.25	CH_3CN	80	2 h	**1a**
7	I_2/2	CH_2Cl_2	r.t.	30 min	**1a**

[a] *Conditions*: Reactions were carried out on a 0.5 mmol scale in solvent (5 mL).
[b] Isolated yield.

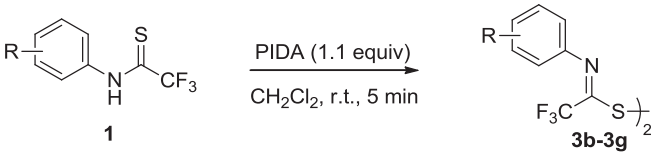
Table 2
Synthesis of 2-trifluoromethylbenzothiazoles[a].



Entry	R (for **1**)	Yield (%)[b]
1	H	**2b**/73
2	*p*-F	**2c**/83
3	*p*-Cl	**2d**/76
4	*p*-Br	–[c]
5	*p*-I	–[c]
6	*p*-CF_3	**2e**/65
7	*p*-COOEt	**2f**/66
8	*p*-NO_2	**2g**/35
9	*p*-CN	**2h**/62
10	2-Naphthyl	**2i**/86
11	*o*-Me	**2j**/78
12	H (CF_2Cl instead of CF_3)	**2k**/81
13	H (CF_2CF_3 instead of CF_3)	**2l**/74

[a] Reactions were carried out on a 0.8 mmol scale in CH_3CN (8 mL) with CAN (1.68 mmol), $NaHCO_3$ (3.36 mmol).
[b] Isolated yield.
[c] The product was the corresponding benzamides.

Table 3
Synthesis of the dimerization product disulfides[a].

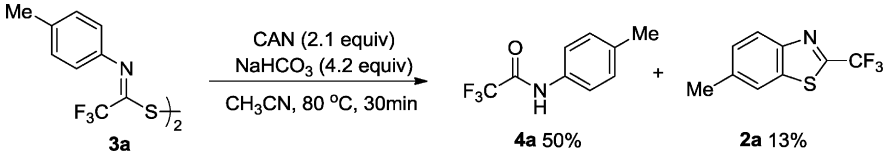


Entry	R (for **1**)	Yield (%)[b]
1	*p*-OMe	**3b**/89
2	H	**3c**/92
3	*p*-I	**3d**/78
4	*p*-Cl	**3e**/87
5	*p*-CF_3	**3f**/62
6	*o*,*o*-diMe	**3g**/90

[a] Reactions were carried out on a 1.0 mmol scale in CH_2Cl_2 (10 mL) with PIDA (1.1 mmol).
[b] Isolated yield.

oxidative systems. The substrates **1** were easily generated from the reaction of 2,2,2-trifluoro-*N*-arylacetimidoyl chlorides with sodium hydrosulfide hydrate in EtOH at room temperature which could obviate using Lawesson's reagent. As summarized in Table 2, by using CAN, an array of benzothiazoles were formed in moderate to good yields. Contrary to what we expected, some electron-withdrawing groups (CF_3, COOEt, NO_2, and CN) were tolerated in this reaction which was not observed in other similar oxidative cyclization of thiobenzanilides (Table 2, entries 6–9). Unfortunately, bromo and iodo substituents could hamper this transformation as the major products were identified as the corresponding benzamides (Table 2, entries 4 and 5), while chloro and fluoro substituents were intact and gave the desired benzothiazoles in good yields (Table 2, entries 2 and 3). When trifluoromethyl group was replaced by chlorodifluoromethyl or pentafluoroethyl group, the corresponding benzothiazoles were formed in 81% and 74% yield, respectively (Table 2, entries 12 and 13).

It is a common knowledge that molecules containing a disulfide moiety play an important role in biochemistry. However, the oxidative dimerization of thiobenzanilides was less reported than the related thiols [13]. After investigating the CAN-oxidative cyclization, we then turned our attention to dimerization of the thiobenzanilides by PIDA. Some trifluoromethylated thiobenzanilides were treated with 1.1 equiv. of PIDA via this transformation to obtain the corresponding disulfides **3**. As indicated in Table 3, the desired disulfides **3** were obtained in high yields even with iodo substituent on the aryl ring (Table 3, entry 3). Disulfide **3f** was not



Scheme 1.

separated as a pure compound through the silica chromatography gel due to its instability of S–S bond (Table 3, entry 5). When the disulfide product **3a** was treated with 2 equiv. of CAN at 80 °C after 30 min, the main product characterized as the corresponding benzamide **4a** was obtained in 50% yield and 34% of **3a** was recovered (Scheme 1).

