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A GREEN METHOD FOR THE SYNTHESIS OF 2-ARYLBENZOTHIAZOLES

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Abstract–Aromatic aldehydes with both electron withdrawing and electron donating substituents were smoothly converted to the corresponding 2-arylbenzothiazoles by direct condensation of aromatic aldehydes with 2-aminothiophenol in one pot in a microoven under solvent-free conditions without any catalyst. The study revealed that the synthesis proceeded in three stages; first the formation of the aryl imine followed by its cyclisation to the benzothiazoline which in turn underwent oxidation and dehydration to the final product benzothiazole. Isolation of intermediates in all the stages confirmed the mechanism. This is therefore the first report of a "green" synthesis of the 2-arylbenzothiazoles under solvent-free conditions in the absence of any catalyst.

INTRODUCTION

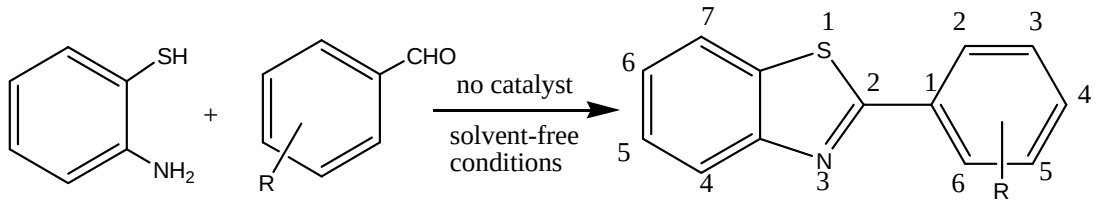
The 2-substituted benzothiazole nucleus is a very interesting system in the arena of medicinal chemistry. This moiety posseses highly potent and selective antitumour activity. A concrete example is that of substituted 2-(4-aminophenyl)benzothiazoles exhibiting nanomolar inhibitory invitro activity against a wide range of cell lines.[1] Two other such important compounds falling under this category are 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole[2] and 2-(4-dimethylaminophenyl)benzothiazole[3] and in all these systems, the 2-arylbenzothiazole nucleus is the key unit. Thus, the synthesis of the 2-arylbenzothiazole moiety is always a great challenge.

The benzothiazole nucleus can be synthesized by a variety of synthetic methods.[4] The most common ones among them being the condensation of 2-aminothiophenols with substituted carboxylic acids, acyl chlorides, aldehydes and nitriles.[4a,4b] Another method employs potassium ferricyanide cyclization of thiobenzanilides (Jacobson's method[5]). Most of these methods suffer from serious drawbacks like high temperature, very long reaction times and cumbersome work-up procedures. Employment of solid

supports for the synthesis of the benzothiazole moiety are also known. In one such method, alumina is being used[6] to synthesise imidazobenzothiazolones and in another, silica-gel is being used[7] to synthesise 2-aryl- and 2-alkylbenzothiazoles.

The protection of the environment is a very important aspect in our overcrowded world of increasing demands. To optimize such aspects, solvent-free organic syntheses using microwave have attracted immense interest as environmentally benign methodologies.[8] Among a few methods that employ microwave techniques for the synthesis of the benzothiazoles are using *p*-toluenesulphonic acid[9] for condensing β-chlorocinnamaldehydes and 2-aminothiophenol or ionic liquids[10] for condensing aromatic aldehydes with 2-aminothiophenol. Although there is reported a solvent-free reaction of 2-amino thiophenol with aromatic or aliphatic β-ketoesters[11] under microwave irradiation, till date, there is no such synthesis that employs direct condensation between the two components, arylaldehydes and 2-amino thiophenol under solvent-free conditions without any catalyst in a microwave oven.

RESULTS AND DISCUSSION



1 2 3

Scheme 1

Thus, a variety of aromatic aldehydes were coupled with 2-aminothiophenol without any catalyst under solvent-free conditions in one-pot under microwave irradiation (Scheme 1, Table 1). Both electron-donating and electron-withdrawing groups on the aromatic nucleus underwent smooth reactions to yield the benzothiazoles in excellent yields. The nitro substituted aldehydes reacted the fastest, because of the ease of the cyclization step (Scheme 2). The reaction has been studied in details with 2-chlorobenzaldehyde (Table 2), and a probable mechanism has been given in Scheme 2. The initial reaction between 2-chlorobenzaldehyde and 2-aminothiophenol yields the imine which then cyclizes to produce the 2-(2-chlorophenyl)benzothiazoline (disappearence of the imine proton at δ 8.97 and appearance of the C_2-H proton at δ 6.66 in ^{1}H NMR and disappearance of the imine carbon at δ 156.5 and appearance of C_2 carbon at δ 65.55 in ^{13}C NMR) and this finally produces 2-(2-chlorophenyl)benzothiazole (conditions given in Table 2). The isolation of the intermediates (4 and 5) in the various stages confirms our mechanism. The final stages of oxidation and dehydration were too fast for the intermediate 6 to be isolated. The condition for the direct conversion of

