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Alkylation of Benzimidazoles

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Abstract

Alkylated benzimidazoles have great medicinal value. By attaching specific alkyl groups to the core ring, chemists enhance its properties. As *N*-alkylated benzimidazoles are biologically active compounds and our interest in devising environmentally benign techniques**,** we have successfully carried out benzylation and methylation of benzimidazoles using benzylchloride and dimethyl sulfate.

Keywords: N-alkylated benzimidazoles, anti-bacterial, anti-fungal, microwave, solvent-free

Introduction

Benzimidazoles constitute an important class of heterocyclic compounds possessing a wide spectrum of biological activities.[1] This ring system is of considerable chemical and biological interest. Of these, *N*-alkylated derivatives have been found be the most potent. N-Alkylated benzimidazoles were screened for their anti-bacterial and anti-fungal activity.[2] These have also been extensively used as pesticides and anti-helmintics.[2] 2-Benzyl derivatives has also been used as analgesics.[4]

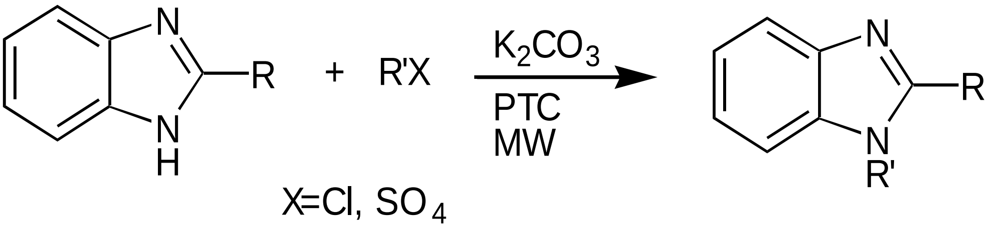
In 1957, a novel class of analgesics related to 2-benzyl benzimidazoles was reported. Some of these compounds were highly active, their potencies in animal tests far exceeding that of morphine and of any synthetic analgesics known at that time.[5] The action of these derivatives appears to be typically morphine like. In common with other classes, analgesics based upon 2-benzyl benzimidazoles possess a flat aromatic system linked to a 2-amino ethyl side chain via a non-hydrogen bearing atom. These features are considered essential for fit at the proposed analgesic receptor site.

Phillips[6] methylated 5(or6)-methyl benzimidazoles using methyl iodide and absolute methyl alcohol at 140^0 for 3 hrs and 5(or6) bromo-1,2-dimethyl benzimidazoles was synthesized by reduction of 4-bromo-2-nitromethyl aniline with tin and 5N HCl. Rao and Ratnam[7] synthesized 5-methyl, 5-chloro or 5-nitro-1-benzyl benzimidazoles and the corresponding 6-substituted 1-benzyl-2-phenyl benzimidazoles by the condensation of the appropriate *N*-benzyl-o-phenylenediamine with benzaldehyde in alcoholic nitrobenzene.

Jerchel et.al[8] prepared 1-benzyl-2-chloromethyl benzimidazoles by the condensation of *N*-benzyl-o-phenylenediamine dihydrochloride and chloroacetic acid in HCl. Reddy et.al[9] synthesized *N*-benzyl benzimidazoles by the condensation of *N*-benzyl-o-phenylenediamine with aromatic aldehydes in alcohol and nitrobenzene. Veeranagaiah et.al[10] prepared 1-benzyl-2-substituted benzimidazoles by the pyrolysis of 1,3-dibenzyl-2-substituted benzimidazolines. Reddy et.al[11] synthesized 1-methyl and 1-benzyl-2-aryl benzimidazoles by the pyrolysis of 1-methyl-3-substituted-2-aryl benzimidaz- olines and 1-benzyl-2-(p-methoxyphenyl)-3-(p-methoxy benzyl) benzimidazolines respectively.

Research Methodology

Keeping in view the importance of *N*-alkylated benzimidazoles as biologically active compounds and our interest in devising environmentally benign techniques**,** we have successfully carried out benzylation and methylation of benzimidazoles using benzylchloride and dimethyl sulfate with potassium carbonate-PTC (tetrabutylammonium bromide) respectively (**Table 1**).



R′X = Benzyl chloride and dimethylsulfate
PTC = Tetrabutyl ammonium bromide
Power= 300W

Table 1 **Benzylation, methylation and ethylation of benzimidazoles using benzyl chloride, dimethyl sulfate and diethyl sulfate potassium carbonate and TBAB (tetrabutyl ammonium bromide) (Power = 300W)**

Entry	R	R’	Reaction temp. (^{0}C)	Time (Min.)	Yield (%)	MP/Lit.MP (^{0}C)
1	CH_3	$CH_2C_6H_5$	70-72	6	50[a]	65-67/68-69
2	$CH=CHC_6H_5$	$CH_2C_6H_5$	120-22	24	60	160-65/166
3	p-$CH_3C_6H_4$	$CH_2C_6H_5$	55-57	2	53[a]	124-126/126.7
4	C_6H_5	$CH_2C_6H_5$	51-53	2	50[b]	129-131/133
5	p-$OCH_3C_6H_4$	$CH_2C_6H_5$	58-60	2	56[c]	133-136/135-6
6	p-ClC_6H_4	$CH_2C_6H_5$	50-52	2	71	130-35/137.5
7	CH_2 C_6H_5	$CH_2C_6H_5$	60-62	15	72	190-193/192
8	CH=CH C_6H_4Cl	CH_3	90-92	4	55[a]	140-42/145-6
9	CH_3	CH_3	170-172	6	56	111-13/113-14
10	C_6H_5	CH_3	100-02	3	52	90-94/97

a: column purified(100%pet.ether)
b: column purified(2% EtOAc in pet. ether)
c: column purified(5%EtOAc in pet. ether)

Discussions

In order to explore the possibility of non-thermal effects of microwave irradaition, reactions were carried out using thermostated oil-baths under similar conditions of time and temperature as for microwave–assisted method (**Table 2**).

Table 2**Comparison of results using microwave method and oil-bath for alkylation of benzimidazoles**

Entry	Method	Time	Temperature	Yield
(Min)	(^{0}C)	(%)		
1	MW	6	70-72	50
Δ 6	72		8	
52 72		34		
8	MW	4	90-92	55
Δ 4	92		6	
48 92		35		

Results

It has been found that significant lower yields were obtained using oil-bath heating than using MW assisted method under identical conditions of time and temperature. The observation demonstrate clearly that the effect of MW irradiation is not purely thermal.

The structures of the products were confirmed by ^{1}H NMR, mass spectra and comparison with authentic sample prepared by already reported methods.

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