3. Conclusion

In conclusion, we have developed a novel method for the synthesis of 2-trifluoromethylbenzothialzoles via intramolecular oxidative cyclization of thiobenzanilides under CAN/$NaHCO_3$ oxidation. On the other hand, dimerization of thiobenzanilides leads to the corresponding sulfides by using PIDA as the oxidant. The application of the resultant disulfides becomes our next focus now.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz) with TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as external standard. ^{13}C NMR spectra were taken on a Bruker AM-400 (100 MHz) spectrometer. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. All reagents were used as received from commercial sources. Column chromatography over silica gel (mesh 300–400) and petroleum ether/ethyl acetate combination was used as the eluent. The characterization data of the benzothiazoles could be found in Ref. [11].

4.2. General procedure for the synthesis of 2-trifluoromethylbenzothiazoles 2 under CAN/$NaHCO_3$ system

A mixture of trifluoromethylated thiobenzanilides **1** (0.8 mmol) and CAN (920 mg, 1.68 mmol) in CH_3CN (8 mL) was stirred at 80 °C for 30 min. Then water (10 mL) was added and the mixture was extracted with ethyl acetate (15 mL × 2). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel using petroleum ether/CH_2Cl_2 as eluent to provide the desired product **2**.

4.3. Spectroscopic data of 2-trifluoromethylbenzothiazoles 2

4.3.1. 2,6-Bis(trifluoromethyl)benzo[d]thiazole (2e)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34–8.29 (m, 2H), 7.86 (d, J = 8.8 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.32 (s, 3F), −62.43 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0 (q, J = 41.1 Hz), 153.9, 135.1, 129.8 (q, J = 33.7 Hz), 125.6, 124.3 (q, J = 3.0 Hz), 123.6 (q, J = 272.2 Hz), 119.9 (q, J = 3.6 Hz), 119.4 (q, J = 273.6 Hz); MS (EI): m/z (%): 271 (100.00) [M^+]; HRMS Calculated for $C_9H_3NF_6S$: 271.9890, Found: 271.9888.

4.3.2. 4-Methyl-2-(trifluoromethyl)benzo[d]thiazole (2j)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, J = 7.5 Hz, 1H), 7.44–7.35 (m, 2H), 2.78 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −61.33 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5 (q, J = 40.1 Hz), 151.8, 135.3, 134.9, 127.6, 127.5, 120.0 (q, J = 271.3 Hz) 119.3, 18.1; MS (EI): m/z (%): 217 (100.00) [M^+]; HRMS Calculated for $C_9H_3NF_3S$: 217.0173, Found: 217.0174.

4.4. General procedure for the synthesis of dimerization products 3 using PIDA as an oxidant

A mixture of trifluoromethylated thiobenzanilides **1** (1.0 mmol) and PIDA (354 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 5 min. Then the reaction mixture was concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel using petroleum ether/ethyl acetate to give the product **3**.

4.5. Spectroscopic data of dimerization products 3

4.5.1. Bis(N-p-methylphenyltrifluoroacetimidoyl) disulfide (3a)

^{1}H NMR (300 MHz, $CDCl_3$): 7.17 (d, J = 8.2 Hz, 4H), 6.77 (d, J = 8.2 Hz, 4H), 2.35 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −64.67 (s, 6F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8 (q, J = 35.6 Hz), 142.9, 136.7, 129.8, 119.2, 117.8 (q, J = 281.6 Hz), 21.0.

MS (EI): m/z (%): 436 (3.97) [M^+], 186 (100.00); HRMS Calculated for $C_{18}H_{14}N_2F_6S_2$: 436.0503, Found: 436.0504; IR (film): ν 2925, 1631, 1503, 1278, 1185, 1151, 950 cm^{-1}.

4.5.2. Bis(N-p-methoxyphenyltrifluoroacetimidoyl) disulfide (3b)

^{1}H NMR (300 MHz, $CDCl_3$): 6.90 (s, 8H), 3.81 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −64.54 (s, 6F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 147.3 (q, J = 35.6 Hz), 138.1, 121.7, 118.0 (q, J = 281.2 Hz), 114.2, 55.3; MS (EI): m/z (%): 468 (6.44) [M^+], 202 (100.00); HRMS Calculated for $C_{18}H_{14}N_2O_2F_6S_2$: 468.0401, Found: 468.0403; IR (film): ν 2949, 2846, 1630, 1504, 1464, 1277, 1250, 1161, 1033, 952 cm^{-1}.

