Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 04 Mar 2009.

To cite this article: Sudhir Pal , Gopal Patra & Sankar Bhunia (2009) Microwave-Assisted Syntheses of 2-Phenylbenzothiazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:7, 1196-1203

To link to this article: http://dx.doi.org/10.1080/00397910802517822

Synthetic Communications®, 39: 1196–1203, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802517822

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Microwave-Assisted Syntheses of 2-Phenylbenzothiazoles

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Abstract: A new and easy synthetic route to 2-phenylbenzothiazoles has been achieved by direct thiation of benzoyl derivatives of aniline, various substituted anilines, and 1-naphthylamine under microwave irradiation. The oxidative cyclization using elemental sulfur in the presence of a catalytic amount of iodine is inexpensive and worked well for a number of anilides.

Keywords: Anilides, benzothiazoles, microwave, oxidative cyclization, thiation

INTRODUCTION

Compounds with benzothiazole skeletons are of paramount interest because of their antitumor,[1] anticancer,[2] and antibacterial[3] activities. These also exhibit nonlinear optical[4] and luminescent[5]/fluorescent[6] properties and are therefore being used in designing sensor molecules of specific interest, so a large number of citations are appearing in recent times that deal with the syntheses of benzothiazoles. All these methods employed either the thiol function[7] at the *ortho*-position of the aniline moieties of the starting materials or initiated cyclization of appropriate thiobenzanilides.[8] We are searching for new methods to prepare sensor molecules that have this heterocyclic ring system and found a new and easy method of preparing 2-phenylbenzothiazole from benzanilide by direct thiation under microwave heating conditions. We then tested the generality of the procedure by taking benzoates of various aromatic

Received August 18, 2008.
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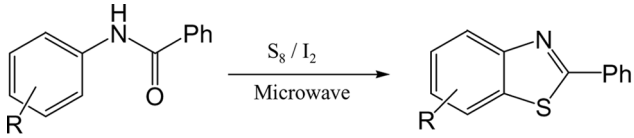


I. R = H
II. R = 4-Me
III. R = 4-OMe
IV. R = 3-Me
V. R = 3-Cl
VI. R = 4-CO_2H
VII. .R = 3-OMe
VIII. R = 4-Br

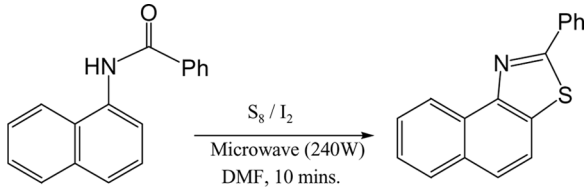
1. R = H
2. R = 6-Me
3 R = 6-OH
4a. R = 5 -Me; 4b. R = 7-Me
5. R = 5-Cl
6. R = 6-CO_2H
7a. R = 5-OMe; **7b.** R = 7-OMe
8a. R = H; **8b.** R = Br

Figure 1. Syntheses of substituted benzothiazoles.

amines with unsubstituted *ortho*-positions. In this communication, we report the results of this simple technique.

RESULTS AND DISCUSSION

The benzoate of 1-napthylamine, aniline, or appropriately substituted aniline (Figs. 1 and 2) is intimately mixed with sulfur and a catalytic amount of iodine and then subjected to microwave irradiation in a domestic microwave oven. We followed microwave irradiation, as the rates of reactions are faster than conventional heating methods. The reactions were carried out in solvent and under solvent-free conditions. The products were isolated in moderate to good yields. The best result with respect to yield and time was found using dimethylformamide (DMF) as solvent. Again some additives were used during the reactions, especially to improve the yield. Addition of a small amount of formic acid gave encouraging results though the reaction in formic acid as solvent was unsuccessful.



IX **9**

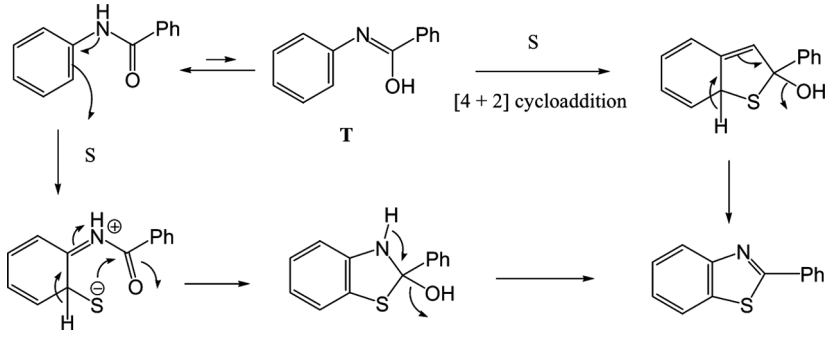
Figure 2. Synthesis of 2-phenyl-naphtho[1,2-d]thiazole.