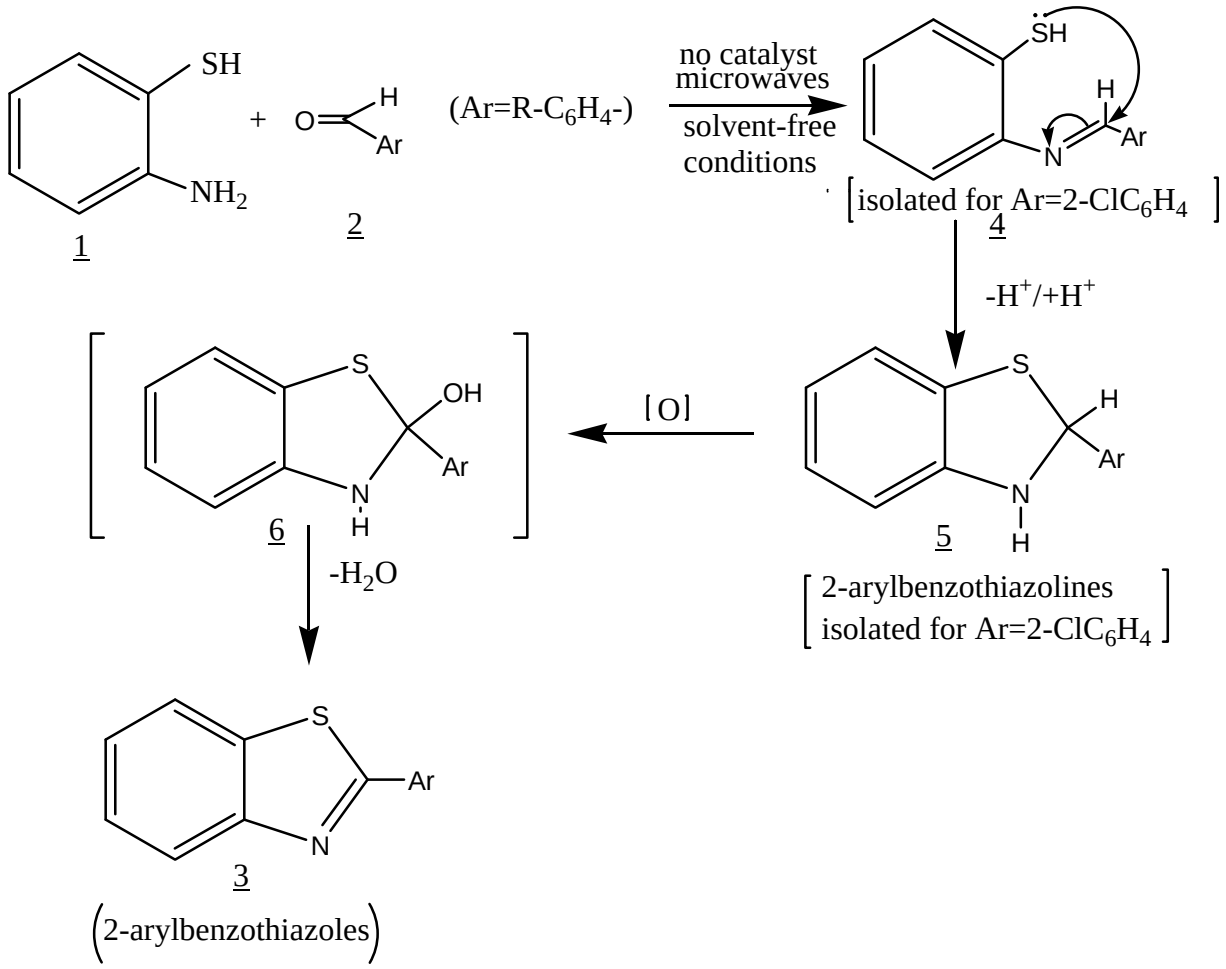
2-chlorobenzaldehyde to benzothiazole is given in Table 1. The advantages of our method are as follows: (a) operational simplicity, being the simplest of the methods available so far (b) absolutely solvent-free reaction procedure, both during the reaction and during work-up (c) environmentally benign technique (d) no hazardous wastes of reagents or solvents (e) very fast and clean reaction (f) very easy work-up procedure (g) an overall "green" methodology.

