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단 신

에틸 2-피리딜 옥살레이트를 이용한 α-케토 에스터의 간편한 합성

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A Convenient Synthesis of α-Keto Esters Using Ethyl 2-Pyridyl Oxalate

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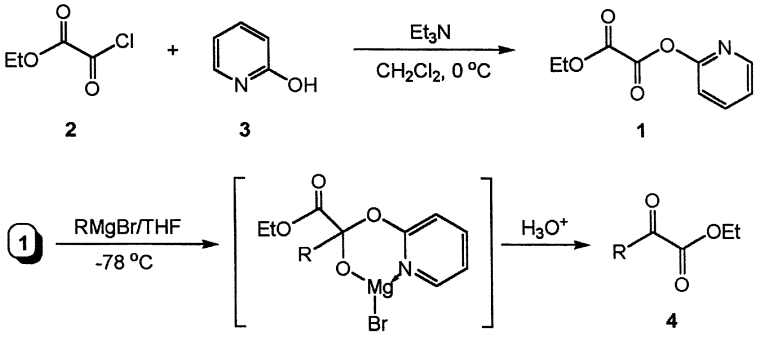
α-Keto esters have attracted interest as precursors of α-keto acids, which play important roles in the biosynthesis of amino acids and enzyme inhibitors.[1] The general methods for the synthesis of α-keto esters involve direct coupling between Grignard or organolithium reagents and derivatives of oxalic esters.[2] The reaction of triethoxyacetonitrile with organolithium reagents leads to the formation of α-keto esters after acidic hydrolysis, but Grignard reagents provide esters.[3] The treatment of alkyl α-oxo-1*H*-imidazole-1-acetates[4] or diethyl oxalate[5] with Grignard reagents affords the corresponding α-keto esters in mild conditions. However, these imidazolides gave low yields when alkyl Grignard reagents were used and the reaction of diethyl oxalate with Grignard reagents required excess oxalate. The preparation of α-oxo alkynoates was successful by the reaction of monoethyloxalic acid-*N*-methoxy-*N*-methylamide[6] and alkynyl lithium reagents, but the corresponding reaction was fruitless when diethyl oxalate or ethyl α-oxo-1*H*-imidazole-1-acetate was used. The cross-coupling reaction of methyl oxalyl chloride[7] with organocopper reagents and the addition of Grignard reagents to 1-[*N*-(alkoxyoxalyl)-*N*-methylamino]-3-methylimidazolium iodides[8] produce the corresponding α-keto esters, but the separation of products is often tedious and the availability of these imidazolium salts is limited. It has also been reported that oxidation of dimethyl hydrazone,[9] ozonolysis of methyl acrylate/reduction with Ph_3P[10] or ethyl 3-hydroxy acrylate derivatives,[11] and oxidative cleavage of cyanoketophosphoranes/subsequent trapping with alcohol[12] could produce α-keto esters, but these routes require for multi-step. In this paper we wish to report that α-keto esters can be conveniently prepared by the treatment of ethyl 2-pyridyl oxalate with Grignard reagents in a one-step.

EXPERIMENTAL

Preparation of ethyl 2-pyridyl oxalate (1). To a solution of ethyl chlorooxoacetate (1.5 mL, 13.4 mmol) in methylene chloride (15 mL) was slowly added a solution of 2-hydroxypyridine (1.28 g, 13.4 mmol) and triethylamine (1.9 mL, 13.6 mmol) in methylene chloride (25 mL) at 0 °C. After stirring for 0.5 h, methylene chloride was evaporated *in vacuo* and the mixture was dissolved in dry tetrahydrofuran, followed by filtering off triethylamine

hydrochloride. The condensed filtrate was purified by Kugelrohr vacuum distillation to afford **1** (2.52 g, 96%) as a colorless liquid. B.p. 118-123 °C/0.3 mm Hg: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J*=7.4 Hz, 1H), 7.39-7.45 (m, 1H), 6.57 (d, *J*=9.3 Hz, 1H), 6.33-6.37 (m, 1H), 4.45 (q, *J*=7.5 Hz, 2H), 1.41 (t, *J*=7.5 Hz, 3H); FT-IR (film) 3060, 2985, 1753 (**CO**O-2-Py), 1730 (**CO**OEt), 1620, 1468, 1182, 764 cm^{-1}; Ms *m*/*z*(%) 195(M$^+$, 7), 150(5), 101(6), 96(8), 95(100), 86(21), 67(74).