Benzanilide I gave an excellent yield of 2-phenylbenzothiazole **1**. Benzoates of 1-naphthyl amine IX and 4-toluidine II afforded only **9** and **2** respectively as sole products in good yields. 4-Anisidine benzoate III also yielded a single product, but it was the corresponding demethylated compound (viz., 6-hydroxy-2-phenylbenzothiazole **3**) rather than the expected 6-methoxy compound. Compound IV, obtained from 3-toluidine, furnished 5-methyl-2-phenylbenzothiazole **4a** as the major product and 7-methyl isomer **4b** as a minor product as expected. 3-Anisidine benzoate VII also gave two products, namely 5- and 7-methoxy-2-phenylbenzothiazoles **7a** and **7b,** but yields are rather low. 3-Chloroaniline benzoate V, however, gave a very good yield of 5-chloro-2-phenylbenzothiazole **5** as the only isolable product. Benzoates of anilines with strong electron-withdrawing substituent (e.g., nitro group) failed to yield any product. Benzoate of 4-aminobenzoic acid VI, however, furnished expected product 6-carboxy-2-phenylbenzothiazole **6** in moderate yield. Reaction of the benzoate of 4-bromoaniline VIII yielded 2-phenylbenzothiazole **8a** in major amount (i.e., bromine is eliminated during the reaction). The normally expected 6-bromo-2-phenylbenzothiazole was obtained in a very small amount. The details of reaction conditions and yield of products are presented in Table 1.

Table 1. Specific reaction conditions and yields

	Conditions				
Reactants	MW	Time (min)	Solvent (additive)	Product (s)[a]	Yield (%)
I	240 W	15	Neat	**1**	40
		15	DMF	**1**	58
		15	DMSO	**1**	55
		15	DMF (+HCOOH)	**1**	80
II	240 W	15	DMF (+HCOOH)	**2**	58
III	240 W	10	DMF (+HCOOH)	**3**	52
IV	160 W	20	DMF (+HCOOH)	**4a**,	32
				4b	25
V	320 W	15	DMF (+HCOOH)	**5**	62
VI	320 W	100	DMF (+HCOOH)	**6**	54
VII	240 W	10	DMF (+HCOOH)	**7a,**	24
				7b	18
VIII	240 W	12	DMF (+HCOOH)	**8a,**	47
				8b	11
		10	DMF	**9**	30
IX	240 W	10	DMF (+HCOOH)	**9**	47

[a]All the products have been characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectral studies.



Scheme 1. Proposed mechanistic routes.

It may be mentioned that imine, obtained from the condensation of benzaldehyde with aniline, has also been reported to undergo this sort of oxidative cyclization with sulfur to furnish benzothiazole on heating, but we found that the result is far from satisfactory. Moreover, imines are not quite stable compounds. In contrast, benzoates are stable and can be easily prepared, and the procedure worked well for the syntheses of quite a number of substituted 2-phenylbenzothiazoles.

Two mechanisms could be probable as shown in Scheme 1: (i) it may involve [4 + 2] cycloaddition of the iminol intermediate tautomer **T** of the benzoate, or (ii) it may proceed via the electrophilic attack of sulfur at C-2 of the benzoate in line with the mechanism of the Willgerodt–Kindler reaction.

EXPERIMENTAL

Preparation of the Benzoates

The respective aniline was benzoylated following the standard procedure of the Schotten–Baumen reaction and then recrystallized from the appropriate solvent. The purity of the samples was checked by melting points reported in the literature.

Preparation of the Benzothiazoles

As a general procedure, the reactants (viz., benzoate of the particular aniline and sulfur in the molar ratio of 1:1.2, along with 10 mol% iodine) were intimately mixed together in a mortar and then subjected to

Table 2. Physical and spectral data of 2-phenylbenzothiazoles

Compound	Melting point (°C)	Spectral data
2-Phenylbenzothiazole **(1)** and **(8a)**	120	Mass: m/z 211 (M^+, base peak), 109 (10%). ^{1}H NMR (300 MHz): δ 8.05–8.07, 3H; 7.86 1H, d ($J = 8$ Hz); 7.44–7.59, 4H, and 7.35, 1H, t ($J = 8$ Hz). ^{13}C NMR (125 MHz): δ 168.11, 154.22, 135.13, 131.0, 129.06, 127.62, 127.49, 126.36, 125.23, 123.3, and 121.66.
6-Methyl-2-phenylbenzothiazole **(2)**	130	Mass, m/z 225 (M^+). ^{1}H NMR (300 MHz): δ 8.07–8.08, 2H; 7.96, 1H, d ($J = 8.4$ Hz); 7.68, 1H, s; 7.47–7.50, 3H; 7.30, 1H, d ($J = 8.4$ Hz), and 2.51, 3H, s. ^{13}C NMR (125 MHz): δ 167.18, 152.76,135.64, 135.56, 134.2, 131.05, 129.32, 128.25, 127.85, 123.22, 121.71, and 21.98.
6-Hydroxy-2-phenylbenzothiazole **(3)**	168	Mass, m/z 227 (M +, base peak), 197 (7%). IR, ν_{max}3451 cm^{-1} (br). ^{1}H NMR (200 MHz): δ 8.85, 1H, s; 8.20, 2H; 7.97, 1H, d ($J = 8.8$ Hz); 7.73, 1H; 7.60–7.70, 2H; 7.50, 1H, d ($J = 2.5$ Hz); 7.06, 1H, dd ($J = 8.8$ & 2.5 Hz). ^{13}C NMR (125 MHz): δ 163.54, 155.20, 147.10, 135.70, 133.17, 129.76, 128.34, 126.38, 122.87, 115.58, and 106.04.
5-Methyl-2-phenylbenzothiazole **(4a)**	140	Mass, m/z 225 (M+). ^{1}H NMR (200 MHz): δ 8.02–8.15, 2H; 7.88, 1H, s (fine splitting, $J = 1$ Hz); 7.78, 1H, d ($J = 8.2$ Hz); 7.45–7.60, 3H; 7.21, d with fine splitting ($J = 8.2$ & 1 Hz), 1H; 2.55, 3H, s. ^{13}C NMR (125 MHz): δ 168.18, 154.62, 136.42, 133.85, 132.10, 130.86, 129.01, 127.54, 126.85, 123.32, 121.12, and 21.54

