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THE ADDITION REACTION OF METALATED 2-ALLYLOXYBENZIMIDAZOLES TO ALDEHYDES AND THE TRANSFORMATION OF THE ADDUCTS TO VINYLOXIRANES

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Treatment of 2-allyloxybenzimidazoles with butyllithium followed by cadmium iodide generates the metalated allylic ethers, which in turn react with aldehydes to form adducts selectively at α-carbon of the allylic ethers. The adducts are converted to vinyloxiranes in good yields on treatment with sodium hydride.

Since the introduction of strong bases such as butyllithium into organic chemistry much effort has been devoted to the generation of carbanions from various types of weakly acidic compounds such as allylic ethers. There appeared several reports on the reaction of the metalated allylic ethers, derived from alkyl allyl ethers, with carbonyl compounds1), and the resulting γ-adducts (enol ethers) were readily converted to the corresponding carbonyl compounds. On the contrary, the α-adducts have limited uses2) in organic synthesis mainly because of the difficulty in the further transformation such as the nucleophilic displacement of the alkyloxy group.

In our recent synthetic investigation using azaaromatic compounds, it was found that oxyazaaromatic groups are readily replaced by various nucleophiles. For example, 2-allyloxybenzimidazoles react with the copper salts of enamines to give the corresponding allylated products along with the elimination of 2-benzimidazolone3).

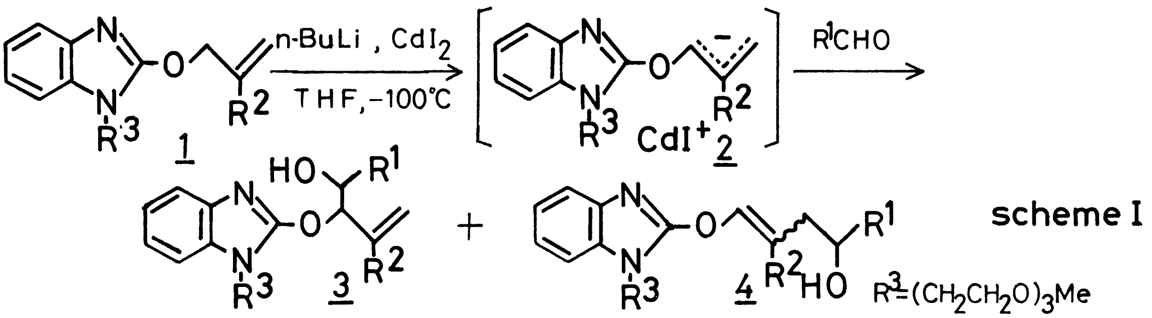
In this communication, we wish to report that the cadmium salts of the allylic ethers (2) derived from 2-allyloxybenzimidazoles (1), react with aldehydes to give selectively the α-adducts (3) in high yields as shown in the scheme I, and the adducts were then converted to vinyloxiranes (5).

At first, the reaction of lithiated allylic ether derived from 2-(2-propenyloxy)-1-(3,6,9-trioxadecyl)benzimidazole (1a) with aldehyde was tried and it was found that the γ-adduct (4) was produced exclusively. In order to obtain the α-adducts (3) selectively, several additives such as cadmium iodide, zinc bromide and magnesium bromide were screened, and it was found that the use of cadmium iodide gave the best result.

Next, the effect of the substituent at the nitrogen in benzimidazolyl group was examined, and as shown in Table I, the introduction of polyether structure plays an important role in increasing the amount of the α-adduct (3). These results were different from those obtained in the reaction of lithiated 2-allyloxybenzimidazoles with alkyl halides, in which case the effect of the substituent on the α/γ ratio was not so significant$^{4)}$.

Based on these observations, the lithiated allylic ethers (2) derived from 2-allyloxy-1-(3,6,9-trioxadecyl)benzimidazoles (1a) were allowed to react with various aldehydes in the presence of cadmium iodide, and it has become apparent that the α-adducts (3) were isolated regioselectively in good yields as listed in Table II.

A typical procedure is described for the reaction of 2-(2-propenyloxy)-1-(3,6,9-trioxadecyl)benzimidazole with benzaldehyde: To a THF (4 ml) solution of 2-(2-propenyloxy)-1-(3,6,9-trioxadecyl)benzimidazole (160 mg, 0.5 mmol) was added a hexane solution (0.37 ml) of butyllithium (0.6 mmol) at -100°C (a methanol-liquid nitrogen bath) under an argon atmosphere, and the mixture was stirred for 30 min to give a pale yellow solution. Then, a THF (5 ml) solution of cadmium iodide (440 mg, 1.2 mmol) was added and the mixture rapidly lost its color. After 30 min at -100°C, a THF (2 ml) solution of benzaldehyde (80 mg, 0.75 mmol) was added and the resulted solution was stirred overnight at -78°C. The reaction was quenched with a samll amount of ethanol and aqueous ammonium chloride. Then, an aqueous solution of sodium sulfide was added in order to remove cadmium salt as cadmium sulfide. The organic materials were extracted with ethyl acetate (3 times), and the combined extracts were dried over $MgSO_4$. 1-Phenyl-2-[1-(3,6,9-trioxadecyl)-benzimidazol-2-yloxy]-3-buten-1-ol (196 mg, 92%) and 1-phenyl-4-[1-(3,6,9-trioxadecyl)benzimidazol-2-yloxy]-3-buten-1-ol (12 mg, 6%) were isolated by thin layer chromatography (silica gel).



scheme I

Table I. The effect of the substituents at the nitrogen in the benzimidazolyl group (R^2=H).

