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A Simple Synthesis of the Aryloxy- or Arylthio- derivatives of 2-Benzothiazolyl Stilbenes

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Abstract : Synthesis of 2-(b -(aryl-X)styryl)benzothiazoles (**2a** - **2z**) (X = O, S) from aromatic or heterocyclic aldehydes and 2-naphthylmethyl-, 2-aryloxymethyl- or 2-arylthiomethyl benzothiazoles is reported. Phthalides **4a** - **4f** were prepared by Gabriel modification of Perkin synthesis. Products were confirmed by NMR spectral and elemental analysis. Prepared compounds were tested on herbicidal and growth - regulating activity. The semiempirical AM1 quantum - chemical method has been used to study an optimal conformation and heats of formation.

Keywords : Aryloxymethylbenzothiazoles, Arylthiomethylbenzothiazoles, Aldol Condensation, Phthalides, AM1 Semiempirical calculations.

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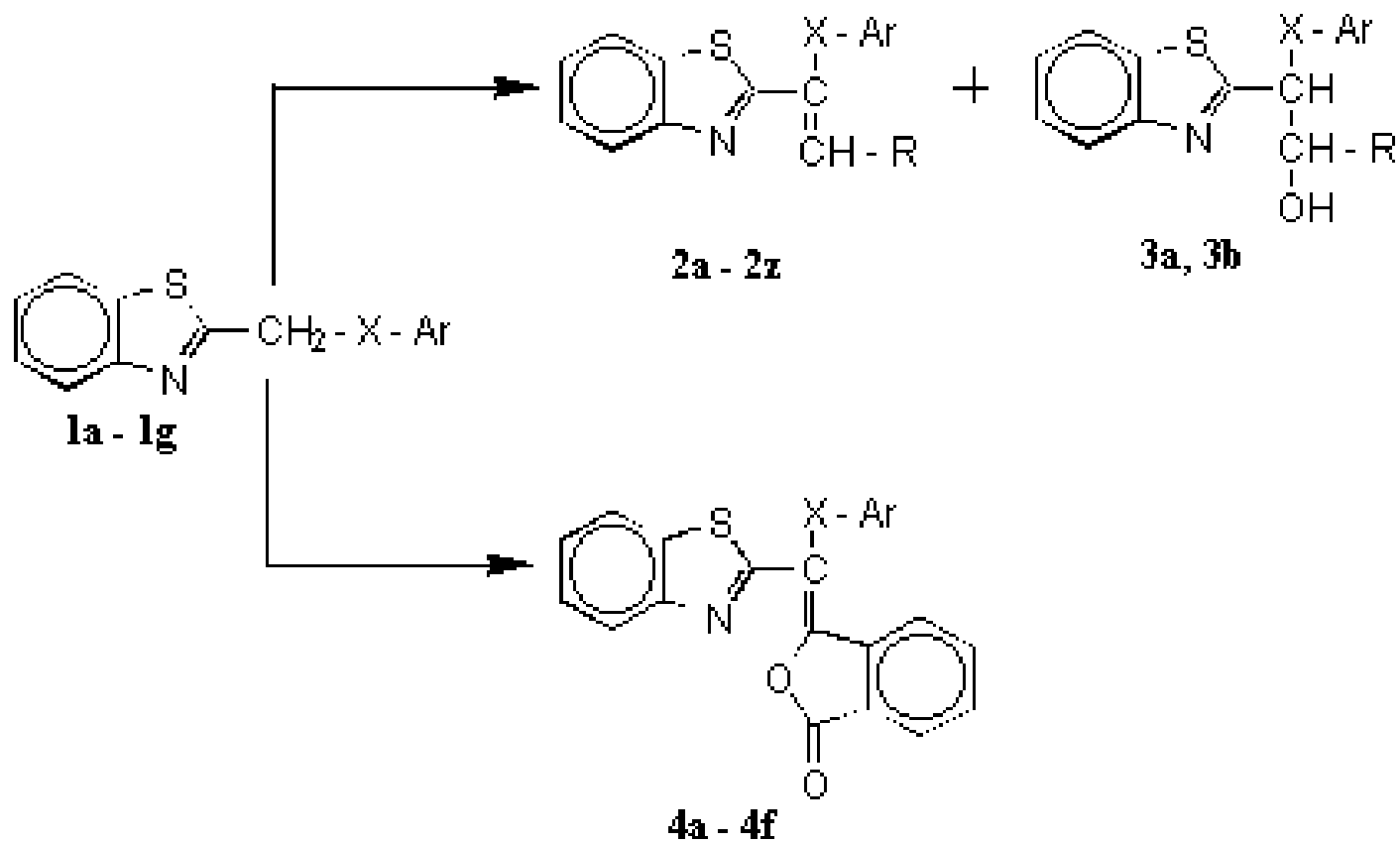
Introduction

