



Synthesis of Several Imidazo[2,1-b]thiazoles

GEORGE BRATULESCU

Faculty of Chemistry, University of Craiova, 13 A.I. Cuza, 200585 Craiova, Romania

Corresponding author: Fax: + 40 251597048; Tel : +40 251597048; E-mail: georgebratulescu@yahoo.com

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Imidazo[2,1-b]thiazole derivatives were obtained from 2-aminothiazoles or 2-amino-2-thiazolines and 4-chloromethyl- ω -bromoacetophenone in three steps. The product syntheses take place in convenient conditions with yields between 50 and 70 %.

Key Words: Imidazo[2,1-b]thiazoles, Halogenoketones, Triethyl phosphite, Arbuzov's reaction.

INTRODUCTION

Imidazo[2,1-b]thiazole derivatives are largely used in practice for their important biological properties such as herbicides¹, immunostimulants^{2,3} and fungicides⁴ in agriculture, pharmaceutical preparations for intensification of cerebral functions^{5,6} antiulcer drugs^{7,8}, antimicrobial⁹, antitumor^{10,11}, antiinflammatory¹², and cardiotoxic agents¹³. Literature described several procedures for imidazo[2,1-b]thiazoles synthesis^{4,14-20}.

EXPERIMENTAL

Reagents used in the synthesis are commercial products. Elemental analyses were carried out with a Carlo Erba model 1106 analyzer. IR spectra were recorded on potassium bromide pellets using a Perkin-Elmer 1600 spectrometer. Melting points were measured using a Boëtius apparatus.

Procedure

4-Chloromethyl- ω -bromoacetophenone synthesis

(a) ***p*-Chloromethylbenzoyl chloride synthesis:** A sample of 0.1 mol of *p*-chloromethylbenzoic acid and 0.2 mol of thionyl chloride in 100 mL of cyclohexane was refluxed for 8 h. When the reaction was complete, the cyclohexane was removed under reduced pressure and the solid residue was recrystallized from petroleum ether. Yield 79 %. m.p. 31°C. Elemental analysis: m.f. C₈H₆OC₂Cl₂, % C (calculated/found) = 50.79 / 50.73, % H (calculated / found) = 3.17 / 3.15.

(b) **(*p*-Diazoacetyl)benzyl chloride synthesis:** In a cold petroleum ether solution containing 30 mL of triethylamine and 0.18 mol of diazomethane (diazomethane is easily generated pouring an aqueous solution of NaOH on Diazald-0.28 mol of *N*-methyl-*N*-nitroso-*p*-toluene sulphonamide) was quickly added 0.15 mol of *p*-(chloromethyl)benzoyl chloride.

The resulting mixture was stirred for 2 h, then, the solvent was evaporated. The remaining residue was washed twice with water and the heterogeneous mixture was extracted with chloroform. Chloroform was removed by distillation and a pure product resulted. Yield 99 %. Product melting point 88 °C. Elemental analysis: m.f. C₇H₇N₂OCl, % C (calculated/found) = 49.26 / 49.23, % H (calculated/found) = 4.10 / 4.08.

(c) **4-Chloromethyl- ω -bromoacetophenone synthesis:** 0.1 mol of (*p*-diazoacetyl)benzyl chloride was dissolved in 300 mL of chloroform, afterwards, 25 mL of 45 % hydrobromic acid and 200 mL of water were poured. The mixture was stirred for 1 h and then the solvent was evaporated (temperature below 40 °C). A pure solid product resulted, yield 99 %. Melting point 85 °C. Elemental analysis: m.f. C₉H₈OC₂ClBr, % C (calculated / found) = 43.63 / 43.57, % H (calculated/found) = 3.23 / 3.19.

Diethyl 4-[6-(2,3-dihydroimidazo[2,1-b]thiazolyl)]benzylphosphonate synthesis, (Table-1, first compound): 0.1 mol of 2-amino-2-thiazoline was dissolved in 150 mL of acetonitrile, then a solution of 0.1 mol of 4-chloromethyl- ω -bromoacetophenone in 100 mL of acetonitrile was poured. The resulting solution was stirred for 10 h, afterwards the obtained precipitate was filtered off. The precipitate was dissolved in 150 mL of ethanol and the new mixture was refluxed for 5 h. The ethanol was removed under reduced pressure and the obtained residue was dissolved in 100 mL of water. The aqueous solution was neutralized with potassium bicarbonate until pH = 8. The product was extracted with 200 mL of chloroform, the organic layer was decanted and dried on magnesium sulfate. Magnesium sulfate was filtered off and then the solvent was distilled from filtrate. The resulting solid residue containing 2,3-dihydro-6-(*p*-chloromethyl) phenyl imidazo[2,1-b]thiazole was added to 0.2 mol of triethyl phosphite and the mixture

