Convenient Method for the Preparation of β-Keto Esters Using 2-Pyridyl Esters

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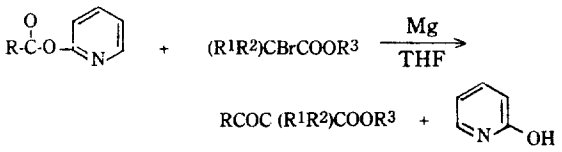
During studies on the synthetic utility of active esters containing 2-pyridyl moiety,[1-2] we have found that Reformatsky reaction could be carried out effectively by 2-pyridyl esters and magnesium. Although various methods[3-5] have been reported for β-keto ester synthesis with Reformatsky reagents,[6] their synthetic applications are sometimes limited due to low yields, competing side reactions, and operational problems. It seems that the success of β-keto ester synthesis depends largely on the nature of acyl derivatives, α-bromoesters, and metals employed.

We now wish to report a convenient method for the preparation of β-keto esters using 2-pyridyl esters and α-bromoesters in the presence of magnesium. The reaction was carried out conveniently by addition of α-bromoesters to a mixture of 2-pyridyl esters and magnesium[7] in tetrahydrofuran. The reaction was normally complete within 3 h with accompanying the precipitate.



Some experimental results were summarized in Table I. Although reaction of α-bromoesters such as ethyl bromoacetate and ethyl 2-bromopropionate with 2-pyridyl benzoate gave a small amount of side products, the present method is generally applicable to preparation of several structurally different β-keto esters. The use of hindered bromoesters such as t-butyl 2-bromopropionate, ethyl 2-bromo-3-methylbutyrate, and ethyl 2-bromoisobutyrate overcomes this difficulty by retarding the self-condensation of α-bromoesters and gave better yields without appreciable side products. Thus, the presence of sterically hindered alkyl group in the alpha or O-alkyl position of α-bromoester seems to be a requisite for high yield β-keto ester formation under the present reaction conditions. Furthermore, the reaction of α-bromoesters with 2-pyridyl esters having bromide and ester functional groups afforded the corresponding β-keto esters without damage to these functional groups.

Compared with previous results,[3-5] the present method appeared to be relatively clean without appreciable side reactions. This seems to result in the formation of six-membered chelate, which decomposes into β-keto ester and magnesium (2-pyridyloxy)bromide, between 2-pyridyl ester and bromomagnesium enolate.

Table 1. Preparation of β-Keto Esters from 2-Pyridyl Esters and α-Bromoesters in the Presence of Magnesium[a]

$$\text{R-COO-2-Py} + (R^1R^2)CBrCOOR^3 \xrightarrow[THF]{Mg} RCOC(R^1R^2)COOR^3$$

R-COO-2-Py R	$(R^1R^2)CBrCOOR^3$ R^1	R^2	R^3	Yield, %[b]
CH_3CH_2	H	Me_2CH	Et	73
$(CH_3)_2CHCH_2$	H	Me_2CH	Et	76
$(CH_3)_2CHCH_2CH_2$	H	Me	t-Bu	80
$(CH_3)_2CH$	Me	Me	Et	83
C_6H_5	H	H	Et	55
	H	Me	Et	72[c]
	Me	Me	Et	92
$(CH_3)_3C$	H	Me	t-Bu	78
2,4,6-$(CH_3)_3$-C_6H_2	Me	Me	Et	91
$MeOOC(CH_2)_4$	Me	Me	Et	86
$Br(CH_2)_5$	Me	Me	Et	85

[a] The reaction was carried out with 1 equiv of 2-pyridyl ester and 1-1.1 equiv of α-bromoester at room temperature for 1-3 h. [b] All products were isolated by silica gel TLC or distillation (Kugelrohr) and their structures were consistent with all spectral analyses. [c] Ethyl benzoate and diethyl 2,4-dimethyl-3-phenyl-3-hydroxy glutarate were also isolated in 5% and 6% yield, respectively.

In conclusion, this method provides a useful alternative to currently available methods in terms of mild conditions, easy operations, and high yields.