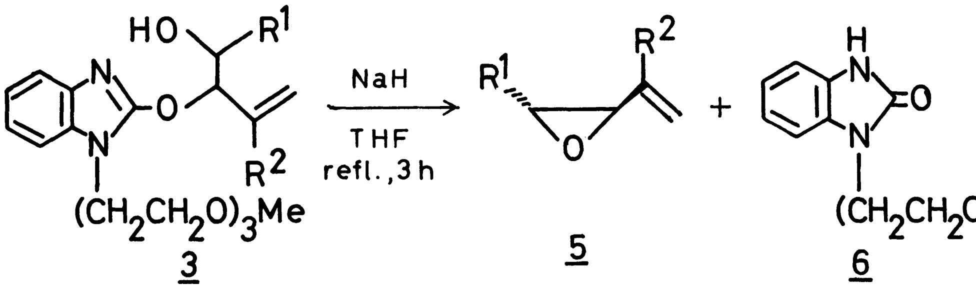
R^3	additive	R^1	3:4	Yield (%)
$(CH_2CH_2O)_3Me$ (1a)	$ZnBr_2$	Et	84:16	81
Me (1b)	$ZnBr_2$	Et	26:74	67
$(CH_2CH_2O)_3Me$ (1a)	CdI_2	$PhCH_2CH_2$	> 90:10	84
Me (1b)	CdI_2	$PhCH_2CH_2$	83:17	76
$n-C_{18}H_{37}$ (1c)	CdI_2	$PhCH_2CH_2$	67:33	63

Table II. The reaction of the metalated allylic ethers with aldehydes.

R^2	R^1	$\underline{3}$:$\underline{4}^{a)}$	Yield (%)
H	Et	> 95:5	71
	n-Am	> 90:10	87
	i-Pr	> 95:5	90
	Ph	94:6	98
	$PhCH_2CH_2$	> 90:10	84
	$CH_2=C(CH_3)$	66:34	87
Me	$PhCH_2CH_2$	> 90:10	86

a) All the products gave satisfactory NMR and IR spectra. For example, spectral data for 4-[1-(3,6,9-trioxadecyl)benzimidazol-2-yloxy]-5-hexen-3-ol are as follow: NMR($CDCl_3$) δ 1.01(3H,t,J=7Hz), 1.2-2.1(2H,m), 3.26(3H,s), 3.38(4H,s), 3.46(4H,s), 3.6-4.3(6H,m), 4.9-5.5(3H,m), 5.7-6.3(1H,m), 6.9-7.1(3H,m), 7.2-7.5(1H,m): IR(neat) 3400cm^{-1}.

The adducts thus obtained are useful synthetic intermidiates, and, for example, on treatment with sodium hydride, the corresponding vinyloxiranes ($\underline{5}$) were obtained in high yields along with 2-benzimidazolone ($\underline{6}$) as shown in the scheme II and Table III. It is noted that the trans oxiranes were formed stereoselectively, and none of peaks corresponding to the cis isomers were observed by NMR spectra.



scheme II

The following procedure was used for the synthesis of 3,4-epoxy-6-phenyl-1-hexene: The mixture of sodium hydride (12 mg, 0.5 mmol) and 1-phenyl-4-[1-(3,6,9-trioxadecyl)benzimidazol-2-yloxy]-5-buten-3-ol (160 mg, 0.35 mmol) was refluxed for 3h under an argon atmosphere. The reaction was quenched with aqueous ammonium chloride, and the organic materials were extracted with ether (3 times). The combined extracts were dried over $MgSO_4$, and the solvents were removed. The residue was chromatographed on silica gel to give 3,4-epoxy-6-phenyl-1-hexene (56 mg, 91%).

Table III. The formation of vinyloxiranes.

R^1	R^2	Yield (%)[a]
$PhCH_2CH_2$	Me	95[b]
$PhCH_2CH_2$	H	91[c]
Ph	H	82[b]

a) All the products gave satisfactory NMR and IR spectra. For example, spectral data for 3,4-epoxy-2-methyl-6-phenyl-1-hexene are as follow: NMR($CDCl_3$) δ 1.57(3H,s), 1.6-2.0(2H,m), 2.6-2.9(3H,m), 2.97(1H,d,J=2Hz), 4.8-5.0(2H,m), 7.08(5H,s); IR(neat) 890, 900cm^{-1}.

b) The product showed single peak by GLC analysis.

c) About 3% of unknown product was detected by GLC analysis.

Of several methods reported for the preparation of vinyloxiranes by carbon-carbon bond formation5),6), only the alkylidene transfer reaction from sulfur or selenium ylids to α,β-unsaturated ketones or aldehydes5) has been known as a synthetically useful method.

It should be noted that the present process provides an alternative efficient method for the stereoselective preparation of vinyloxiranes starting from aldehydes and 2-allyloxybenzimidazoles, readily prepared from allyl alcohols.

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