The aim of this work was to investigate the condensation of 2-aryl-X-methylbenzothiazole with aldehydes and phthalanhydrides. As is known from literature and practice the benzothiazole ring and derivatives of arylacetic acid are involved in many biologically active compounds. For example, Benzthiazuron and Metabenzthiazuron are utilised as preemergent herbicides. 2-Aryloxyacetic acids belong to biologically highly effective compounds. They are the herbicides known as growth regulators. Combination of both biologically active compounds is important for studies of the dependence of biological activity on the products structures. 2-Aryloxymethylbenzothiazoles are readily obtainable from o-aminothiophenol and aryloxyacetic acids. These starting compound were also tested on herbicidal and growth - regulating activity.

This work was done in connection with our study of aldol condensation of aryloxyacetic acids [1, 2]. It was found that the condensation products of aryloxyacetic acid rendered low yields (20 - 30 %). On the other hand 2-methylbenzothiazoles or 2-benzylbenzothiazoles are effective agents for condensation reaction [3 - 6].

Results and Discussion

We found, that the optimal procedure for the preparation of compounds **2a** - **2z** is quiet simple. The reaction is performed at room temperature in dimethyl sulfoxide solution and under excess of aqueous sodium hydroxide. The best reaction time was found to be 30 - 45 minutes. It ought to be noted that the reactions carried out with nitroaldehydes must be cooled down to -10 °C. The final reaction product is composed of alcohols **3** and their dehydration products **2** as is shown in the Scheme 1.



X Ar R X Ar R

1a - C₆H₅ - **2o** O 2,4-Cl₂-C₆H₃ C₆H₅

1b - 1-C₁₀H₇ - **2p** O 2,4-Cl₂-C₆H₃ 4-Cl-C₆H₄

1c O C₆H₅ - **2q** O 2,4-Cl₂-C₆H₃ 4-NO₂-C₆H₄

1d O 4-Cl-C₆H₄ - **2r** O 2,4-Cl₂-C₆H₃ 4-CH₃O-C₆H₄

1e O 2,4-Cl₂-C₆H₃ - **2s** O 2,4-Cl₂-C₆H₃ 4-(CH₃)₂N-C₆H₄

1f O 3-CH₃-C₆H₄ - **2t** S C₆H₅ C₆H₅

1g S C₆H₅ - **2u** S C₆H₅ 4-Cl-C₆H₄

2a O C₆H₅ C₆H₅ **2v** S C₆H₅ 4-NO₂-C₆H₄

2b O C₆H₅ 4-Cl-C₆H₄ **2w** S C₆H₅ 3-NO₂-C₆H₄

2c O C₆H₅ 3-Cl-C₆H₄ **2x** S C₆H₅ 4-(CH₃)₂N-C₆H₄

2d O C₆H₅ 4-CH₃O-C₆H₄ **2y** - 1-C₁₀H₇ 4-Cl-C₆H₄

2e O C₆H₅ 3,4-(CH₂)O₂-C₆H₃ **2z** - 1-C₁₀H₇ 4-NO₂-C₆H₄

2f O C₆H₅ 4-(CH₃)₂N-C₆H₄ **3a** - C₆H₅ C₆H₅

2g O C₆H₅ 2-furyl **3b** O C₆H₅ C₆H₅

2h O C₆H₅ 2-thienyl **4a** - C₆H₅ -

2i O C₆H₅ C₆H₅-CH=CH₂ **4b** - 1-C₁₀H₇ -

2j O 4-Cl-C₆H₄ C₆H₅ **4c** O C₆H₅ -

2k O 4-Cl-C₆H₄ 4-Cl-C₆H₄ **4d** O 4-Cl-C₆H₄ -

2l O 4-Cl-C₆H₄ 4-NO₂-C₆H₄ **4e** O 2,4-Cl₂-C₆H₃ -

2m O 4-Cl-C₆H₄ 4-CH₃O-C₆H₄ **4f** O 3-CH₃-C₆H₄ -

Scheme 1

The separation of both compounds was realised by crystallization in ethanol. The alcohol **3** was soluble in ethanol. The insoluble part of **2** was crystallized from acetic acid. The dehydration products **2** could be isolated as only one product by recrystallization in acetic acid. Our experiments showed that the yields of condensation products did not depend on bridge atoms X of starting compounds **1a** - **1f**. Besides the wide variety of substituted aldehydes we used also phthalanhydride as carbonyl component in the reaction with compounds **1a** - **1f** under conditions of the Perkin synthesis. The best yields (25 - 35 %) were achieved at 180 - 200 °C without solvent and with CH₃COOK as base. These reaction conditions were found to be unsuitable aldehydes. Similarly the conditions were unfit for the condensation of phthalanhydride in aqueous sodium hydroxide. The prepared compounds were proved by elemental analysis and ¹H NMR - spectra. The signals in the region of aromatic protons of **2** were identified as multiplets at 6.77 - 8.07 ppm. For example in the case of compound **2d** there are singlet at 3.65 and multiplet at 6.70 - 8.02. The compounds **3a**, **3b** showed doublets of ethylene groups.