4.5.3. Bis(N-phenyltrifluoroacetimidoyl) disulfide (3c)

^{1}H NMR (300 MHz, $CDCl_3$): 7.42–7.35 (m, 4H), 7.27–7.20 (m, 2H), 6.85 (d, J = 7.4 Hz, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −64.78 (s, 6F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5 (q, J = 35.9 Hz), 145.5, 129.3, 126.6, 118.9, 117.8 (q, J = 281.2 Hz); MS (EI): m/z (%): 408 (3.22) [M^+], 172 (100.00); HRMS Calculated for $C_{16}H_{10}N_2F_6S_2$: 408.0190, Found: 408.0192; IR (film): ν 2929, 1645, 1277, 1150, 1137, 955 cm^{-1}.

4.5.4. Bis(N-p-iodophenyltrifluoroacetimidoyl) disulfide (3d)

^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (d, J = 8.8 Hz, 4H), 6.61 (d, J = 8.8 Hz, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.01 (s, 6F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9 (q, J = 36.7 Hz), 144.9, 138.4, 120.7, 117.6 (q, J = 282.0 Hz), 91.2; MS (EI): m/z (%): 660 (1.60) [M^+], 298 (100.00); HRMS Calculated for $C1_8H_8N_2F_6S_2I_2$: 659.8123, Found: 659.8127; IR (film): ν 1635, 1476, 1278, 1150, 955 cm^{-1}.

4.5.5. Bis(N-p-chlorophenyltrifluoroacetimidoyl) disulfide (3e)

^{1}H NMR (300 MHz, $CDCl_3$): 7.36 (d, J = 8.5 Hz, 4H), 6.80 (d, J = 8.5 Hz, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −64.99 (s, 6F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.0 (q, J = 36.0 Hz), 143.7, 132.4, 129.5, 120.3, 117.6 (q, J = 281.6 Hz); MS (EI): m/z (%): 476 (2.76) [M^+], 206 (100.00); HRMS Calculated for $C_{16}H_8N_2F_6S_2Cl_2$: 475.9410, Found: 475.9408; IR (film): ν 2917, 1634, 1483, 1279, 1154, 955 cm^{-1}.

4.5.6. Bis(N-o,o-dimethylphenyltrifluoroacetimidoyl) disulfide (3g)

^{1}H NMR (300 MHz, $CDCl_3$): 7.05–7.02 (m, 6H), 2.03 (s, 12H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −64.75 (s, 6F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8 (q, J = 35.9 Hz), 128.4, 125.6, 125.0, 117.5 (q, J = 281.2 Hz), 17.1; MS (EI): m/z (%): 464 (3.26) [M^+], 200 (100.00); HRMS Calculated for $C_{20}H_{18}N_2F_6S_2$: 464.0816, Found: 464.0815; IR (film): ν 2924, 1639, 1467, 1280, 1209, 1151, 955 cm^{-1}.

Acknowledgement

The authors thank the National Natural Science Foundation of China (NNSFC) (20772145) for financial support.

References

[1] (a) M.F.G. Stevens, C.J. McCall, P. Lelievald, P. Alexander, A. Richter, D.E. Davies, J. Med. Chem. 37 (1994) 1689–1695;
(b) X. Wang, K. Sarris, K. Kage, D. Zhang, S.P. Brown, T. Kolasa, C. Surowy, O.F. El Kouhen, S.W. Muchmore, J.D. Brioni, A.O. Stewart, J. Med. Chem. 52 (2009) 170–180;
(c) C.G. Mortimer, G. Wells, J.-P. Crochard, E.L. Stone, T.D. Bradshaw, M.F.G. Stevens, A.D. Westwell, J. Med. Chem. 49 (2006) 179–185;
(d) V. Trapani, V. Patel, C.O. Leong, H.P. Ciolino, G.C. Yeh, C. Hose, J.B. Trepel, M.F.G. Stevens, E.A. Sausville, A.I. Loaiza-Pérez, Br. J. Cancer 88 (2003) 599–605;
(e) T.D. Bradshaw, S. Wrigley, D.F. Shi, R.J. Schultz, K.D. Paull, M.F.G. Stevens, Br. J. Cancer 77 (1998) 745–752;
(f) V.R. Solomon, C. Hu, H. Lee, Bioorg. Med. Chem. 17 (2009) 7585–7592;
(g) F. Delmas, A. Avellaneda, C. Di Giorgio, M. Robin, E. De Clercq, P. Timon-David, J.-P. Galy, Eur. J. Med. Chem. 39 (2004) 685–690.