Table1. Synthesis of 2-arylbenzothiazoles by direct condensation of aromatic aldehydes and 2-aminothiophenol under solvent-free conditions

Entry	2: R=	Power (watt)	Time (min) (total of almost two equal irradiations with 1 min. interval)	Product 3: Yield (%)	Melting point(°C) of product 3:		References
					Observed	Reported	
1	a: 4-OMe	360	07	a : 95	120-121	121-122	4a, 12
2	b: 3-OH	600	08	b: 92	161-163	160-162	10
3	c: 4-OH	600	15	c: 88	225-226	227-228	07
4	d: 4-Cl	360	20	d: 85	115-117	117-118	4a, 13
5	e: 4-NO_2	240	04	e: 94	228-230	229-230	4a, 7
6	f:3-NO_2	240	03	f: 87	181-182	183-185	4b
7	g: 2-Cl	600	20	g: 84	84-85	82	7
8	h: 2-NO_2	240	03	h: 92	135-136	138-140	7
9	i:3-OMe-4-OH	600	05	i: 94	162-164	161-163	10
10	j: 4-NMe_2	600	03	j: 85	160-162	160-161	3
11	k: H	600	05	k: 83	112-114	114-115	4a, 12
12	l: 2-OMe	600	10	l: 89	101-103	101-102	7
13	m: 3-Br	720	15	m: 93	84-86	83-84	14
14	n: 2-OH	600	10	n: 95	125-126	127-128	7
15	o: 2-cinnamyl	120	10	o: 87	110-111	112	4b

Table 2. Stepwise synthesis of 2-(2-chlorophenyl)benzothiazole from 2-chlorobenzaldehyde

Entry	Starting Materials	Reaction Conditions of microwave irradiation	Product	Yield (%) (w.r.t. starting materials)	References
1	**1** + **2g**	Power=120 watt Time= 4 minutes	**4g**	72	15
2	**4g**	Power=240 watt Time=3 minutes	**5g**	78	16
3	**5g**	Power=720 watt Time=18 minutes	**3g**	82	7



Scheme 2

CONCLUSION

To summarise, the present procedure of the synthesis of the 2-arylbenzothiazoles by direct condensation of the aromatic aldehydes and 2-aminothiophenol in one-pot under microwave irradiation is the simplest

of all the procedures available till date. The present technique is therefore highly cost effective and a "green" method. We very much hope that our methodology will be highly appreciated in both academia and industry in the near future.

EXPERIMENTAL

A typical experimental procedure for the synthesis of the benzothiazoles is as follows: Aromatic aldehyde (3.5 mmol) and 2-aminothiophenol (3.5 mmol) were mixed thoroughly. The mixture was taken in a 50 mL Erlenmeyer flask placed in an alumina bath inside a microwave oven (BPL-Sanyo, BMO-700T, 2450 MHz, 1200 watt) and irradiated at a specified power level for the specified time period (Table 1), till the TLC showed the absence of the starting aldehyde. The crude product was removed from the oven and directly recrystallised from ethyl acetate/petroleum ether (60-80 °C) to yield the pure 2-arylbenzothiazoles. All the products were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopic analyses. The detailed spectroscopic data for the imine, benzothiazoline and benzothiazole obtained from 2-chlorobenzaldehyde (reaction conditions given in Table 2) are given below:

(i) **Imine from 2-chlorobenzaldehyde and 2-aminothiophenol (4g)** (Table 2, entry1): mp 73-74 °C (lit.,[15] mp 75 °C); IR (KBr): 3427, 2923, 2369, 1607, 1440, 1273, 1038 and 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.97 (s, 1H, -N=CH), 8.41-8.38 (m, 1H, aromatic C_3-H), 7.67 (dd, J=6.0Hz and 2.1 Hz, 1H, C_6-H), 7.48-7.37 (m, 4H, C_4-H/ C_5-H and aromatic C_4-H, C_5-H and C_6-H), 7.21 (dt, J=6.0 Hz and 2.1 Hz, 1H, C_5-H/ C_4-H), 7.14 (dd, J=6.9 Hz and 2.0 Hz, 1H, C_3-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 156.50, 148.75, 136.20, 133.08, 132.47, 132.42, 129.95, 129.16, 127.35, 127.27, 127.04, 126.11, 117.43.

