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Synthesis Of Biologically Active N-Alkyl And N-Acyl 2-(4-Thiazolyl) -1H-Benzimidazoles

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ABSTRACT

Various N-alkyl and N-acyl derivatives of 2-(4-thiazolyl)-1H-benzimidazole have been synthesized using polymer-supported reactions, speed and simple work-up are the crucial features of the method.

INTRODUCTION

Sulfur and/or nitrogen heterocycles have acquired an immense importance among the heterocycles, possessing pharmaceutical activities and pest management potency and widely occur in the nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. The utility of thiazoles in curative treatment has been firmly established. They exhibit anti-bacterial, anti-hypertensive, anti-anginal, anti-arrhythmetic, anti-histaminic, narcotic antagonist, etc. activities. Thiazole nucleus is found in many antibiotics and vitamins in one or another form[1,2]. The benzimidazole compounds have been proved to be the most important group of fungicides with systemic activity and are well known for their pronounced ability to control a large number of fungal diseases[1,2]. Benomyl, thiabendazole and thiophnate methyl are main examples of this fungicide class. Because of their systematic activity, they can help to control some diseases after infection. Benzimidazole fungicides are also used to prevent post-harvest rots and in soil-drench treatments. The 2-(4-thiazolyl)-1H-benzimidazoles are structurally analogous to benzimidazoles, well known as an anthelminitic agent and systemic fungicide. It's fungicidal properties[3-5] and systemic properties in plants[6] have already been reported fungicide with protective and curative action. It is used to control of aspergillus, botrytis, ceratocystis, cercospora, colletotrichum, corticium, diaporthe, diplodia, fusarium, gibberella, gloeosporium, oospora, penicillium, phoma, rhizoctonia, sclerotinia, septoria, thielaviopsis, verticillium spp., etc. in asparagus, avocados, bananas, barley, beans, cabbage, celery, chicory, cherries, citrus, cotton, some cucurbits, flax, mangoes, mushrooms, oats, onions, ornamentals, pawpaws, pome fruit, potatoes, rice, soyabeans,

strawberries, sugar beet, sweet potatoes, tobacco, tomatoes, turf, vines and wheat. Also used for control of storage diseases of fruits and vegetables and for control of Dutch elm disease. It is commonly used as an anthelminitic in human and veterinary medicine too. Again thiabendazole has significant anthelmentic activity for gastrointestinal parasites in sheep, goats, cattle, horses, swine, dogs, and poultry. This compound is well-tolerated and does not stain the skin, hair or wool of animals. It may be given orally for therapeutic use or in feed or mineral supplements for the prophylactic control of parasites in domestic animals[7,8]. Benzimidazole and thiazole analogues have found applications in medicine and agriculture. Therefore development of a simple, fast and flexible method to generate libraries of such compounds was desirable[9,10]. The structural modification or derivatization and bioassay is highly essential to establish structure-activity relationships in order to exploit the molecules having better potency and efficacy. In continuation of our work on synthesis of biologically active compound using polymer-supported reactions[11-15], we report herein a simple, rapid and safer method for the preparation of N-alkyl and N-acyl derivatives of 2-(4-thiazolyl)-1H-benzimidazole. Easy separation of products with higher yield and purity by simple work-up, and speed are crucial features of the method.

EXPERIMENTAL

2-(4-Thiazoly)-1H-benzimidazole (Aldrich), alkyl halides and acid chlorides (s.d.fine chemicals) were commercial synthetic grade chemicals, Cinnamyl chloride and Phenyl acetyl chlorides were prepared in the laboratory[16]. Amberlite IRA-400 (chloride form) was activated before use. The acetone as solvent was double distilled and dried. Melting points and boiling points are uncorrected.

General procedure for the preparation of polymer-supported 2-(4-thiazolyl)-1H-benzimidazoles