[2] (a) A. Ben-Alloum, S. Bakkas, M. Soufiaoui, Tetrahedron Lett. 38 (1997) 6395–6396;
(b) K. Bahrami, M.M. Khodaei, F. Naali, J. Org. Chem. 73 (2008) 6835–6837;
(c) S. Yao, K.J. Schafer-Hales, K.D. Belfield, Org. Lett. 9 (2007) 5645–5648;
(d) C. Praveen, K.H. Kumar, D. Muralidharan, P.T. Perumal, Tetrahedron 64 (2008) 2369–2374;
(e) F. Ge, Z. Wang, W. Wan, W. Lu, J. Hao, Tetrahedron Lett. 48 (2007) 3251–3254.

[3] (a) P. Jacobson, Chem. Ber. 19 (1886) 1067;
(b) D.-F. Shi, T.D. Bradshaw, S. Wrigley, C.J. McCall, P. Lelieveld, I. Fichtner, M.F.G. Stevens, J. Med. Chem. 39 (1996) 3375–3384.

[4] N.K. Downer-Riley, Y.A. Jackson, Tetrahedron 64 (2008) 7741–7744.

[5] D.S. Bose, M. Idrees, J. Org. Chem. 71 (2006) 8261–8263.

[6] (a) D.S. Bose, M. Idrees, Tetrahedron Lett. 48 (2007) 669–672;
(b) D.S. Bose, M. Idrees, B. Srikanth, Synthesis (2007) 0819–0823.

[7] X.-J. Mu, J.-P. Zou, R.-S. Zeng, J.-C. Wu, Tetrahedron Lett. 46 (2005) 4345–4347.

[8] (a) C. Benedí, F. Bravo, P. Uriz, E. Fernández, C. Claver, S. Castillón, Tetrahedron Lett. 44 (2003) 6073–6077;
(b) G. Evindar, R.A. Batey, J. Org. Chem. 71 (2006) 1802–1808;
(c) L.L. Joyce, G. Evindar, R.A. Batey, Chem. Commun. (2004) 446–447;
(d) H.C. Ma, X.Z. Jiang, Synlett (2008) 1335–1340;
(e) S. Murru, P. Mondal, R. Yella, B.K. Patel, Eur. J. Org. Chem. 2009 (2009) 5406–5413;
(f) G. Shen, X. Lv, W. Bao, Eur. J. Org. Chem. 2009 (2009) 5897–5901;
(g) D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong, Y. Jiang, Angew. Chem. Int. Ed. 48 (2009) 4222–4225;
(h) T. Itoh, T. Mase, Org. Lett. 9 (2007) 3687–3689;
(i) C.-L. Li, X.-G. Zhang, R.-Y. Tang, P. Zhong, J.-H. Li, J. Org. Chem. 75 (2010) 7037–7040.

[9] K. Inamoto, C. Hasegawa, K. Hiroya, T. Doi, Org. Lett. 10 (2008) 5147–5150.

[10] L.L. Joyce, R.A. Batey, Org. Lett. 11 (2009) 2792–2795.

[11] J. Zhu, Z. Chen, H. Xie, S. Li, Y. Wu, Org. Lett. 12 (2010) 2434–2436.

[12] (a) H. Xie, J. Zhu, Z. Chen, S. Li, Y. Wu, J. Org. Chem. 75 (2010) 7468–7471;
(b) S. Li, Y. Yuan, J. Zhu, H. Xie, Z. Chen, Y. Wu, Adv. Synth. Catal. 352 (2010) 1582–1586;
(c) Z. Chen, J. Zhu, H. Xie, S. Li, Y. Wu, Y. Gong, Synlett (2010) 1418–1420;
(d) Z. Chen, J. Zhu, H. Xie, S. Li, Y. Wu, Y. Gong, Adv. Synth. Catal. 352 (2010) 1296–1300;
(e) Z. Chen, J. Zhu, H. Xie, S. Li, Y. Wu, Y. Gong, Chem. Commun. 46 (2010) 2145–2147;
(f) Z. Chen, J. Zhu, H. Xie, S. Li, Y. Wu, Y. Gong, Org. Lett. 12 (2010) 4376–4379;
(g) J. Zhu, H. Xie, Z. Chen, S. Li, Y. Wu, Synlett (2009) 3299–3302;
(h) J. Zhu, H. Xie, Z. Chen, S. Li, Y. Wu, Chem. Commun. (2009) 2338–2340.

[13] D. Singh, F.Z. Galetto, L.C. Soares, O.E.D. Rodrigues, A.L. Braga, Eur. J. Org. Chem. 2010 (2010) 2661–2665, and references therein.