The optimal structures and some quantum chemical parameters were calculated for the phenyl-X-acetic acid and some compounds **1a**, **1c** and **1g** by AM1 method [7] with full optimization and standard parametrization (keyword PRECISE). For C=N bond and X atom of and 2-(phenyl-X-methyl)benzothiazoles the antiperiplanar conformation appeared to be energetically the most favourable. The energy of the dissociation of the hydrogen proton of the methylene group has been calculated. In the agree with experiment, the most advantaged energy dissociation was obtain for compound where X = S (Table 1) and the most disadvantaged energy for X = O.

Table 1 : Calculated values of the heats of formation (D H_f) and dissociation energies of the hydrogen protons for the 2-(phenyl-X-methyl) benzothiazol and their anion.

Compound	D H _f , kJmol ⁻¹	E, kJmol ⁻¹
1a	356.2	-
1a - anion	223.3	85.1
1c	239.2	-
1c - anion	128.6	107.4
1g	417.1	-
1g - anion	256.1	57.1

Similarly results have been obtained for phenyl-X-acetic acid (Table 2).

Table 2 : Calculated values of the heats of formation (D H_f) and dissociation energies of the hydrogen protons for the phenyl-X-acetic acid and their anion.

acid	D H _f , kJmol ⁻¹	E, kJmol ⁻¹
phenylacetic	-315.8	-
phenylacetic - anion	-412.1	121.6
phenoxyacetyl	-422.1	-
phenoxyacetyl - anion	-489.1	151.0
phenylthioacetyl	-245.0	-
phenylthioacetyl - anion	-341.1	121.9
acetic acid	-430.9	-

The investigation of herbicidal and growth - regulating activity of the starting and prepared compounds did not exhibit any remarkable results. The herbicidal activity did not exceed 50 % of that of the standard (2-methyl-4-chlorophenoxyacetic acid). The growth - regulating tests proved no significant activity as well.

Experimental Part

The ¹H NMR spectra of saturated solutions of prepared compounds were measured on a TESLA BS 487 instrument (80 MHz).

The standard herbicidal screening was performed using the following model plants: *Avena sativa*, *Panicum miliaceum*, *Fagopyrum vulgare*, *Lepidum sativum*, and *Sinapis alba*. 2-Methyl-4-chlorophenoxyacetic acid was used as a standard. Doses of 0.50 and 0.25 g m⁻² were employed by preemergent and postemergent application, respectively. The appearance of plants was evaluated after 2 weeks by scale 0 - 5, where 0 means undamaged plant and 1 - 5

	319.4	67.96	3.75	3.75	19.38	-		
2i	C ₂₂ H ₁₇ NOS	77.71	4.82	3.94	9.02	-	51	169 - 173
	355.5	77.42	4.77	3.77	8.77	-		
2j	C ₂₂ H ₁₄ ClNOS	72.42	3.88	3.97	8.76	9.86	88	178 - 179
	363.9	72.20	4.01	3.88	9.16	10.02		
2k	C ₂₁ H ₁₃ Cl ₂ NOS	62.42	3.18	3.40	8.03	17.80	86	188 - 189
	398.3	62.27	3.27	3.52	8.06	17.63		
2l	C ₂₁ H ₁₄ ClN ₂ O ₃ S	61.45	3.19	6.54	8.59	8.33	54	192 - 194
	408.6	61.76	3.18	6.86	8.57	8.05		
2m	C ₂₂ H ₁₆ ClNO ₂ S	66.89	4.07	3.49	8.06	8.91	68	144 - 145
	363.9	67.17	4.07	3.59	8.14	8.90		
2n	C ₂₃ H ₁₉ ClN ₂ OS	68.26	4.78	6.79	7.79	8.54	48	174 - 176
	406.9	67.98	4.97	6.89	7.88	8.62		
2o	C ₂₁ H ₁₃ Cl ₂ NOS	62.42	3.18	3.40	8.03	17.80	82	126 - 127
	398.3	63.58	3.27	3.52	8.14	17.44		
2p	C ₂₁ H ₁₃ Cl ₃ NOS	57.72	2.71	3.18	7.22	24.57	80	170 - 172
	432.8	57.94	2.94	3.24	7.42	24.10		
2q	C ₂₁ H ₁₂ Cl ₂ N ₂ O ₃ S	56.80	2.72	6.27	7.00	15.99	62	208 - 211
	443.3	57.01	2.71	6.33	7.22	15.42		
2r	C ₂₂ H ₁₅ Cl ₂ NO ₂ S	61.77	3.50	3.23	7.33	16.29	78	155 - 157
	428.3	61.82	3.51	3.27	7.49	16.39		

