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Conversion of thiobenzamides to benzothiazoles via intramolecular cyclization of the aryl radical cation

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ABSTRACT

A new and general method has been developed for the intramolecular cyclization of thiobenzamides to benzothiazoles via aryl radical cations as reactive intermediates. The method utilizes phenyliodine(III) bis(trifluoroacetate) (PIFA) in trifluoroethanol or cerium ammonium nitrate (CAN) in aqueous acetonitrile at room temperature to effect cyclization within 30 min in moderate yields.

1. Introduction

2-Substituted benzothiazoles are now of great interest due to their potent antitumor and other pharmacological activity.[1,2] The most common method for their synthesis from thiobenzamides is the Jacobson synthesis, which involves the use of potassium ferricyanide with sodium hydroxide.[3] Recently, several new methods have emerged, which utilize various oxidants such as Dess–Martin periodinane,[4] manganese triacetate,[5] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[6] to facilitate formation of the thiyl radical from the thiobenzamide, which cyclizes with loss of a hydrogen atom to produce the benzothiazole (Scheme 1).

In our quest to develop new methods (not involving the thiyl radical) for cyclization of thiobenzamides to benzothiazoles, the use of iodine was explored.[7] This reagent promotes cyclization of thiobenzamides to benzothiazoles via the sulfenyliodide. It was found, however, that reaction of thiobenzamides, which possess *ortho*-alkoxy groups, with iodine, leads to benzoxazoles. The present paper reports our further attempts at synthesis of benzothiazoles from thiobenzamides.

2. Results and discussion

Hypervalent iodine reagents have facilitated synthetic transformations involving carbon–carbon and carbon–heteroatom bond formation. Phenyliodine(III) diacetate (PIDA) has successfully been used to promote umpolong formation aiding cyclization of *N*-2-phenyl formimidamides to benzimidazoles.[8] Reaction of thiobenzamides with PIDA in a similar manner was therefore considered as a route to benzothiazoles via the sulfenyliodide. Unlike the reaction of 2-methoxythiobenzamides with iodine, the sulfenyliodide generated in this reaction was not sufficiently electrophilic to allow attack of the *ortho*-methoxy group resulting in benzoxazole formation. Reaction of 2-methoxythiobenzamides **1a–c** with PIDA in toluene at reflux for 3 h, however, showed only minor conversion to benzothiazoles with the corresponding benzamides as the major products (Scheme 2).

Another useful hypervalent iodine reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA), has been reported to facilitate nucleophilic attack onto aryl ethers in polar non-nucleophilic solvents by promoting formation of the aryl radical cation.[9,10] These reactions are of particular interest to us as formation of a radical cation of a thiobenzamide could lead to intramolecular nucleophilic attack to produce a benzothiazole (Scheme 3).

Treating the thiobenzamides **1a–n** (prepared from readily available anilines) with PIFA (1.1 equiv) in trifluoroethanol and stirring for 30 min at room temperature led to the corresponding benzothiazoles. As shown in Table 1, reaction of PIFA with *ortho*-methoxythiobenzamides **1a–e** (entries 1–5) showed conversion to benzothiazole in only 0–52% yield. Thiobenzamide **1d**, which