(ii) **2-(2-Chlorophenyl)benzothiazoline (5g)** (Table 2, entry 2): mp 76 °C (lit.,[16] mp not reported); IR (KBr): 3344, 3063, 2371, 1573, 1462, 1240, 1033 and 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.77-7.71 (m, 1H, aromatic C_3-H), 7.40-7.31 (m,1H, C_4-H), 7.28-7.18 (m, 2H, aromatic C_4-H and C_6-H), 7.04 (dd, J=7.5 Hz and 0.9 Hz, 1H, C_7-H), 6.95 (dt, J=9.0 Hz and 1.3Hz, 1H, C_5-H/C_6-H), 6.79-6.71 (m, 2H, C_6-H/C_5-H and aromatic C_5-H), 6.66 (s,1H, C_2-H), 4.43 (brs,1H, N-H); ^{13}C NMR ($CDCl_3$, 75MHz), δ: 146.13, 139.99, 131.60. 129.60, 129.29, 127.41, 127.33, 126.32, 125.48, 121.96, 121.06, 110.37, 65.55.

(iii) **2-(2-Chlorophenyl)benzothiazole (3g)** (Table 2, entry 3): mp 84-85 °C (lit.,[7] mp 82 °C); IR (KBr): 3435, 2363, 1423, 1266, 1053 and 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.21-8.18 (m, 1H, aromatic C_3-H), 8.12 (dd, J=9.0 Hz and 0.6 Hz, 1H, C_7-H), 7.94 (dd, J=7.8 Hz and 0.6 Hz, 1H, C_4-H), 7.54-7.49 (m, 2H, aromatic C_4-H and aromatic C_6-H), 7.44-7.38 (m, 3H, C_5-H, C_6-H and aromatic C_5-H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 164.15, 152.50, 136.10, 132.70, 132.28, 131.74, 131.10, 130.78, 127.08, 126.26, 125.41, 123.45 and 121.36.

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REFERENCES

1. T. D. Bradshaw, S. Wrigley, D.-F. Shi, R. J. Schulz, K. D. Paull, and M. F. G. Stevens, *Br. J. Cancer*, 1998, **77**, 745.
2. C. G. Mortimer, G. Wells, J.-P. Crochard, E. L. Stone, T. D. Bradshaw, M. F. G. Stevens, and A. D. Westwell, *J. Med. Chem.*, 2006, **49**, 179.
3. C. A. Mathis, Y. Wang, D. P. Holt, G. F. Huang, M. L. Debnath, and W. E. Klunk, *J. Med. Chem.*, 2003, **46**, 2740.
4. a) A. Ben-Alloum, S. Bakkas, and S. Soufiaoui, *Tetrahedron Lett.*, 1997, **38**, 6395. b) Y. Li, W.-L. Wang, and J.-Y. Wang, *Chem. Lett.*, 2006, **35**, 460. c) T. Kondo, S. Yang, K.-T. Huh, M. Kobayashi, S. Kotachi, and Y. Watanabe, *Chem. Lett.*, 1991, **20**, 1275. d) F. F. Stephens, *Nature*, 1949, **164**, 243. e) K. Nakagawa H. Onoue, and J. Sugita, *Chem. Pharm. Bull.*, 1964, **12**, 1135. f) M. Yoshifujii, R. Nagase, T. Kawashima, and N. Inamoto, *Heterocycles*, 1978, **10**, 57. g) S. K. Talapatra, P. Chaudhuri, and B.Talapatra, *Heterocycles*, 1980, **14**, 1279. h) R. S. Varma, R. K. Saini, and O. Prakash, *Tet. Lett.*, 1997, **38**, 2621.
5. D. F. Shi, T. D. Bradshaw, S. Wrigley, C. J. McCall, P. Lelieveld, I. Fichtner, and M. F. G. Stevens, *J. Med. Chem.*, 1996, **39**, 3375.
6. R. Mahesh, R. V. Perumal, and P. V. Pandi, *Pharmazie*, 2005, **60**, 411.
7. M. Kodomari, Y. Tamaru, and T. Aoyama, *Synth. Commun.*, 2004, **34**, 3029.
8. R. S. Varma, *Green Chemistry*, 1999, **1**, 43.
9. S. Paul, M. Gupta, and R. Gupta, *Synth. Commun.*, 2002, **32**, 3541.
10. B. C. Ranu, D. Ranjan, and S. Suvendu, *Chem. Lett.* 2004, **33**, 274.
11. S. Kamila, H. Zhang, and E. R. Biehl, *Heterocycles*, 2005, **65**, 2119.
12. R. H. Tale, *Org. Lett.* 2002, **4**, 1641.
13. D. L. Boger, *J. Org. Chem.*, 1978, **43**, 2296.
14. L. W. Wattenburg, M. A. Page and J. L. Leong, *Cancer Research*, 1968, **28**, 2539.
15. R. M. Abdel-Rahman, Z. El-Gendy, and M. B. Mahmoud, *J. Indian Chem. Soc.*, 1990, **67**, 61.
16. K. Tatsuya, *Inorg. Chim. Acta*, 2000, **300-302**, 512.