THE PREPARATION OF α,β-UNSATURATED KETONES BY THE GRIGNARD REACTION WITH β-(N-ALKYL-N-ACYLAMINO)ENONES

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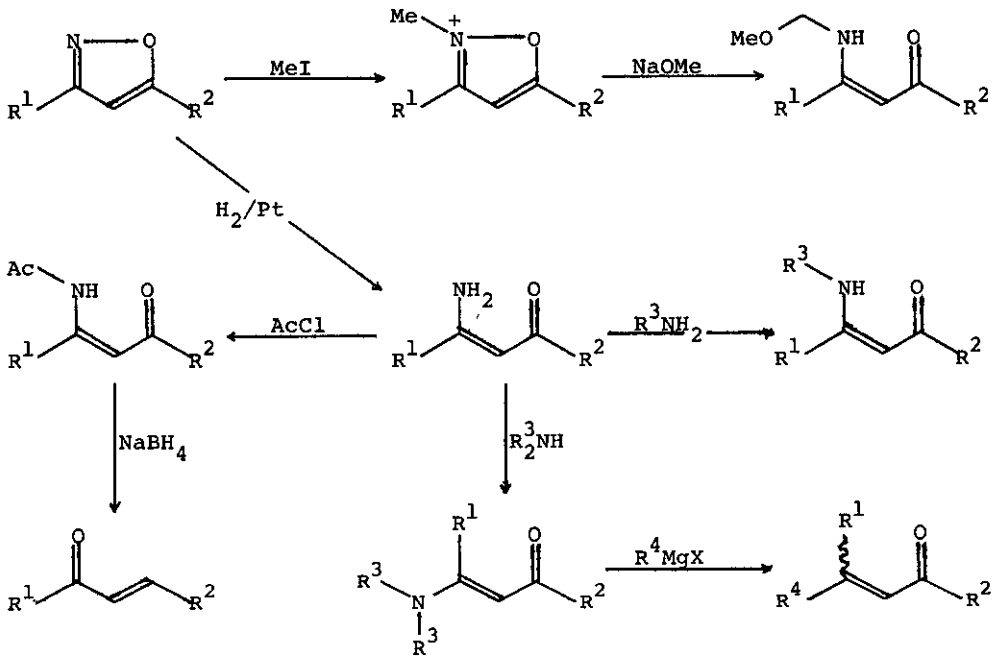
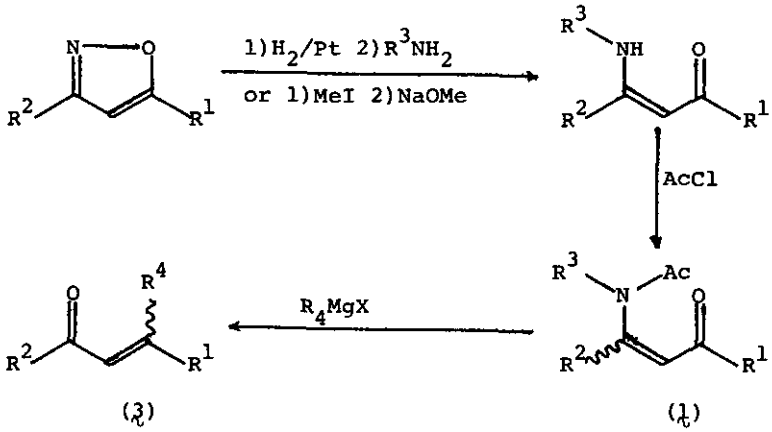
Abstract——The Grignard reaction of β-(N-alkyl-N-acylamino)enones afforded regioselectively α,β-unsaturated β-(N-alkyl-N-acylamino)-alcohols, which were converted into α,β-unsaturated ketones by hydrolysis accompanying dehydration. The resulting α,β-unsaturated ketones were regioisomeric with α,β-unsaturated ketones derived from β-(N,N-dialkylamino)enones by the Grignard reaction.