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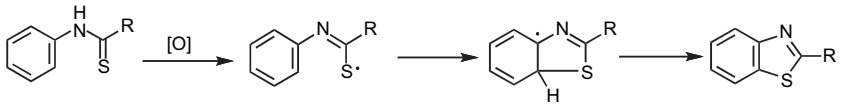
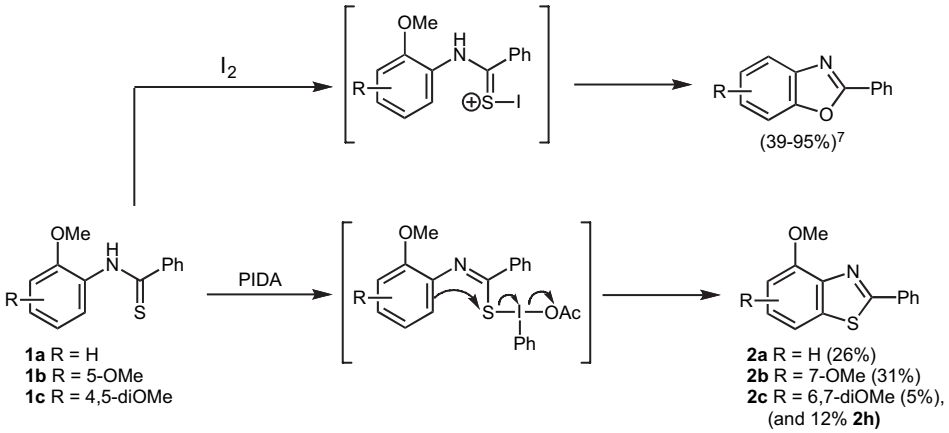
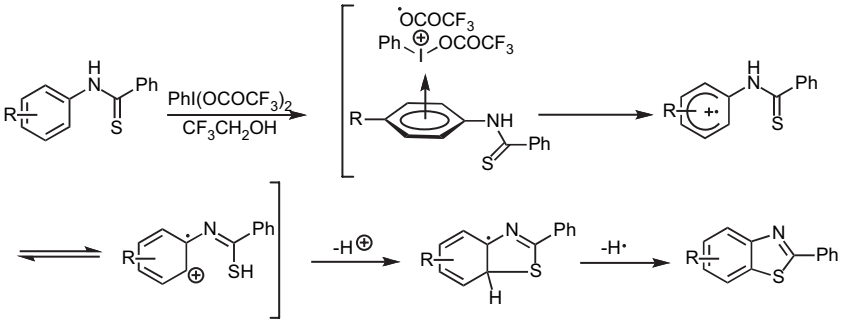


Scheme 1.



Scheme 2. Iodine and PIDA-mediated cyclization of 2-methoxythiobenzamides.



Scheme 3. PIFA-mediated cyclization of thiobenzamides.

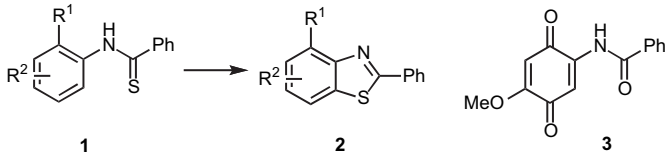
possesses a highly activated primary ring, was quickly oxidized by PIFA to amidoquinone **3**. Reaction of PIFA with other thiobenzamides bearing electron-donating substituents on the primary ring (entries 6–11) yielded benzothiazoles **2f–k** in 71–98% yield. Thiobenzamide **1n** bearing the electron-withdrawing nitro group (entry 14) could not be cyclized using this reaction and the corresponding benzamide was obtained in quantitative yield. The low conversion of the *ortho*-methoxythiobenzamides **1a–e** to benzothiazoles suggests that the presence of the *ortho*-methoxy group may be hindering cyclization to the benzothiazole resulting in the corresponding benzamide as byproduct.

A rational mechanism is proposed for the oxidation of *ortho*-methoxythiobenzamides to benzamides under these reaction conditions (Scheme 4). Reaction of the thiobenzamide with PIFA yields thiol radical cation **5**, along with aryl radical cation **4a**, which is required for cyclization to the benzothiazole. Reactivity of radical cation **4a** is reduced by the presence of the methoxy group, which is able to quench the positive charge to produce **4b**. The competing reaction of thiol radical cation **5** with water in the mixture is therefore preferred yielding benzamide as a byproduct.

In continuing our investigation into the use of aryl radical cations as intermediates for benzothiazole synthesis, reaction of thiobenzamides with ceric(IV) ammonium nitrate (CAN) was explored. CAN is a well-known one-electron oxidant and like PIFA, it has proven to be useful in the construction of carbon–carbon and carbon–heteroatom bonds.[11] In aqueous acetonitrile, aryl methyl ethers react with CAN to produce quinones.[12] It was therefore expected that upon formation of the radical cation of thiobenzamides **1a–f**, cyclization to the benzothiazole could compete with reaction with water to generate the *p*-quinones. Thus, reaction of the thiobenzamides with one molar equivalent CAN in aqueous acetonitrile was attempted. After stirring at room temperature for 30 min, the thiobenzamides were completely converted to a mixture of benzothiazoles and benzamides (Table 1). Once again, the *ortho*-methoxythiobenzamides (entries 1–5) were converted to benzothiazoles in significantly lower yields (9–37%) than the other substrates used, which had activated primary rings (entries 6–11, 30–94%). The effect of the *ortho*-methoxy group on the mechanism of this reaction is thought to be as shown in Scheme 4. Reaction of thiobenzamides with CAN is, however, carried out in aqueous medium and as such attack of the intermediate thiol radical cation by water to produce the benzamide is very likely. This would account for the higher conversion of thiobenzamides to benzothiazoles by PIFA when compared to CAN.