(*Continued*)

Table 2. Continued

Compound	Melting point (°C)	Spectral data
7-Methyl-2-phenylbenzothiazole **(4b)**	131	Mass, m/z 225 (M^+, 30%), 211 (base peak). ^{1}H NMR (200 MHz): δ 7.83–7.90, 3H; 7.43–7.60, 3H; 7.20–7.40, 1H; 6.95, 1H, d ($J = 7.5$ Hz); and 2.36, 3H, s. ^{13}C NMR (125 MHz): 165.95, 138.85, 137.90, 134.99, 131.63, 128.75, 128.59, 127.06, 125.30, 121.07, 117.51, and 21.40.
5-Chloro-2-phenylbenzothiazole **(5)**	118	Mass, m/z 245 (M^+, base peak), 247 ($M^+ + 2$, 33%). ^{13}C NMR (125 MHz): 169.95, 155.07, 133.38, 133.34, 132.38, 131.37, 129.13, 127.66, 125.69, 123.10, and 122.33.
6-Carboxy-2-phenylbenzothiazole **(6)**	123	Mass, m/z 255 (M^+). IR, ν_{max} 3305 cm^{-1} (br.), 1702 cm^{-1}. ^{1}H NMR (300 MHz): δ 10.26, 1H, br.s; 8.12–8.15, 3H; 7.60–7.63; 2H, and 7.30–7.41, 3H.
5-Methoxy-2-phenylbenzothiazole **(7a)**	139	Mass, m/z 241 (M^+). ^{1}H NMR (500 MHz): δ 8.11–8.13, 2H; 7.35, 1H, d ($J = 9$ Hz); 7.57, 1H, d ($J = 1.7$ Hz); 7.47–7.49, 3H; 7.03, 1H, dd ($J = 9$ & 1.7 Hz) and 3.90, 3H, s.
4,5-Benzo-2-phenylbenzothiazole (or 2-phenylnaphtho [1,2-*d*]thiazole) **(9)**	110	Mass, m/z 261 (M^+). ^{1}H NMR (200 MHz): δ 9.00, 1H, d ($J = 8$ Hz); 8.23–8.25, 2H; 7.91–7.98, 2H; 7.83, 1H, d ($J = 8$ Hz); 7.71, 1H, t ($J = 8$ Hz); 7.61, 1H, t ($J = 8$ Hz); and 7.50–7.56, 3H. ^{13}C NMR (125 MHz): δ 167.08, 150.50, 134.06, 132.11, 131.72, 130.61, 129.06, 128.85, 128.10, 127.37, 126.97, 126.16, 125.94, 124.08, and 8.99.

microwave heating in an open vessel with or without solvent. The reactions were carried out in a domestic microwave oven (model 23SC1: IFB). The power and time was gradually increased. The reaction was monitored from time to time by thin-layer chromatography (TLC). After completion, the reaction mixture was extracted with ether, dried, and chromatographed over silical gel (Merck, 60–120 mesh).

Physical and Spectral Data of Some of the Benzothiazoles

IR spectra (Shimadzu spectrophotometer) were recorded in KBr discs. All the products are soluble in chloroform, and so their ^{1}H and ^{13}C NMR spectra (Brucker instruments) were recorded in $CDCl_3$ using tetramethysilane (TMS) as an internal standard. The data are presented in Table 2.

In conclusion, we have established a direct thiation of benzoyl derivatives of anilines as an easy route to 2-phenylbenzothiazoles. The method could be extended to the syntheses of 2-arylbenzothiazoles, that is, similar products with substituent(s) at the phenyl ring at the 2-position. We are exploring this possibility currently.

ACKNOWLEDGMENTS

The authors acknowledge the financial assistance of UGC in the form of minor research project. The help of Prof. A. Sarkar, Prof. D. Mal, Bimalendu Roy, Dr. Subrata K. Pal, and Kaushik Chandra in collecting spectra of products and of Dr. Kumaresh Ghosh for discussions in the course of the work is thankfully acknowledged.

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