2s	C ₂₃ H ₁₈ Cl ₂ N ₂ OS	62.34	4.17	6.03	6.83	16.06	51	142 - 143
	441.3	62.67	4.08	6.32	7.06	16.28		
2t	C ₂₁ H ₁₅ NS ₂	73.47	4.27	4.00	18.55	-	70	138 - 140
	345.5	73.09	4.34	4.08	18.55	-		
2u	C ₂₁ H ₁₄ CINS ₂	66.19	3.63	3.56	17.02	9.22	74	165 - 166
	344.5	66.36	3.69	3.69	16.88	9.23		
2v	C ₂₁ H ₁₄ N ₂ O ₂ S ₂	64.59	3.61	7.17	16.42	-	58	199 - 201
	390.5	64.82	3.55	7.10	16.41	-		
2w	C ₂₁ H ₁₄ N ₂ O ₂ S ₂	64.59	3.61	7.17	16.42	-	60	169 - 171
	390.5	64.84	3.35	7.06	16.69	-		
2x	C ₂₃ H ₂₀ N ₂ S ₂	71.13	5.15	7.21	16.50	-	38	213 - 213
	380.5	70.88	5.15	7.05	16.51	-		
2y	C ₂₅ H ₁₆ CINS	75.56	4.03	3.52	8.06	-	62	162 - 164
	397.9	75.68	4.01	3.39	8.37	-		
2z	C ₂₅ H ₁₆ N ₂ O ₂ S	73.53	3.92	6.86	7.84	-	47	210 - 212
	408.5	73.69	3.74	6.58	7.60	-		
3a	C ₂₁ H ₁₇ NOS	76.11	5.17	4.22	9.65	-	10	156 - 158
	331.4	75.92	5.11	4.13	9.69	-		
3b	C ₂₁ H ₁₇ NO ₂ S	72.64	4.93	4.03	9.23	-	11	121 - 123
	347.4	72.22	4.67	3.83	8.90	-		
4a	C ₂₂ H ₁₃ NO ₂ S	74.34	3.68	3.94	9.02	-	15	214

								- 216
	355.5	74.10	3.61	3.62	8.70	-		
4b	C ₂₆ H ₁₅ NO ₂ S	77.02	3.73	3.45	7.90	-	10	265 - 268
	405.4	76.82	3.65	3.20	7.58	-		
4c	C ₂₂ H ₁₃ NO ₃ S	71.14	3.53	3.77	8.63	-	19	230 - 232
	371.4	70.86	3.42	3.44	8.25	-		
4d	C ₂₂ H ₁₂ ClNO ₃ S	65.18	2.96	3.45	7.90	8.64	18	235 - 237
	405.9	64.92	2.95	3.48	7.96	8.70		
4e	C ₂₂ H ₁₁ Cl ₂ NO ₃ S	60.01	2.51	3.18	7.26	16.10	18	250 - 252
	440.3	59.82	2.46	2.92	7.11	15.90		
4f	C ₂₃ H ₁₅ NO ₃ S	71.67	3.92	3.63	8.30	-	17	177 - 180
	385.4	71.92	3.83	3.48	8.15	-		

3-(2-Benzothiazolyl)-3-(aryl-X-methylen)phthalides (4a - 4f)

A mixture of sublimated phthalanhydride (0.3 g, 20 mmol), the corresponding benzothiazole derivative (10 mmol) and freshly melted potassium acetate (0.2 g) was stirred at 180 - 200 \diamond C for 5 hrs with removal of reaction water. After cooling water (50 ml) and sodium hydrogen carbonate (1.0 g) was added and stirred 3 hrs. The precipitate was filtered, dried and crystallized from ethanole. The soluble part was unreacted compound **1**. The insoluble part was crystallized from acetic acid.

Conclusion

In this work it was found that the route of preparation of benzothiazole stilbens **2** is very effective and simple. Interestingly no products **2** were isolated in the reaction under Perkin conditions (180 - 200 \diamond C).

The phthalides **4**, on the other hands could be prepared only at 180 - 200 \diamond C by Perkin modification of the aldol synthesis.

Prepared compounds showed only marginal effectivity in herbicidal and growth - regulating activity.

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Comments

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