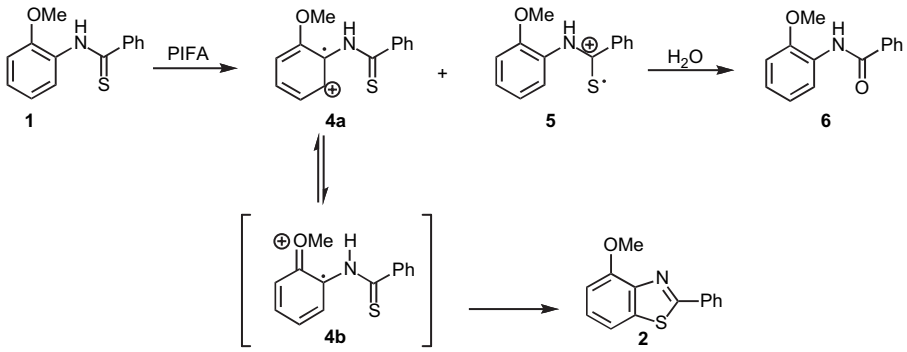
In conclusion, a novel strategy has been developed for the conversion of thiobenzamides to benzothiazoles in moderate yield via the aryl radical cation as reactive intermediate. The aryl radical cation may be generated by reaction with PIFA in trifluoroethanol or CAN in aqueous acetonitrile.

Table 1
Reaction of thiobenzamides with PIFA and CAN



Entry	Substrate			Benzothiazole product	% Yield	
		R^1	R^2		PIFA	CAN
1	**1a**	OMe	H	**2a**	50[e]	9[g]
2	**1b**	OMe	5-OMe	**2b**	52[d]	37[d]
3	**1c**	OMe	4-OMe	**2c**	41[c]	14[e]
4	**1d**	OMe	4,5-diOMe	**2h**	—[a]	32[a]
5	**1e**	OMe	4-Br, 5-OMe	**2e**	26[f]	—[b]
6	**1f**	H	3-OMe	**2f**	71	49
7	**1g**	H	4-OMe	**2g**	73	66
8	**1h**	H	3,4-diOMe	**2h**	98	94
9	**1i**	Me	H	**2i**	77	30[f]
10	**1j**	H	3-Me	**2j**	71	90
11	**1k**	H	4-Me	**2k**	84	36[d]
12	**1l**	H	H	**2l**	46[d]	23[f]
13	**1m**	Br	H	**2m**	42[e]	36[f]
14	**1n**	H	4-NO_2	—	—[h]	—[h]

[a] Amidoquinone **3** was recovered from the reaction mixture (60%).
[b] Intractable mixture was obtained.
[c] Benzamide was isolated from the reaction mixture in 11–20% yield.
[d] Benzamide was isolated from the reaction mixture in 21–30% yield.
[e] Benzamide was isolated from the reaction mixture in 41–50% yield.
[f] Benzamide was isolated from the reaction mixture in 61–70% yield.
[g] Benzamide was isolated from the reaction mixture in 81–90% yield.
[h] Quantitative amide formation.



Scheme 4. A plausible mechanism for the PIFA-mediated oxidation of thiobenzamides to benzamides.

3. Experimental

3.1. General

IR spectra were obtained on a Perkin–Elmer 735B FT-IR spectrometer as KBr discs. NMR spectra (Bruker 200 and 500 MHz) were obtained in $CDCl_3$ solution and the resonances are reported in δ units downfield from TMS as an internal standard; J values are given in hertz. Elemental analyses were carried out by MEDAC Ltd, Egham, Surrey, UK. Column chromatography was carried out using silica gel as adsorbent. For all known compounds, ^{1}H NMR spectroscopic data were identical to that reported in the literature.

