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Palladium(0)-catalyzed Synthesis of 2-Alkylbenzothiazoles by a Novel Thiation of 1-Amino-2-iodoarenes with Thioamides†

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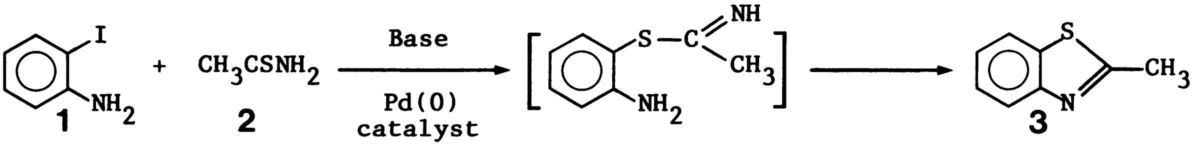
Pd(0) catalyzed the reaction of 1-amino-2-iodoarenes with thioamides giving rise to 2-XCH_2-substituted benzothiazoles (X=H, CH_3, OCH_3, and CN) directly.

It has been demonstrated in several instances that an inertness of nonactivated aryl halides towards a nucleophilic displacement can be overcome by using transition metal complex as a catalyst. A typical example of such formal S_NAr is a thiation of aryl halides with thiourea, which is achieved by making use of a nickel(0) complex as a catalyst.1) During the course of our studies on an extension of the thiation to thioamides as a nucleophile, we found a novel and efficient synthetic procedure of benzothiazoles from 1-amino-2-iodoarenes and thioamides.



Although the reaction between iodobenzene and thioacetamide (2) did not give satisfactory results,2,3) the related reaction of o-iodoaniline (1) with 2 proceeded readily in the presence of a catalytic amount of a palladium(0) complex to afford 2-methylbenzothiazole (3) directly in a good yield. Representative results are summarized in Table 1. The presence of base such as CaO afforded better yields and a phosphorus ligand, especially 1,1'-bis(diphenylphosphino)ferrocene (dppf), supported an excellent turnover. It is to be noted that derivatives of 3 could likewise be synthesized by using appropriate 1-amino-2-iodoarenes and 2-substituted thioacetamides in place of 1 and 2. In this way, 2-alkyl, 2-alkoxymethyl, 2-cyanomethyl, and 5- or 6-substituted benzothiazoles (4-10) were provided without any difficulty, although a change in a reaction medium from N,N-dimethylformamide (DMF), used ordinarily, to acetonitrile (AN) was necessary in the case of 2-cyanomethyl derivatives. Since α-substituted 2-alkylbenzothiazoles are especially useful intermediates in both chemical laboratories and industries,4) these syntheses extend the utility of our general method. The present method, however, failed in synthesizing 2-aryl derivatives: in the reaction of 1 with thiobenzamide as a nucleophile, benzonitrile was obtained predominantly accompanied with only a small amount of 2-phenylbenzothiazole (11). Thus, this palladium(0)-catalyzed reaction offers a facile and effi-

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†This paper is dedicated to the late Professor Ryozo Goto, Kyoto University.

Table 1. Synthesis of 2-Methylbenzothiazole (3)[a)]

Run	Catalyst[b)]		Time/h	Yield/%[c)]
	Pd*/molar %	P-Ligand		3
1	1	PPh_3	3	99
2	0.5	PPh_3	24	11
3[d)]	1	PPh_3	24	18
4	1		24	3
5	0.25	dppf	1	(98)
6[e)]	1	dppf	6	5[f)]

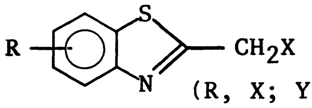
a) Every run was carried out in DMF at 60 °C under nitrogen. Molar ratio of each component (1/2/CaO/Pd(0)) was 1.0/1.0-1.4/1.0-2.0/0.005-0.02.

b) Molar ratio of Pd*/PPh_3 was 1/8. Molar ratio of Pd*/dppf was 1/4. Pd*=$Pd_2(dba)_3 \cdot CHCl_3$, tris(dibenzilideneacetone)(chloroform)-di-palladium(0).

c) Yields were determined by GLC. Yields in parentheses were isolated ones.

d) Run without CaO. e) Run using thiobenzamide in place of 2.

f) Yield of 11 accompanied with 12% of benzonitrile. The conversion was 33%.



(R, X; Yield)

4 (H, CH_3; 99%)
5 (H, CN; 92%)
6 (H, OCH_3; 97%)
7 (4-Br, H; 90%)
8 (5-Cl, H; 97%)
9 (5-CH_3, H; 90%)
10 (5-CF_3, CN; 92%)

cient synthetic procedure of a great variety of 2-alkylbenzothiazoles from readily available starting materials[5)] through a novel thiation.[6)]

References

1) K. Takagi, Chem. Lett., 1985, 1307.

2) In these runs, diphenyl sulfide was obtained mainly, but only in a low yield: e. g. a stirring of a mixture of iodobenzene, 2, CaO, 2 molar % of Pd(0)-4PPh_3, and DMF at 60 °C for 24 h afforded diphenyl sulfide in a yield of 8% along with 84% of iodobenzene. This product is not, however, unexpected, since (i) 2 serves as a synthetic equivalent to sodium sulfide under basic conditions and (ii) a thiation of aryl halides with thiolate anions is catalyzed by Pd(0).[7, 8)]

3) Intramolecular displacement is known: M. J. Spitulnik, J. Heterocyclic Chem., 14, 1073 (1977); W. R. Bowman, H. Heaney, and P. H. G. Smith, Tetrahedron Lett., 23, 5093 (1982); 25, 5821 (1984).

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5) W. Walter and K. D. Bode, Angew. Chem., Int. Ed. Engl., 5, 447 (1966); J. L. LaMattina and C. J. Mularski, J. Org. Chem., 51, 413 (1986).

6) Typical example is as follows: A mixture of 1-amino-5-chloro-2-iodobenzene (1.0 mmol), thioacetamide (1.0 mmol), CaO (1.0 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.005 mmol), dppf (0.02 mmol), and DMF (1 mL) was stirred at 60 °C for 1 h under nitrogen. The resultant mixture was chromatographed on a silica-gel column using hexane-ethyl acetate as the eluant. 179 mg of 5-chloro-2-methylbenzothiazole was obtained (97%). Mp 65-67 °C (lit.,[9)] 62 °C).

7) E. Hammerschmidt, W. Bieber, and F. Vogtle, Chem. Ber., 111, 2445 (1978).

8) T. Migita, T. Shimizu, Y. Asami, J. Shiobara, Y. Kato, and M. Kosugi, Bull. Chem. Soc. Jpn., 53, 1385 (1980).

9) W. König, P. Seidel, and G. Stuhmer, Chem. Ber., 61, 2065 (1928).

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