One-Pot Preparation of 2-(Alkyl)arylbenzothiazoles from the Corresponding *o*-Halobenzanilides

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Abstract: Thionation of *o*-halobenzanilides was carried out in the presence of Lawesson's reagent. Subsequently, the formed thioamides reacted with cesium carbonate to give the corresponding benzothiazole derivatives in the same pot.

Key words: one-pot reaction, benzothiazole, cesium carbonate, Lawesson's reagent, cyclization

Benzothiazoles are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and development for the treatment of tumors, diabetes, epilepsy, inflammation, microbial infection, Parkinson's disease and find industrial applications as antioxidants and vulcanization accelerators.[2]

There are various existing methods for the construction of the benzothiazole moiety.[3] During the course of a medicinal chemistry project, we needed to prepare diverse benzothiazoles. We focused our attention on the *i*ntramolecular *n*ucleophilic *a*romatic *s*ubstitution of *o*-halothio*ob*enzanilides (INASOB) promoted by a base.[4] As for the oxidative radical cyclization of thioanilides by the treatment with potassium ferricyanide,[5] INASOB required first the conversion of an amide into the corresponding thioamide by using P_4S_{10} or Lawesson's reagent (LR).[4c,6] We reasoned that one-pot reaction from amides should lead to the formation of benzothiazoles. The present paper reports the synthesis of 2-(alkyl)arylbenzothiazoles using this strategy.

In order to determine the optimized reaction conditions, *N*-acetyl-2-bromoaniline[7] (**1**) was allowed to react with LR in the presence of a base under various reaction conditions to obtain 2-methylbenzothiazole (**2**) and the results are shown in Table 1. The reaction of **1** with LR in refluxing organic bases (triethylamine, pyridine) only afforded the corresponding thioamide **3** in good yields (entries 1 and 2). Next, the reaction was performed in refluxing toluene as solvent. Bases such as pyridine, sodium carbonate, potassium carbonate or cesium carbonate (Cs_2CO_3) were used (entries 3–6). Only Cs_2CO_3 (entry 6) gave **2** in a modest yield of 33%. Variation of the amount of LR or Cs_2CO_3 did not improve the yield of **2** (entries 7 and 8). As **1** was still present in the reaction medium and the yield of **2** stayed low, we envisaged changing the reaction conditions. LR was first allowed to react with **1** in refluxing toluene for three hours, and then Cs_2CO_3 was added to the reaction mixture to obtain **2**. Using this protocol and varying the amount of LR or Cs_2CO_3, **2** was obtained in a better but still modest yield of 42% (entries 9 and 10). Next, toluene was replaced by xylene to perform the reaction (entry 11). The new protocol involved the thionation of **1** at 110 °C for about 2.5 hours (thionation monitored by TLC) and the cyclization of **3** in refluxing xylene. Using this sequence, **2** was then obtained in a good 74% yield.

The synthesis of 2-(alkyl)arylbenzothiazoles by the treatment of various *N*-(acetyl)benzoyl-2-halogenoanilines[7–11] and LR (0.6 equiv) in the presence of two equivalents of Cs_2CO_3 in refluxing xylene was next examined. These results, summarized in Table 2, showed that the reaction was efficient with different halogeno derivatives. The thionation of the amides **4**–**10** took about two hours for completion. In the case of amides **4**–**6**, the cyclization step was complete after five hours. The iodo derivative gave the best yield in the case of these acetylated aniline derivatives. In the case of amides **7**–**10**, the time needed for cyclization was between three and five hours. The fluoro and iodo derivatives gave the shorter time of reaction, and the iodo derivative led to the best yield in the case of these benzoylated aniline derivatives.

In summary, we have succeeded in the synthesis of 2-(alkyl)arylbenzothiazoles by the reaction of the corresponding *N*-(acetyl)benzoyl-2-halogenoanilines with LR and Cs_2CO_3 via a one-pot reaction in refluxing xylene.[12] To the best of our knowledge, this is the first time that this sequence has been described. In these conditions, the thioamide generated in situ did not need to be isolated for further cyclization. As a consequence, the global time of reaction is decreased and the quantity of solvent needed during this process is less than that usually needed in the two-step reaction. Although the efficiency of the reaction is greater with iodo and fluoro starting materials, the reaction also worked well with chloro and bromo derivatives which are less expensive and more easily available compounds than the fluoro and iodo ones. The scope of the reaction outlined is currently being explored in terms of functional group tolerance.

