A Facile Route to Acylated 1, 2, 4-Oxadiazole Derivatives

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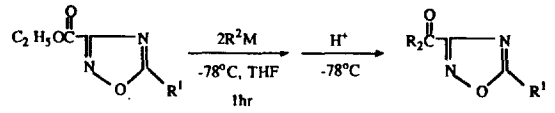
The 1, 2, 4-oxadiazole structure in heterocyclic chemistry is a quite important framework because the various derivatives have been found to possess biological activities, especially, in drugs and pesticides[1]. Although numerous synthetic routes to 3, 5-disubstituted 1, 2, 4-oxadiazoles, which are prepared mainly *via* the condensation of amidoximes with carboxylic acid derivatives[2] or *via* the dipolar cycloaddition of nitrile oxides to nitriles[3], have been found, efficient general procedures for the synthesis of 3 or 5-acyl-1, 2, 4-oxadiazoles have not yet been developed. The easy attack of hydroxylamine toward the acyl group of acyl cyanides in the preparation of the corresponding amidoximes accounts for the lack of the reports concerning about 3 or 5-acyl-1, 2, 4-oxadiazoles.

In spite of the synthetic usefulness[4-7] of 3 or 5-acyl-1, 2, 4-oxadiazoles, which involves the chemical transformation of carbonyl group to other functional groups[4,5] and thermal rearrangement[6,7] of corresponding oximes or hydrazones to other heterocyclic compounds, there are only three reports on the synthesis of 3 or 5-acyl-1, 2, 4-oxadiazoles: (1) reaction of 2-aminoimidazoles with nitrous acid followed by heating in water[4], (2) hydrolysis and recyclization of nitrosoimidazoles[8], and (3) reaction of N-(1, 1-diethoxyacetylated)-amidine with hydroxylamine.[9] However, these methods lack generality[4,8,9], result in low chemical yield[9] and utilize starting material which is not easily accessible[8]. In this communication we outline a facile and general synthetic route to 3 or 5-acyl-1, 2, 4-oxadiazole derivatives.

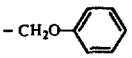
3-Ethoxycarbonyl-1, 2, 4-oxadiazoles **1**, which are easily prepared from the reaction of ethoxycarbonyl formamidoxime[10] with acyl chlorides, were found to react with various Grignard reagents (2 eq.) at −78℃ to afford the corresponding 3-acyl-1, 2, 4-oxadiazoles **2** in moderate to excellent yields. The use of the alkyllithium reagents instead of alkyl Grignard reagents provided the corresponding products in less than 10% yields and mainly caused decomposition. Whereas the use of acetylenic lithium reagent provided the corresponding product in moderate yield, the reaction of **1** with acetylenic Grignard reagent did not occur at all under the same reaction condition. The results of these reactions are summarized in Table 1.

It was interesting to note that the carbinols **4** arising from attack of organomagnesium/lithium reagent on the carbonyl compounds **2** could not be detected. The selectivity of the reaction to give only ketones **2** appears to be due to the relative stability of the intermediate metalated hemiketals **3** in which magnesium or lithium metal may coordinate with a nitrogen of the ring system[11,12]. In order to investigate the stability of intermediate metalated hemiketals **3** depending on temperature, a variation of the reaction conditions

Table 1. Reactions of 3-Ethoxycarbonyloxadiazoles with Organometallic reagents

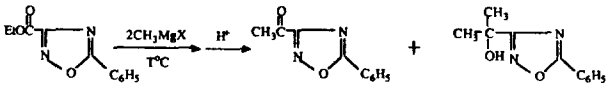


1 **2**

R^1	R^2M	Yield(%)[a]
	CH_3MgBr	87
	$n\text{-}C_3H_7MgBr$	85
	C_6H_5MgBr	81
	$C_6H_5CH_2MgBr$	84
	$C_3H_7C{\equiv}CMgBr$	no reaction
	$C_3H_7C{\equiv}CLi$	52
	CH_3MgBr	82
	$n\text{-}C_3H_7MgBr$	80
	$n\text{-}C_4H_9MgBr$	80
	$n\text{-}C_4H_9Li$	9
	C_6H_5MgBr	76
	$C_6H_5CH_2MgBr$	83
	$C_3H_7C{\equiv}CLi$	44

[a]Isolated yield.

