Palladium-Catalyzed Amination with Benzophenone Imine as a New, Safe and Practical Alternative to Nitration for the Synthesis of 7-Amino-2,1,3-benzothiadiazoles

Yugang Liu,* Mahavir Prashad,* Oljan Repič and Thomas J. Blacklock

Process R & D, Chemical & Analytical Development
Novartis Pharmaceuticals Corporation
One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

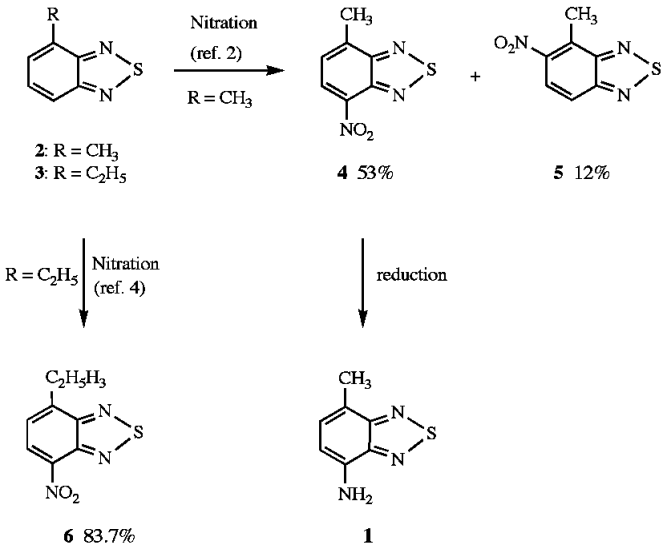
Received April 11, 2003

Palladium-catalyzed amination of 7-bromo-4-methyl-2,1,3-benzothiadiazole (**7**) with benzophenone imine as an ammonia equivalent is described as a new, safe and practical alternative to nitration for the synthesis of 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**) in high yield. This methodology was successfully scaled-up in the pilot plant on 14.0-kg scale of **7** and was also utilized for the synthesis of 7-amino-4,6-dimethyl-2,1,3-benzothiadiazole (**12**) by the amination of 7-bromo-4,6-dimethyl-2,1,3-benzothiadiazole (**10**).

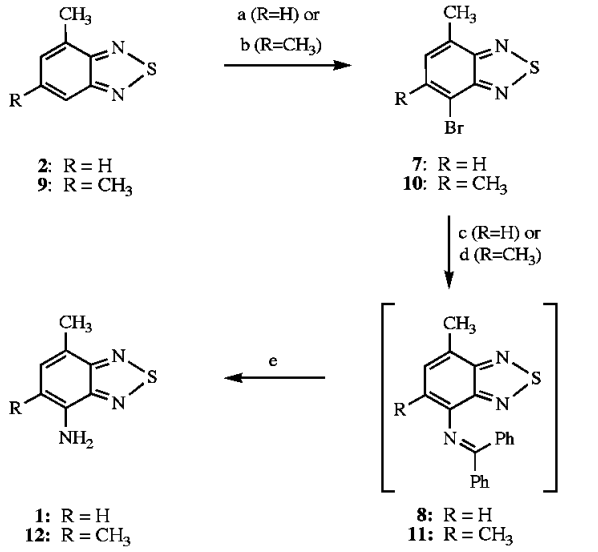
J. Heterocyclic Chem., **40**, 713(2003).