3.2. Preparation of thiobenzamides

A mixture of the aniline (1.0 g) and benzoyl chloride (1.1 mol equiv) in dry toluene (6 mL) and pyridine (5 mL) was heated at reflux for 2 h then poured into water (100 mL) and extracted with ethyl acetate (2×15 mL). The organic layer was washed with 1 M HCl (50 mL) followed by aqueous sodium bicarbonate solution (50 mL) then water (50 mL), dried (Na_2SO_4), and concentrated in vacuo to obtain pure benzamide. A mixture of the benzamide (1.0 g) and Lawesson's reagent (0.6 mol equiv) in dry toluene (40 mL) was heated at reflux under an atmosphere of nitrogen for 2 h, after which it was concentrated, purified by column chromatography (EtOAc/hexanes 1:4) and recrystallized from methanol.

*3.2.1. N-(2-Methoxyphenyl)thiobenzamide (**1a**)*
Yellow needles. Yield: 0.13 g, 67% from *o*-anisidine; mp 78–79 °C (lit.[2] 121–122 °C).

*3.2.2. N-(2,5-Dimethoxyphenyl)thiobenzamide (**1b**)*
Yellow needles. Yield: 0.14 g, 81% from 2,5-dimethoxyaniline; mp 61–62 °C (lit.[13] 58–61 °C).

*3.2.3. N-(2,4-Dimethoxyphenyl)thiobenzamide (**1c**)*
Yellow oil. Yield: 0.13 g, 73% from 2,4-dimethoxyaniline. (Found: C, 65.88; H, 5.69; N, 4.93. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12%); ν_{max}/cm^{-1} 3312, 1719, 1514; δ_H 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.56 (2H, m, 3,5-H), 7.48 (3H, m, 3′,4′,5′-H), 7.85 (2H, m, 2′,6′-H), 8.91 (1H, m, 6-H), 9.42 (1H, s, N–H); δ_C 55.6, 56.0, 98.7, 103.2, 122.2, 123.0, 126.7, 128.6, 130.9, 143.9, 151.5, 158.4, 195.2.

*3.2.4. N-(2,4,5-Trimethoxyphenyl)thiobenzamide (**1d**)*
Yellow needles. Yield: 0.10 g, 62% from 2,4,5-trimethoxyaniline; mp 104–105 °C (lit.[14] 104–105 °C).

*3.2.5. N-(4-Bromo-2,5-dimethoxyphenyl)thiobenzamide (**1e**)*
Fine yellow crystals. Yield: 0.09 g, 85% from *N*-(4-bromo-2,5-dimethoxyphenyl)thiobenzamide; mp 157–158 °C (lit.[13] 154–156 °C).

*3.2.6. N-(3-Methoxyphenyl)thiobenzamide (**1f**)*
Yellow needles. Yield: 0.14 g, 71% from *m*-anisidine; mp 81–82 °C (lit.[2] 81–82 °C).

*3.2.7. N-(4-Methoxyphenyl)thiobenzamide (**1g**)*
Yellow needles. Yield: 0.13 g, 68% from *p*-anisidine; mp 129–130 °C (lit.[2] 131–133 °C).

*3.2.8. N-(3,4-Dimethoxyphenyl)thiobenzamide (**1h**)*
Fine yellow crystals. Yield: 0.11 g, 63% from 3,4-dimethoxyaniline; mp 152–153 °C (lit.[2] 154–155 °C).

*3.2.9. N-(2-Methylphenyl)thiobenzamide (**1i**)*
Viscous yellow oil. Yield 0.14 g, 67% from *o*-toluidine.[15]

*3.2.10. N-(3-Methylphenyl)thiobenzamide (**1j**)*

Yellow feathers. Yield: 0.14 g, 65% from *m*-toluidine; mp 80–81 °C. (Found: C, 73.90; H, 5.83; N, 6.13%. Anal. Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16%); ν_{max}/cm^{-1} 3175, 1607, 1357; δ_H 2.37 (3H, s, CH_3), 7.08 (1H, d, *J* 7.5, 4-H), 7.24–7.52 (6H, m, 2,5,6-H and 3′,4′,5′-H), 7.80 (2H, m, 2′,6′-H), 9.03 (1H, s, N–H); δ_C 21.4, 120.9, 124.3, 126.7, 127.8, 128.6, 128.9, 131.2, 138.9, 139.1, 143.1, 198.4.