Table 2. Reaction of 3-Ethoxycarbonyloxadiazole with Methylmagnesium Halide under Various Temperature Conditions

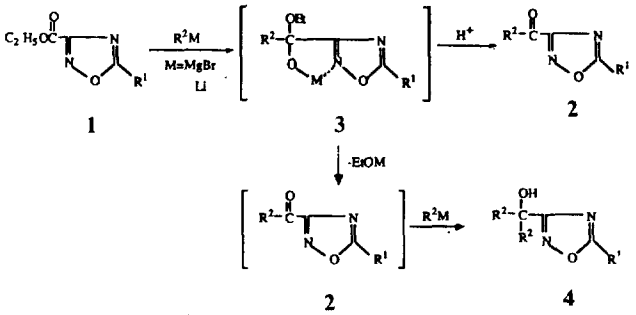


2a **4a**

T(℃)	Reaction Time(hr)	Yield(%)[a]	**2a:4a**[b]
−78	1	82	100:0
−78	3	82	100:0
−78/−30	1/1	80	78:22
−78/0	1/1	70	50:50

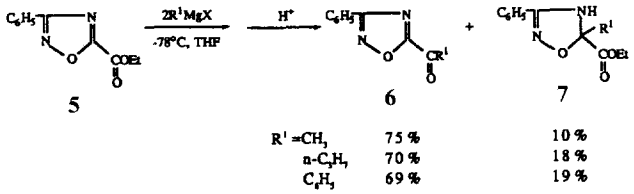
[a]Isolated yield. [b]Ratio was obtained from isolated yield of each compounds.

was employed. Thus, when the reaction was carried out at −78℃ followed by warming slowly, a mixture of ketone **2a** and carbinol **4a** was obtained (Table 2). As can be seen from Table 2, higher yield of the carbinol **4a** was derived from the reaction at higher temperature.



1 **3** **2** **2** **4**

5-Acyl-1, 2, 4-oxadiazoles **6** can also be prepared in a similar manner from the reaction of 5-ethoxycarbonyl-1, 2, 4-oxadiazole **5**[2a] with organomagnesium reagents. In contrast to the previous reaction for the preparation of 3-acyl-1, 2, 4-oxadiazole, which provided only one product, the reaction of **5** with Grignard reagents provided adduct **7** occured at 4-double bond of oxadiazole along with adduct **6**. The formation of **7** may be rationalized by the greater resonance effect of negative charge on 4-nitrogen as compared with that on 2-nitrogen. The similar result was observed in the rection of 3-methyl-5-phenyl-1, 2, 4-oxadiazole with n-BuLi[13].



In a typical procedure, a 50 m*l* two-neck flask, equipped with a septum port, a magnetic stir bar, and a nitrogen tee connected to a source of nitrogen, was charged with 3-ethoxycarbonyl-5-phenyl-1, 2, 4-oxadiazole (0.654 g, 3 mmole) and 30 m*l* dry THF. The reaction mixture was cooled to −78℃ by using Dry-Ice/isopropanol slush and 3 m*l* (6 mmole) of propylmagnesium chloride (2 M solution) was added dropwise at −78℃. After stirring at −78℃ for 1 hour, the reaction mixture was quenched with HCl saturated ether solution. The mixture was poured into 30 m*l* of H_2O, extracted with ether (30 m*l*×2) and dried the ether layer with anhydrous $MgSO_4$. Column chromatography (25% ethylacetate in hexane) provided 0.55 g (85% yield) of 3-butanoly-5-phenyl-1, 2, 4-oxadiazole: mp 38-39℃; ^{1}H NMR ($CDCl_3$) δ 8.25-7.90 (m, 2H) , 7.60-7.27 (m, 3H) , 3.05 (t, J=7.3 Hz, 2H), 1.80 (m, J=7.3 Hz, 2H), 1.02 (t, J=7.3 Hz, 3H); IR (KBr) 1705 (C=O); MS 216 (M^+, parent ion).

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Sodium Halates-Halotrimethylsilanes. New Reagents for Aromatic Halogenation Reactions

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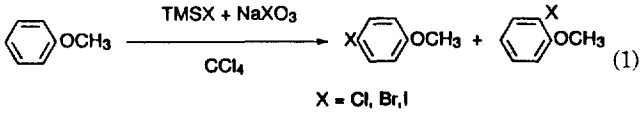
There have been many recent reports on the halogenation of aromatic compounds using inorganic halogen compounds in the presence of various oxidizing agents[1]. Nitric acid[2], hydrogen peroxide and peracids[3], halates and perhalates[4], and transition metal compounds of higher oxidation states[5] are among such oxidizing agents used for this purpose.

In connection with the continued search for the new reagents utilizing each pairs of inorganic compounds and halotrimethylsilanes[6], we found that sodium chlorate, bromate and iodate in combination with the corresponding halotrimethylsilane serves as efficient halogenating agents. We now wish to report our preliminary results on nuclear halogenation reactions of aromatic compounds using these pairs of reagents.



(1)

When one to the three equivalents of chlorotrimethylsilane were reacted with the 3:1 mixture of toluene and sodium chlorate in dichloromethane at room temperature, a mixture of *o*- and *p*-chlorotoluene was formed. The ratio of the *o*- and *p*-chlorotoluene turned out to be 35:66 and did not vary significantly depending upon the ratio of sodium halate and halotrimethylsilane. Similar *o*- and *p*- isomeric ratios were exhibited for chlorinations of toluene by Cl_2-Fe pair or sulfuryl chloride as the chlorinating agent[7]. Little or no side chain chlorination was observed. Various xylenes produced expected monochloroxylene. Introduction of the second chlorine into the aromatic rings turned out to be much more difficult than the first chlorination. Anisole also reacted with chloro-