7-Amino-2,1,3-benzothiadiazoles, such as 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**) and 7-amino-4,6-dimethyl-2,1,3-benzothiadiazole (**12**), are interesting intermediates in the synthesis of biologically important molecules [1]. Regioselective nitration of 4-methyl-2,1,3-benzothiadiazole (**2**) at the 7-position to give 7-nitro-4-methyl-2,1,3-benzothiadiazole (**4**), followed by the reduction, would afford the synthesis of 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**). Whereas the nitration of 4-ethyl-2,1,3-benzothiadiazole (**3**) was reported to be completely regioselective to afford the 7-nitro regioisomer (**6**) exclusively in 83% yield, surprisingly, the nitration of 4-methyl-2,1,3-benzothiadiazole (**2**) yielded a mixture of 7-nitro (**4**) and 5-nitro (**5**) regioisomers in 53% and 12% yields respectively (Scheme 1) [2-3]. Nitration of 4-chloromethyl-2,1,3-benzothiadiazole was also known to be completely regioselective to afford exclusively 7-nitro-4-chloromethyl-2,1,3-benzothiadiazole in 81% yield [4]. The low yield (53%) of 7-nitro-4-methyl-2,1,3-benzothiadiazole (**4**) made the nitration route for the synthesis of 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**) impractical for large scale. Another limitation of this route was the safety concerns associated with the nitration reaction on a large scale. This led us to develop an alternative to nitration for the synthesis of 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**) that is safe and amenable for the pilot plant. We have previously reported [5-6] the synthesis of anilines *via* a palladium-catalyzed amination [7] of aromatic halides with benzophenone imine as an ammonia equivalent originally reported by Buchwald [8]. Herein, we report a safer and efficient synthesis of 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**) *via* the palladium-catalyzed amination of 7-bromo-4-methyl-2,1,3-benzothiadiazole (**7**) with benzophenone imine as an alternative to nitration

Scheme 1



Scheme 2



(a) Br_2 (1.5 eq), CH_3CO_2H-H_2O, 55-60 °C, 1.5 h; (b) Br_2 (1.6 eq), 48% HBr, 65-70 °C, 0.5 h; (c) Ph_2C=NH (1.05 eq), $Pd_2(dba)_3$ (0.25 mol%), BINAP (0.75 mol%), CH_3ONa (1.4 eq), toluene, 83-87 °C, 24 h; (d) Ph_2C=NH (1.2 eq), $Pd_2(dba)_3$ (0.24 mol%), BINAP (0.75 mol%), *t*-BuONa (1.4 eq), toluene, 110 °C, 4 h; (e) (i) 37% HCl, 70-80 °C, 0.5 h; (ii) 5 N NaOH, 55-65 °C.

(Scheme 2). Palladium-catalyzed amination of heterocyclic halides is a topic of current interest [9].

Our new approach for the synthesis of **1** relied on the regioselective bromination of 4-methyl-2,1,3-benzothiadiazole (**2**) at the 7-position to give 7-bromo-4-methyl-2,1,3-benzothiadiazole (**7**). Contrary to nitration, the bromination of 4-methyl-2,1,3-benzothiadiazole (**2**) [4] was reported to be completely regioselective affording 7-bromo-4-methyl-2,1,3-benzothiadiazole (**7**) exclusively and in excellent yield [10-11]. Thus, the bromination of **2** with bromine in aqueous acetic acid at 55-60 °C afforded **7** regioselectively in 81.4% yield with >99% purity (Scheme 2). The product **7** crystallized from the reaction mixture during the bromine addition and was isolated by a simple filtration. This process scaled-up well in the pilot plant on a 13.0-kg scale of **2** to afford **7** in 86% yield. Palladium-catalyzed amination of **7** with benzophenone imine (1.05 equiv) in the presence of sodium methoxide (1.4 equiv), [5] tris(dibenzylideneacetone)-dipalladium(0) (0.25 mol%), and (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.75 mol%) in toluene at 85 °C for 24 h afforded a crude solution of imine intermediate **8** after an aqueous work-up and phase separation. Hydrolysis of **8** in toluene with aqueous HCl at 70 °C afforded the crystalline HCl salt of **1** that crystallized during hydrolysis and was isolated by filtration. Neutralization of this salt with 5 *N* sodium hydroxide afforded 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**) in 90.7% yield with >99% purity. This procedure scaled-up successfully in the pilot plant on a 14.0-kg scale of **7** to afford **1** in 86% yield (Table 1). The palladium content of **1** was 40 ppm but was reduced to <2 ppm in subsequent steps. A closed system was necessary for the amination reaction to avoid the escape of an unknown basic gas that was produced during the reaction. Use of sodium *t*-butoxide as the base also afforded **1** in 90% yield.

Table 1

Scale-up of Bromination and Amination Steps

	Lab Scale (% Yield)	Pilot Plant Scale (% Yield)
Bromination of **2**	0.087 kg (81.4%)	13.0 kg (86.0%)
Pd-Catalyzed Amination of **7**	0.107 kg (90.7%)	14.0 kg (86.0%)

Thus, a new, safe and practical alternative to the nitration for the synthesis of 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**) in high yield was developed (Table 2).