*3.2.11. N-(4-Methylphenyl)thiobenzamide (**1k**)*

Yellow feathers. Yield: 0.15 g, 73% from *p*-toluidine; mp 129–130 °C (lit.[16] 128–129.5 °C).

*3.2.12. N-Phenylthiobenzamide (**1l**)*

Yellow needles. Yield: 0.18 g, 80% from aniline; mp 97–98 °C (lit.[5] 115–116 °C).

*3.2.13. N-(2-Bromophenyl)thiobenzamide (**1m**)*

Fine yellow crystals. Yield: 0.13 g, 75% from *o*-bromoaniline; mp 61–62 °C (lit.[17] 85–86 °C).

*3.2.14. N-(4-Nitrophenyl)thiobenzamide (**1n**)*

Yellow needles. Yield: 0.12 g, 63% from *p*-nitroaniline; mp 143–144 °C (lit.[18] 145–146 °C).

3.3. Reaction of thiobenzamides with PIFA

To a solution of the thiobenzamide (0.10 g) in CF_3CH_2OH (1 mL) under an atmosphere of nitrogen was added PIFA (1.1 mol equiv). The mixture was then stirred at room temperature for 30 min, evaporated in vacuo and then purified by column chromatography. The benzothiazoles were recrystallized from ethanol.

*3.3.1. 4-Methoxy-2-phenylbenzothiazole (**2a**)*

White feathers. Yield: 0.05 g, 50% from **1a**; mp 99–100 °C (lit.[2] 103–104 °C).

*3.3.2. 4,7-Dimethoxy-2-phenylbenzothiazole (**2b**)*

White needles. Yield: 0.05 g, 52% from **1b**; mp 118–119 °C (lit.[13] 122–124 °C).

*3.3.3. 4,6-Dimethoxy-2-phenylbenzothiazole (**2c**)*

White needles. Yield: 0.04 g, 41% from **1c**; mp 125–126 °C (lit.[19] 125–127 °C).

*3.3.4. 6-Bromo-4,7-dimethoxy-2-phenylbenzothiazole (**2e**)*

White needles. Yield: 0.03 g, 26% from **1e**; mp 120–121 °C (lit.[13] 123–125 °C).

*3.3.5. 5-Methoxy-2-phenylbenzothiazole (**2f**)*

Fine white crystals. Yield: 0.07 g, 71% from **1f**; mp 75–77 °C (lit.[14] 75–77 °C).

*3.3.6. 6-Methoxy-2-phenylbenzothiazole (**2g**)*

White feathers. Yield: 0.07 g, 73% from **1g**; mp 113–114 °C (lit.[2] 114–115 °C).

*3.3.7. 5,6-Dimethoxy-2-phenylbenzothiazole (**2h**)*

White needles. Yield: 0.10 g, 98% from **1h**; mp 145–146 °C (lit.[2] 142–144 °C).

*3.3.8. 4-Methyl-2-phenylbenzothiazole (**2i**)*

Fine white crystals. Yield: 0.08 g, 77% from **1i**; mp 123–124 °C (lit.[19] 124–125 °C).

*3.3.9. 5-Methyl-2-phenylbenzothiazole (**2j**)*

White needles. Yield: 0.07 g, 71% from **1j**; mp 147–148 °C (lit.[20] 150–151 °C).

*3.3.10. 6-Methyl-2-phenylbenzothiazole (**2k**)*

Fine white crystals. Yield: 0.08 g, 84% from **1k**; mp 118–119 °C (lit.[21] 121–122 °C).

*3.3.11. 2-Phenylbenzothiazole (**2l**)*

White needles. Yield: 0.05 g, 46% from **1l**; mp 111–112 °C (lit.[17] 114 °C).

*3.3.12. 4-Bromo-2-phenylbenzothiazole (**2m**)*

White needles. Yield 0.04 g, 42% from **1m**; mp 91–92 °C. (Found: C, 53.96; H, 2.88; N, 4.71%. Anal. Calcd for $C_{13}H_8NSBr$: C, 53.81; H, 2.78; N, 4.83%); ν_{max}/cm^{-1} 1479, 972, 757, 685; δ_H 7.23 (1H, d, *J* 7.8, 5-H), 7.50 (3H, m, 3′,4′,5′-H), 7.70 (1H, dd, *J* 1.1 and 7.8, 6-H), 7.81 (1H, dd, *J* 1.1 and 8.0, 7-H), 8.11 (2H, m, 2′,6′-H); δ_C 116.9, 120.8, 126.0, 127.8, 129.0, 129.8, 131.4, 133.2, 135.9, 152.3, 168.6.