The typical experimental procedure is as follows. To a mixture solution of 2-pyridyl benzoate (398.4 mg, 2 mmol) and magnesium (53.5 mg, 2.2 mmol) in tetrahydrofuran (6 m*l*) at room temperature under nitrogen was added ethyl 2-bromoisobutyrate (294 u*l*, 2 mmol). After being stirred for 1 h at room temperature, reaction mixture was quenched with saturated NH_4Cl and extracted with methylene chloride (30 m*l*) three times. The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated to dryness under vacuum. The crude product was purified by distillation with a Kugelrohr apparatus to give ethyl 2,2-dimethyl benzoylacetate in 92% yield. Bp 91-95°C/1.7 mm [lit.[4] 151-152°C (15 mm)]; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, J = 7 Hz), 1.67 (s, 6H), 4.18 (q, 2H, J = 7 Hz), 7.15-7.60 (m, 3H), 7.72-8.00 (m, 2H); IR (film) 1690, 1740 cm^{-1}.

Acknowledgement. We gratefully acknowledge financial support from Korea Science and Engineering Foundation.

References

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7. Zinc was less effective than magnesium. The reaction of 2-pyridyl isobutyrate with ethyl 2-bromoisobutyrate proceeded slowly and required 7 h for completion of the reaction. Furthermore, the reaction of 2-pyridyl benzoate with ethyl 2-bromoisobutyrate afforded the product in only 10% yield for 6 h with recovery of 2-pyridyl benzoate in 86% yield.

Remarkable Effects of Lithium Salt in Grignard Reaction

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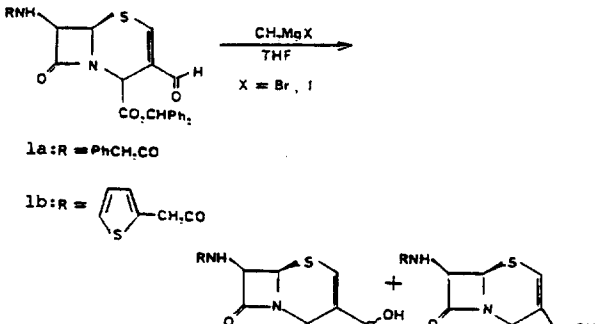
During our ongoing efforts to develop new antibiotics, we discovered remarkable effects of lithium salt in Grignard reaction. We needed compound **2a** as a key intermediate for new compounds which had broad spectrum antibacterial activities. Preparation of the compound **2b** from corresponding aldehyde **1b** was documented in the literature[1]. However, when we tried this transformation of **1a**, we isolated less than 30% of a mixture of diastereoisomeric carbinols **2a** with 50% of lactone **3a** and 10% of recovered starting material **1a** under the optimized condition (e.g. 5 equivalents of Grignard reagent $-CH_3MgBr$ or CH_3MgI- at -78°C).[2]



2 a,b **3** a,b

It was believed that an alkoxide which was generated *in situ* by addition of Grignard reagent to aldehyde at C-3 attacked ester at C-4 to form lactone **3a**. In order to obtain considerable amount of key intermediate-compound **2a**, we were looking for a condition to surpress lactone formation and facilitate the addition to completion.

Trimethylsilyl chloride was known to activate carbonyl groups for various nucleophilic attack. Recently, it was elegantly employed to promote 1,4-addition of cuprate by different researchers.[3] It was also known that it did not react with cuprate[3a] at -78°C. We expected that it might trap the resulting alkoxide from Grignard reaction and also facilitate the addition by activation of carbonyl group. We tried the reaction with 2 equivalents of trimethylsilyl chloride and 7 equivalents of Grignard reagent at -78°C. Under this condition, we isolated 40% of desired carbinols **2a** and 50% of lactone **3a**. We could not detect any starting meterial **1a**. It showed that trimethylsilyl chloride promoted addition but failed to trap the alkoxide to prevent lactone formation. We changed ratios of reagents but obtained similar results. From these results, we turned out attention to more effective reagents. Lithium salts were widely used for stereoselective aldol condensations[4] and regioselective enolate formations.[5] They were also used to control E and Z geometry in Wittig reaction.[6] Lithium cation was known to tightly coordinate with oxygen atom. When we tried reaction with 7 equivalents of anhydrous lithium chloride and 7 equivalents of Grignard reagent, we obtained remarkable result. There was no starting material remaining. We isolated 80% of desired carbinols **2a** and less than 5% of lactone **3a**. We increased the amount of lithium chloride but obtained almost the same result.

It was believed that lithium cation was very effectively coordinated to oxygen atom at carbonyl group to prevent lactone formation and also to facilitate the addition to completions. From these results, we expected that methyllithium might give similar results. However, when we tried reaction with methyllithium. We observed that methyllithium attacked both aldehyde and ester function to give no desired carbinols. We are presently looking for possible extention of the reaction.

References and Notes

1. Spry, D. O. United States Patent, 1977, 4,012380.
2. All yields refer to isolated products and all new compounds gave satisfactory spectral data.
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