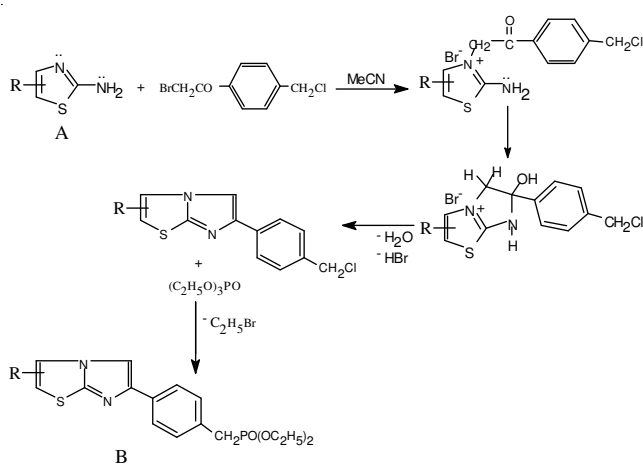
TABLE-1
CHARACTERISTIC DATA OF IMIDAZO[2,1-B]THIAZOLE DERIVATIVES

Reagent (A)	Final product (B) X = <i>p</i> -C ₆ H ₄ CH ₂ PO(OEt) ₂	Elemental analysis calculated found (%)			m.p. (°C)	Yield (%)	IR (cm ⁻¹)
		C	H	N			
		54.54 54.43	5.96 5.87	7.95 7.90	107.5 108 ²⁰	63	v(C=N) :1540 m v(P=O) :1240 vs
		55.73 55.70	6.28 6.14	7.65 7.57	96 96 ²⁰	59	v(C=N) :1538 m v(P=O) :1242 vs
		49.67 49.56	5.17 5.12	7.24 7.11	118	55	v(C=N) :1548 m v(P=O) :1249 vs
		54.85 54.73	5.42 5.31	8.00 7.92	131 130 ²⁰	71	v(C=N) :1547 m v(P=O) :1242 s
		49.93 49.84	4.68 4.57	7.28 7.15	139	63	v(C=N) :1549 m v(P=O) :1239 s
		56.04 55.89	5.76 5.66	7.69 7.62	127 128 ²⁰	68	v(C=N) :1553 m v(P=O) :1245 s
		57.44 57.31	5.58 5.46	7.44 7.39	163	52	v(C=N) :1544 m v(P=O) :1242 vs

was heated for 6 h at 155 °C. Non-reacted triethyl phosphite was distilled under reduced pressure and the resulting residue was recrystallized from ethyl acetate to produce the pure product. The physical properties of the product are shown in Table-1. The others products were similarly synthesized (Table-1).

RESULTS AND DISCUSSION

The synthesis of the compounds presented below was done by a proceeding which use as raw materials, α -halogeno-ketones and 2-aminothiazoles or 2-amino-2-thiazolines,^{4,14,15} involving Arbuzov's reaction. The syntheses were shown by subsequent reactions:



Condensation reaction between 2-aminothiazole (or 2-amino-2-thiazoline) derivatives and 4-chloromethyl- ω -bromoacetophenone in acetonitrile solvent occurs at the nitrogen atom from heterocyclic ring. The resulting ammonium salts has two reaction sites within molecule. The ammonium salt undergoes intramolecular addition of the amino group onto carbonyl group, *via* a cyclic intermediate. Afterwards, water and hydrobromic acid elimination reactions lead to 6-(*p*-chloromethyl) phenyl imidazo[2,1-b]thiazoles (or 2,3-dihydro-

6-(*p*-chloromethyl) phenyl imidazo[2,1-b]thiazoles). The condensation reaction of this last compound with triethyl phosphite by Arbuzov' reaction gives diethyl 4-[6-(imidazo[2,1-b]thiazolyl)] benzylphosphonates (or diethyl 4-[6-(2,3-dihydroimidazo[2,1-b]thiazolyl)] benzylphosphonates).

Physical properties of the new synthesized compounds and the entire yields of the synthesis are reported in Table-1.

The synthesis reaction yields proceed with quite reasonable yields. For synthesis of diethyl 4-[6-(imidazo[2,1-b]thiazolyl)] benzylphosphonate the yield was 71 %.

The characteristic IR absorptions of C=N and P=O groups in the heterocyclic products show medium and high intensities in agreement with literature data of similar substances²¹.

Conclusion

The synthesis of imidazo[2,1-b]thiazole derivatives was accomplished using 2-aminothiazoles, 2-amino-2-thiazolines, halogeno-ketones and triethyl phosphite. The entire yields of the three step synthesis were reasonable, 50-70 %.

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