3.4. Reaction of thiobenzamides with CAN

To a solution of the thiobenzamide (0.10 g) in acetonitrile (6 mL) was added a solution of CAN (1.1 mol equiv) in water (4 mL). The mixture was then stirred at room temperature for 30 min, extracted into EtOAc (2×10 mL), dried, evaporated in vacuo, and then purified by column chromatography.

*3.4.1. N-(4-Methoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)-benzamide (**3**)*

Orange solid. Yield: 0.05 g, 60% from **1d**; mp 246–247 °C (decomp.). (Found: C, 65.52; H, 4.26; N, 5.41%. Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44%); ν_{max}/cm^{-1} 3395, 3052, 1649; δ_H 3.89 (3H, s, OCH_3), 6.59 (1H, s, 3-H), 7.53 (3H, m, 3′,4′,5′-H), 7.87 (2H, m, 2′,6′-H), 8.29 (1H, s, 6-H), 8.43 (1H, s, N–H); δ_C 56.5, 97.4, 105.3, 120.8, 127.0, 128.8, 131.7, 135.1, 142.4, 142.8, 145.1.

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References and notes

1. Bradshaw, T. D.; Wrigley, S.; Shi, D.; Schultz, R. J.; Paull, K. D.; Stevens, M. F. G. *Br. J. Cancer* **1998**, *77*, 745.
2. Stevens, M. F. G.; McCall, C. J.; Lelieveld, P.; Alexander, P.; Richter, A. *J. Med. Chem.* **1994**, *37*, 1689.
3. Jacobson, P. *Chem. Ber.* **1886**, *19*, 1067.
4. Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261.
5. Mu, X.; Zou, J.; Zeng, R.; Wu, J. *Tetrahedron Lett.* **2005**, *46*, 4345.
6. Bose, D. S.; Idrees, M. *Tetrahedron Lett.* **2007**, *48*, 669.
7. Downer-Riley, N. K.; Jackson, Y. A. *Tetrahedron* **2007**, *63*, 10276.
8. Ramsden, C. A.; Rose, H. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 615.
9. Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627.
10. Kita, Y.; Takada, T.; Mihara, S.; Tohma, H. *Synlett* **1995**, 211.
11. (a) Chu, C.-M.; Gao, S.; Sastry, M. N. V.; Kuo, C.-W.; Lu, C.; Liu, J.-T.; Yao, C.-F. *Tetrahedron* **2007**, *63*, 1863; (b) Hwu, J. R.; King, K.-Y. *Curr. Sci.* **2001**, *8*, 1043; (c) Nair, V.; Matthew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997**, 127.
12. (a) Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627; (b) Radeke, H. S.; Digits, C. A.; Bruner, S. D.; Snapper, M. L. *J. Org. Chem.* **1997**, *62*, 2823.
13. Lyon, M. A.; Lawrence, S.; Williams, D. J.; Jackson, Y. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 437.
14. Downer, N. K.; Jackson, Y. A. *Org. Biomol. Chem.* **2004**, *2*, 3039.
15. Poor-Barltork, I. M.; Khodaei, M. M.; Nikoofar, K. *Tetrahedron Lett.* **2003**, *44*, 591.
16. Yonemoto, K.; Shibuya, I.; Tsuchiya, T.; Yasumoto, M.; Taguchi, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2933.
17. Bunnett, J. F.; Hrutfiord, B. F. *J. Am. Chem. Soc.* **1961**, *83*, 1691.
18. Okamoto, K.; Yamamoto, T.; Kanbara, T. *Synlett* **2007**, 2687.
19. Charrier, J.; Landreau, C.; Deniaud, D.; Reliquet, F.; Reliquet, A.; Meslin, J. C. *Tetrahedron* **2001**, *57*, 4195.
20. Perry, R. J.; Wilson, B. D. *Organometallics* **1994**, *13*, 3346.
21. Perregaard, J.; Lawesson, S. O. *Acta Chem. Scand., Ser. B* **1977**, *31*, 203.