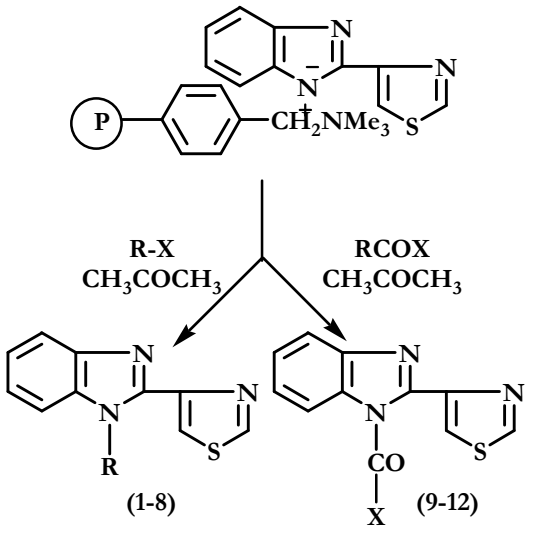
Strongly basic anion exchange resin in chloride form [Amberlite IRA-400(Cl^-)] was packed in a column and washed with aqueous potassium salt of 2-(4-thiazolyl)-1H-benzimidazoles, (prepared by dissolving 100 mmole of 2-(4-thiazolyl)-1H-benzimidazoles in 100 ml 1N potassium hydroxide) until complete removal of chloride ion. The resin was then successively washed with water, ethanol and acetone and finally dried in vacuo at 50^0C over phosphorous pentoxide for 6 hrs.

The exchange capacity of resin was determined by passing aqueous 1 M potassium chloride(100ml) through 1 gm resin packed in a column. The amount of 2-(4-thiazolyl)-1H-benzimidazoles anion in an eluent was titrated with 0.01 N HCl using methyl orange as an indicator.

The capacity was found to be 1 mmoles of 2-(4-thiazolyl)-1H-benzimidazole anion per gm of dry resin.

Synthesis of N-alkyl 2-(4-thiazolyl)-1H-benzimidazoles (1-8)

A mixture of polymer-supported anion of 2-(4-thiazolyl)-1H-benzimidazole(5gm, 5mmoles) and alkyl halide(s)(5 mmoles) in acetone(25ml) was stirred for 20-30 min; depending on the reactivity of alkyl halides. The progress of the reaction was monitored by silica gel TLC(C_6H_6:$CHCl_3$, 8:2). After completion of the reaction, the resin was separated by filtration and washed with acetone(3×5ml). The distillation of solvent furnished the corresponding N-alkyl product(s) in a high yield in essentially pure form, as listed in the TABLE 1.



SCHEME 1: Synthesis of N-alkyl and N-acyl 2-(4-thiazolyl)-1H-benzimidazoles

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SCHEME 1: Synthesis of N-alkyl and N-acyl 2-(4-thiazolyl)-1H-benzimidazoles

Compd	Substituent R	m.p. / b.p.[4,17] + ^{0}C	Yield %	Ir (cm^{-1})	^{1}H NMR (δ, ppm) Solvent	
1	CH_3	139	90			
2	CH_3CH_2	78	92	1611, 1479, 1404, 1325, 1254	$CDCl_3$	4.75(q, 2H, CH2), 1.44(t, 3H, CH_3)
3	$CH_3CH_2CH_2$	66	92			
4	$(CH_3)_2CH$	98	94		DMSO-d_6	5.88(septet/m, 1H, CH), 1.65(d, 6H, $2CH_3$ gem)
5	$CH_3(CH_2)_2CH_2$	70	93			
6	CH_2=$CHCH_2$	78	93			
7	$C_6H_5CH_2$	175	91			
8	HO_2CCH_2	268	90			
9	CH_3CO	224	90			
10	C_6H_5CO	147	96	1688, 1601, 1580, 1422, 1325, 1293		
11	C_6H_5CH=$CHCO$	180	92		DMSO-d_6	7.85(d, ^{1}H, CH-O), 7.55- 7.30 (m, 5H, Ar-H), 6.48 (d, ^{1}H, -COCH=)
12	$C_6H_5CH_2CO$	150+	94	1712, 1602, 1585, 1496, 1454, 1300, 1232		

Synthesis of N-acyl 2-(4-thiazolyl)-1H-benzimidazoles(9-12)

N-acyl 2-(4-thiazolyl)-1H-benzimidazoles were prepared by the above procedure using acid chlorides instead of alkyl halides, as listed in the TABLE 1. The acid chloride(5mmoles) was added slowly dropwise in the solution of polymer-supported 2-(4-thiazolyl)-1H-benzimidazole anion (5gm, 5mmoles) in acetone(25ml) with constant stirring at room temperature. Depending upon the reactivity of the acid chlorides, these reactions were completed within 5 to 15 min.

All the synthesized N-alkyl and N-acyl 2-(4-thiazolyl)-1H-benzimidazoles products were characterized by their physical constants[4,17], comparative TLC with authentic samples and also newer compounds by p.m.r. and i.r.spectroscopic techniques.

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