This new route was also used to synthesize 7-amino-4,6-dimethyl-2,1,3-benzothiadiazole (**12**), which was originally prepared using the nitration route [1]. Thus, regioselective bromination of 4,6-dimethyl-2,1,3-benzothiadiazole (**9**) [12] with bromine in 48% HBr at 65-70 °C afforded 7-bromo-4,6-dimethyl-2,1,3-benzothiadiazole (**10**) in 90% yield after a recrystallization from acetonitrile and water. Palladium-catalyzed amination of **10** with benzophenone imine (1.2 equiv) in the presence of sodium *t*-butoxide (1.4 equiv), $Pd_2(dba)_3$ (0.24 mol%), and BINAP (0.75 mol%) in toluene at 110 °C for 4 hours afforded 7-amino-4,6-dimethyl-2,1,3-benzothiadiazole (**12**) in 88% yield after the hydrolysis of the resulting imine (**11**) with aqueous HCl and neutralization with 5 *N* sodium hydroxide. Use of sodium methoxide [5] as the base also afforded **12** in 85% yield.

Table 2

Comparison of Two Routes to 7-Amino-4-methyl-2,1,3-benzothiadiazole (**1**)

	Nitration Route	Pd-Catalyzed Amination Route
Overall Yield (%) of **1**	40	73.8
Advantages	Cheap raw materials	Safe route
Disadvantages	Safety concerns	Costly catalyst and ligand

In summary, palladium-catalyzed amination of 7-bromo-4-methyl-2,1,3-benzothiadiazole (**7**) with benzophenone imine as an ammonia equivalent provided a new, safe and practical alternative to nitration for the synthesis of 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**) in high yield. This methodology was successfully scaled-up in the pilot plant on 14.0-kg scale of **7** and was also utilized for the synthesis of 7-amino-4,6-dimethyl-2,1,3-benzothiadiazole (**12**) by the amination of 7-bromo-4,6-dimethyl-2,1,3-benzothiadiazole (**10**).

EXPERIMENTAL

7-Bromo-4-methyl-2,1,3-benzothiadiazole (**7**).

A mixture of 87.0 g (0.58 mol) of 4-methyl-2,1,3-benzothiadiazole (**2**) [4], 400 mL of acetic acid, and 100 mL of water was heated to an internal temperature of 55-57 °C and 139.0 g (0.87 mol) of bromine was added over a period of 1.5 hours while maintaining the internal temperature at 55-60 °C. A solid crystallized during the bromine addition. The mixture was heated for an additional 1.5 hours at 55-60 °C. Water (400 mL) was added in 20 minutes at 45-55 °C, and the mixture was stirred for an additional 1 hour. The reaction mixture was cooled to an internal temperature of 20-25 °C over a period of 3 hours and the solid was collected by filtration. The solid was washed sequentially with 200 mL of 10% sodium thiosulfate, 600 mL of water, and 300 mL of cold (0-5 °C) ethanol, and dried to afford 7-bromo-4-methyl-2,1,3-benzothiadiazole (**7**), 108.0 g (81.4%), m.p. 133-135 °C, lit. (11) m.p. 136-138 °C; ^{1}H NMR ($CDCl_3$): δ 2.68 (s, 3H), 7.22 (d, 1H, *J*=8.93 Hz), 7.73 (d, 1H, *J*=8.93 Hz).

Anal. Calcd. for $C_7H_5BrN_2S$: C, 36.70; H, 2.20; N, 12.23; S, 14.00. Found: C, 36.62; H, 2.10; N, 12.29; S, 13.97.

7-Bromo-4,6-dimethyl-2,1,3-benzothiadiazole (**10**).