Recently we have succeeded in the preparation of isoxazoles having the different substituent groups on C-3 and C-5 position.[1] Isoxazole ring is easily cleaved into β-aminoenones by hydrogenation of isoxazoles[2] or the reaction of corresponding 2-methylisoxazolium salts with sodium methoxide.[3] For the sake of the extension of the synthetic utilities of isoxazoles, we have investigated the chemical properties of β-aminoenones. By the treatment with acyl chloride at low temperature, acylation of β-aminoenones is possible to control at nitrogen atom.[4] Further, the reactivity[5] and regioselectivity[6] of N-substituted β-aminoenones with various nucleophiles are dependent on the properties of N-substituent groups. The β-aminoenones having the electron-donating group on nitrogen react with nucleophiles at β-carbon, while β-aminoenones having the electron-withdrawing group react at carbonyl carbon. Although N-unsubstituted or N-monosubstituted β-aminoenones do not react with Grignard reagents, β-(N,N-dialkylamino)enones regioselectively afford the α,β-unsaturated ketones by the reaction with Grignard reagents at β-position.[7] Therefore, the Grignard reaction of β-(N-alkyl-N-acylamino)enones, which had the electron-deficient nitrogen on β-position, was carried out.



As a typical example, 3-(N-butylacetamido)-1-phenyl-2-buten-1-one (1a) was treated with methylmagnesium iodide. From the ir (3400, 2950, 1620 and 1400 cm^{-1}) and the nmr spectra [δ= 0.9 (t, 3H), 1.2-1.7 (m, 6H), 1.65 (s, 6H), 1.90 (s, 3H), 5.75 (s, 1H) and 7.1-7.5 ppm (m, 5H)], the product was found to be 4-(N-butylacetamido)-2-phenyl-3-penten-2-ol (2a) which was hydrolyzed without isolation by hydrochloric acid to give 4-phenyl-3-penten-2-one (3a) in 50 % yield based on 1a. This α,β-unsaturated ketone 3a was regioisomeric with 3-methyl-1-phenyl-2-buten-1-one (4a), which was obtained by the reaction of 3-(N,N-dimethylamino)-1-phenyl-2-buten-1-one with methylmagnesium iodide. Similarly, some β-(N-alkyl-N-acylamino)enones were treated with Grignard reagents to afford α,β-unsaturated ketones listed in Table.

From these results, the Grignard reagents seemed to attack on carbonyl carbon of β-(N-alkyl-N-acylamino)enones to afford α,β-unsaturated ketones, while the Grignard reagents attacked on β-carbon of β-(N,N-dialkylamino)enones. Thus isoxazoles having a various substituent group on C-3 and C-5 carbons are concluded to be useful precursor for the preparation of α,β-unsaturated ketones via β-aminoenones.



(3) (1)

R^1=Me, Pr, Ph R^2=Me, Ph R^3=Me, Bu, CH_2OMe R^4=Me, Pr, Ph

Table

Starting Material				Reactant	Product	Yield*
	R^1	R^2	R^3	(R^4MgX)		(%)
1a	Ph	Me	Bu	MeMgI	4-Phenyl-3-penten-2-one	50
1b	Ph	Me	Me	MeMgI	4-Phenyl-3-penten-2-one	44
1b	Ph	Me	Me	PhMgBr	4,4-Diphenyl-3-buten-2-one	71
1c	Me	Me	Me	MeMgI	4-Methyl-3-penten-2-one	83
1c	Me	Me	Me	PhMgBr	4-Phenyl-3-penten-2-one	80
1c	Me	Me	Me	PrMgBr	4-Methyl-3-hepten-2-one	86
1d	Pr	Me	Me	MeMgI	4-Methyl-3-hepten-2-one	46
1e	Me	Ph	Me	MeMgI	3-Methyl-1-phenyl-2-buten-1-one	43
1e	Me	Ph	Me	PhMgBr	1,3-Diphenyl-2-buten-1-one	54
1f	Me	Me	$MeOCH_2$	MeMgI	4-Methyl-3-penten-2-one	92
1g	Pr	Me	$MeOCH_2$	MeMgI	4-Methyl-3-hepten-2-one	40

* Yields of products were based on β-(N-alkyl-N-acylamino)enones (1).

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