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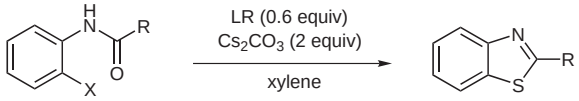
Table 1 One-Pot Cyclization of *N*-Acetyl-2-bromoaniline

1 **2** **3**

Entry	LR (equiv)	Base (equiv)	Solvent (reflux)	Yield (%)[a]		
				1	**2**	**3**
1	1	–	pyridine	–	–	85
2	0.6	–	triethylamine	–	–	83
3	1	pyridine (2)	toluene	40	–	39
4	0.6	Na_2CO_3 (1.05)	toluene	44	–	40
5	0.6	K_2CO_3 (1.05)	toluene	44	–	45
6	0.6	Cs_2CO_3 (1.05)	toluene	20	33	20
7	1	Cs_2CO_3 (3)	toluene	19	21	37
8	0.6	Cs_2CO_3 (2)	toluene	17	41	25
9	0.6	Cs_2CO_3 (2)	toluene	–	42	39
10	1	Cs_2CO_3 (1.1)	toluene	–	30	57
11	0.6	Cs_2CO_3 (2)	xylene	–	74	5

[a] Yield after silica gel chromatography.

Table 2 Cyclization of Various *N*-(Acetyl)benzoyl-2-halogenoanilines



X = F, Cl, Br, I
R = Me, Ph

Compound	R	X	Thionation		Cyclization		Yield (%)[a]
			Temp (°C)	Time (h)	Temp	Time (h)	
4	Me	F	105–115	2.5	reflux	5	77
5	Me	Cl	105–115	2.5	reflux	5	68
6	Me	I	105–115	2	reflux	5	79
7	Ph	F	105–115	2.5	reflux	3	84
8	Ph	Cl	105–115	2.5	reflux	5	72
9	Ph	Br	105–115	2	reflux	4	81
10	Ph	I	105–115	2.5	reflux	3	87

[a] Yield after silica gel chromatography.

References and Notes

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(2) (a) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261. (b) Li, Y.; Wang, Y.; Wang, J. *Chem. Lett.* **2006**, *35*, 460. (c) Chakraborti, A. K.; Rudrawar, S.; Kaur, G.; Sharma, L. *Synlett* **2004**, 1533; and references cited in these articles.

(3) (a) Ulrich, H. In *Science of Synthesis*, Vol. 11; Schaumann, E., Ed.; Thieme: Stuttgart, **2001**, 835–912. (b) Chakraborti, A. K.; Selvam, C.; Kaur, G.; Bhagat, S. *Synlett* **2004**, 851; and references cited in these articles.

(4) Sodium hydride: (a) Spitulnik, M. J. *Synthesis* **1976**, 730. (b) Mortimer, C. G.; Wells, G.; Crochard, J.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2006**, *49*, 179. (c) Van Zandt, M. C.; Jones, M. L.; Gunn, D. E.; Geraci, L. S.; Jones, J. H.; Sawicki, D. R.; Sredy, J.; Jacot, J. L.; DiCioccio, A. T.; Petrova, T.; Mitschler, A.; Podjarny, A. D. *J. Med. Chem.* **2005**, *48*, 3141. Sodium methoxide: (d) Kim, J. S.; Sun, Q.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **1996**, *4*, 621. (e) Yoshino, K.; Kohno, T.; Uno, T.; Morita, T.; Tsukamoto, G. *J. Med. Chem.* **1986**, *29*, 820. (f) Potassium carbonate: Hutchinson, I.; Stevens, M. F. G.; Westwell, A. D. *Tetrahedron Lett.* **2000**, *41*, 425.

(5) (a) Lyon, M. A.; Lawrence, S.; Williams, D. J.; Jackson, Y. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 437. (b) Downer, N. K.; Jackson, Y. A. *Org. Biol. Chem.* **2004**, *2*, 3039.

(6) Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, 1929.

(7) Compounds **1**, **4** and **5** were prepared according to literature procedure: Ilies, M. A.; Vullo, D.; Pastorek, J.; Scozzafava, A.; Ilies, M.; Caproiu, M. T.; Pastorekova, S.; Supuran, C. T. *J. Med. Chem.* **2003**, *46*, 2187.

(8) Compound **6** was prepared according to literature procedure: Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546.

(9) Compound **7** was prepared according to literature procedure: Chen, S.; Zhang, X.; Ma, H.; Lu, Y.; Zhang, Z.; Li, H.; Lu, Z.; Cui, N.; Hu, Y. *J. Organomet. Chem.* **2005**, *690*, 4184.

(10) Compounds **8** and **9** were prepared according to literature procedure: Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802.

(11) Compound **10** was prepared according to literature procedure: Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777.

(12) **Typical Procedure**: In a 10-mL flask were placed the appropriate amide (1.17 mmol), Lawesson's reagent[13] (0.6 equiv, 0.29 g), xylene (3 mL) and a magnetic stirring bar. The mixture was stirred under argon at 105–115 °C for 2.5 h. Then Cs_2CO_3 (2 equiv, 0.81 g)was added and the reaction mixture was stirred under reflux for the indicated time. The solvent was evaporated to dryness and the crude product was chromatographed on silica gel (cyclohexane–EtOAc, 97:3) to afford the desired benzothiazole derivative.

(13) During this study we used commercial and synthesized LR, prepared according to the literature procedure: Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223.

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