A mixture of 130.0 g (0.79 mol) of 4,6-dimethyl-2,1,3-benzothiadiazole (**9**) [12] and 700 mL of 48% HBr was heated to an internal temperature of 65 °C and 202.9 g (1.268 mol) of bromine was added over a period of 45 minutes while maintaining the

internal temperature at 65-80 °C. A solid crystallized during the bromine addition. The mixture was heated for an additional 30 minutes at 65-70 °C. The reaction mixture was cooled to an internal temperature of 20-25 °C over a period of 2 hours and the solid was collected by filtration. The solid was washed twice with 200 mL each of water and dried to afford 190.5 g of crude product. This crude product was suspended in 1.0 L of acetonitrile and heated to reflux. Water (80 mL) was added at 78-80 °C to obtain a clear solution. The solution was cooled to 25 °C over a period of 2.5 hours and then to 0 °C over 30 minutes. The suspension was stirred at 0-5 °C for an additional 2 hours. The solid was collected by filtration, washed twice with 200 mL each of 50% acetonitrile-water mixture, and dried to afford 7-bromo-4,6-dimethyl-2,1,3-benzothiadiazole (**10**), 173.5 g (90%), m.p.109-110 °C; ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H), 2.60 (s, 3H), 7.28 (s, 1H).

Anal. Calcd. for $C_8H_7BrN_2S$: C, 39.52; H, 2.90; N, 11.52; S, 13.19. Found: C, 39.30; H, 2.75; N, 11.39; S, 13.07.

7-Amino-4-methyl-2,1,3-benzothiadiazole (**1**).

A 2-L flask was charged sequentially with 107.0 g (467.0 mmol) of 7-bromo-4-methyl-2,1,3-benzothiadiazole (**7**), 2.18 g (3.5 mmol) of (±)-2,2'-bis(diphenyl-phosphino)-1,1'-binaphthyl (BINAP), 35.3 g (653.8 mmol) of sodium methoxide, 1.07 g (1.17 mmol) of tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$), and 88.9 g (490.4 mmol) of benzophenone imine and was evacuated and flushed with nitrogen twice. Dry and deairated toluene (700 mL) was added. The mixture was stirred, evacuated and flushed with nitrogen twice. The mixture was heated to an internal temperature of 83-87 °C in 30 minutes with the nitrogen outlet valve open. The nitrogen outlet valve was closed when the internal temperature reached 83-87 °C, and the mixture was stirred at this temperature for an additional 24 hours under a positive pressure of nitrogen. The reaction mixture was cooled to an internal temperature of 23-27 °C, and toluene (400 mL) and water (300 mL) were added. After stirring for 10 minutes, the organic layer was separated and heated to an internal temperature at 68-72 °C. Concentrated HCl (53.5 mL) was added during 30 minutes while maintaining an internal temperature at 70-80 °C. The mixture was stirred at this temperature for an additional 30 minutes and cooled to 23-27 °C over a period of 2 hours. The resulting solid was collected by filtration, washed with isopropyl acetate (200 mL) and dried to afford 107.0 g of the hydrochloride salt of 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**). This solid was dissolved in water (500 mL) by heating the suspension to an internal temperature at 55-65 °C. A 5 *N* sodium hydroxide solution (80.0 mL) was added over a period of 20 minutes while maintaining the internal temperature at 55-70 °C to adjust the pH to 7-9. The suspension was cooled to 22-25 °C over 2 hours, and the resulting red solid was collected by filtration. After washing the solid with water (300 mL), it was dried to afford 7-amino-4-methyl-2,1,3-benzothiadiazole (**1**), 70.0 g (90.7%), m.p. 80-82 °C, contained 40 ppm palladium; ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 3H), 4.50 (bs, 2H), 6.55 (d, 1H, *J*=8.82 Hz), 7.13 (d, 1H, *J*=8.82 Hz).

Anal. Calcd. for $C_7H_7N_3S$: C, 50.89; H, 4.27; N, 25.43; S, 19.41. Found: C, 50.79; H, 4.04; N, 25.26; S, 19.26.

7-Amino-4,6-dimethyl-2,1,3-benzothiadiazole (**12**).

A 3-L flask was charged with 120.0 g (494.0 mmol) of 7-bromo-4,6-dimethyl-2,1,3-benzothiadiazole (**10**), 2.46 g (3.7 mmol) of (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 66.5 g (692.0 mmol) of sodium *t*-butoxide, 1.13 g (1.2 mmol) of tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$), and 107.3 g (593.0 mmol) of benzophenone imine and dry and deairated toluene (1.2 L). The mixture was stirred, evacuated and flushed with nitrogen twice. The mixture was heated to an internal temperature at 110 °C in 15 minutes and stirred at this temperature for an additional 4 hours. The reaction mixture was concentrated under reduced pressure to collect 950 mL of toluene. To the resulting residue was added isopropyl acetate (1.0 L) and water (400 mL), and the mixture was heated to an internal temperature of 70 °C in 15 minutes. After stirring for 30 minutes at this temperature, the bottom aqueous layer was discarded and to the top organic layer was added concentrated HCl (95.0 mL) during 10 minutes while maintaining the internal temperature at 70 °C. The mixture was cooled to an internal temperature of 20-25 °C over a period of 2 hours. The resulting solid was collected by filtration and washed with isopropyl acetate (400 mL) to afford the hydrochloride salt of 7-amino-4,6-dimethyl-2,1,3-benzothiadiazole (**12**). This solid was dissolved in water (1.0 L) by heating the suspension to an internal temperature at 50 °C. A 5 *N* sodium hydroxide solution (200.0 mL) was added over 10 minutes while maintaining the internal temperature at 50-60 °C. After stirring for 1 hour at 50 °C, the suspension was cooled to 22-25 °C over a period of 1 hour, and the resulting red solid was collected by filtration. After washing the solid with water (400 mL), it was dried to afford 86.0 g of crude 7-amino-4,6-dimethyl-2,1,3-benzothiadiazole (**12**). This crude product was suspended in methanol (1.0 L) and refluxed to obtain a clear solution. To this clear solution was added water (200 mL) over a period of 30 minutes while maintaining the internal temperature at 65 °C. The solution was cooled to an internal temperature at 20-25 °C over 3 hours and then to 0 °C in 30 minutes. After stirring at this temperature for an additional 2 hours, the solid was collected by filtration and washed with a 50% mixture of methanol and water (400 mL). The solid was dried to afford 7-amino-4,6-dimethyl-2,1,3-benzothiadiazole (**12**), 78.0 g (88%), m.p.116-118 °C, contained 80 ppm palladium; ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H), 2.57 (s, 3H), 4.35 (bs, 2H), 7.08 (s, 1H).

Anal. Calcd. for $C_8H_9N_3S$: C, 53.60; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.79; H, 4.94; N, 23.36; S, 17.16.

Acknowledgments.

We thank Judy Wong for the scale-up of bromination and amination reactions in the pilot plant.

REFERENCES AND NOTES

[1] B. P. Neumann, World Patent WO 99/40089, August 12, (1999); *Chem. Abstr*., **131**, 144607 (1999).

[2] K. Pilgram, *J. Heterocyclic Chem.*, **11**, 835 (1974).

[3] D. D. M. Casoni, E. Sandri, C. Brizzi,*Ann. Chim. (Rome)*, **54**, 462 (1964).

[4] P. Vanelle, C. T. Liegeois, J. Meuche, J. Maldonado and M.P.Crozer, *Heterocycles*, **45**, 955 (1997).

[5] M. Prashad, B. Hu, Y. Lu, R. Draper, D. Har, O. Repič and T. J. Blacklock, *J. Org. Chem*., **65**, 2612 (2000).

[6] M. Prashad, B. Hu, D. Har, O. Repic˘ and T. J. Blacklock, M. Acemoglu, *Adv. Synth. Catal*., **343**, 461 (2001).

[7] A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, **219**, 131 (2002).

[8] J. P. Wolfe, J. Ahman, J. P. Sadighi, R. A. Singer and S. L. Buchwald, *Tetrahedron Lett*., **38**, 6367 (1997).

[9] M. W. Hooper, M. Utsunomiya and J. F. Hartwig, *J. Org. Chem.*, **68**, 2861 (2003).

[10] K. H. Pilgram, US 3577427, May 4, (1971); *Chem. Abstr.*, **75.** 36050 (1971).

[11] K. Pilgram, M. Zupan and R. Skiles, *J. Heterocyclic Chem*., **7**, 629 (1970).

[12] S. Mataka, K. Takahashi, S. Shiwaku and M. Tashiro, *J.Chem. Soc., Chem. Commun.*, 1136 (1983).