Preparation of ethyl 2-oxo-2-(*p*-methylphenyl)acetate (4c) <typical procedure>. To a solution of ethyl 2-pyridyl oxalate (586 mg, 3.0 mmol) in tetrahydrofuran (25 mL) cooled to -78 °C under argon was added dropwise a solution of *p*-methylphenylmagnesium bromide (15.0 mL, 0.2 M in THF, 3.0 mmol) *via* cannula over 45 min. After stirring for 0.5 h at -78 °C, the reaction mixture was quenched with saturated NH_4Cl (2 mL). Tetrahydrofuran was evaporated *in vacuo* and the reaction mixture was extracted with methylene chloride (3×20 mL) and washed with saturated NH_4Cl (20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The crude product was purified by Kugelrohr vacuum distillation to give **4c** (415 mg, 72%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 4.45 (q, *J*=7.2 Hz, 2H), 2.44 (s, 3H), 1.43 (t, *J*=7.2 Hz, 3H); FT-IR (film) 3054, 2984, 1736 (**CO**O), 1681 (CO), 1606, 1446, 1175, 1024, 827 cm^{-1}; Ms *m*/*z*(%) 192(M$^+$, 1), 120(12), 119(100), 91(45), 65(16). Spectral data, **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01-8.04 (m, 2H), 7.65-7.67 (m, 1H), 7.50-7.55 (m, 2H), 4.44 (q, *J*=7.2 Hz, 2H), 1.44 (t, *J*=7.2 Hz, 3H); FT-IR (film) 3066, 2985, 1736 (**CO**O), 1688 (CO), 1597, 1451, 1201, 1017, 741, 689 cm^{-1}; Ms *m*/*z*(%) 178(M$^+$, 1), 150(5), 106(10), 105(100), 77(46). **4b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J*=7.8 Hz, 1H), 7.48-7.53 (m, 1H), 7.31-7.36 (m, 2H), 4.45 (q, *J*=7.2 Hz, 2H), 2.63 (s, 3H), 1.43 (t, *J*=7.2 Hz, 3H); FT-IR (film) 3064, 2983, 1736 (**CO**O), 1682 (CO), 1601, 1457, 1195, 1017, 729 cm^{-1}; Ms *m*/*z*(%) 192(M$^+$, 2), 120(11), 119(100), 91(50), 65(16). **4d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J*=8.7 Hz, 2H), 6.97 (d, *J*=8.7 Hz, 2H), 4.44 (q, *J*=7.2 Hz, 2H), 3.89 (s, 3H), 1.43 (t, *J*=7.2 Hz, 3H); FT-IR (film) 3068, 2983, 1735 (**CO**O), 1675 (CO), 1600, 1511, 1209, 1020, 840 cm^{-1}; Ms *m*/*z*(%) 208(M$^+$, 3), 136(14), 135(100), 107(12), 92(16), 77(18). **4e:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J*=6.9 Hz, 2H), 7.49 (d, *J*=6.9 Hz, 2H), 4.45 (q, *J*=7.2 Hz, 2H), 1.42 (t, *J*=7.2 Hz, 3H); FT-IR (film) 3080, 2985, 1736 (**CO**O), 1687 (CO), 1589, 1494, 1202, 1013, 830 cm^{-1}; Ms *m*/*z*(%) 212(M$^+$, 1), 141(35), 139(100), 113(11), 111(33), 75(17). **4f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J*=9.0 Hz, 1H), 7.08 (d, *J*=9.0 Hz, 2H), 4.38 (q, *J*=7.2 Hz, 2H), 2.27 (s, 6H), 1.42 (t, *J*=7.2 Hz, 3H); FT-IR (film) 3063, 2983, 1732 (**CO**O), 1675 (CO), 1595, 1465, 1195, 1020, 776 cm^{-1}; Ms *m*/*z*(%) 206(M$^+$, 1), 134(13), 133(100), 105(42), 77(15). **4g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (d, *J*=8.1 Hz, 1H), 8.09 (d, *J*=8.1 Hz, 1H), 7.97 (d, *J*=7.2 Hz, 1H), 7.89 (d, *J*=7.5 Hz, 1H), 7.65-7.69 (m, 2H), 7.50-7.57 (m, 1H), 4.48 (q, *J*=7.2 Hz, 2H), 1.43 (t, *J*=7.2 Hz, 3H); FT-IR (film) 3053, 2983, 1730 (**CO**O), 1668 (CO), 1593, 1462, 1371, 1165, 1073, 774 cm^{-1}; Ms *m*/*z*(%) 228(M$^+$, 11), 156(15), 155(100), 127(69), 126(14). **4h**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.29 (m, 2H), 7.16-7.22 (m, 3H), 4.30 (q, *J*=7.2 Hz, 2H), 2.85 (t, *J*=7.2 Hz, 2H), 2.67 (t, *J*=7.2 Hz, 2H), 1.99 (quintet, *J*=7.5 Hz, 2H), 1.35 (t, *J*=7.2 Hz, 3H); FT-IR (film) 3063, 2986, 2939, 1728 (slightly broad, overlapped **CO**O & CO), 1454, 1069, 749, 701 cm^{-1}; Ms *m*/*z*(%) 220(M$^+$, 2), 202(30), 147(87), 129(23), 104(40), 91(100). **4i**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (t, *J*=7.2 Hz, 2H), 2.83 (t, *J*=7.2 Hz, 2H), 1.57-1.63 (m, 2H), 1.27-1.39 (m, 10H), 1.37 (t, *J*=7.2 Hz, 3H), 0.88 (t, *J*=6.7 Hz, 3H); FT-IR (film) 2983, 2934, 2856, 1726 (slightly broad, overlapped **CO**O & CO), 1450, 1274, 1068 cm^{-1}; Ms *m*/*z*(%) 214(M$^+$, 2), 142(11), 141(100), 71(39), 57(40). **4j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (q, *J*=7.2 Hz, 2H), 3.00-3.03 (m, 1H), 1.78-1.90 (m, 6H), 1.30-1.37 (m, 4H), 1.35 (t, *J*=7.2 Hz, 3H); FT-IR (film) 2934, 2856, 1726 (slightly broad, overlapped **CO**O & CO), 1450, 1273, 1067 cm^{-1}; Ms *m*/*z*(%) 184 (M$^+$, 3), 111(39), 84(7), 83(100), 55(43).



Scheme 1

RESULTS AND DISCUSSION

Ethyl 2-pyridyl oxalate (**1**) was prepared by the addition of a solution of 2-hydroxypyridine (**3**) and triethylamine to ethyl chlorooxoacetate (**2**) in methylene chloride at 0 ℃ (*Scheme* 1). After completion of the reaction, methylene chloride was evaporated under vacuum and the reaction mixture was dissolved in dry tetrahydrofuran, followed by filtering off triethylamine hydrochloride. The condensed residue was purified by vacuum distillation (Kugelrohr) to afford **1** in 96% yield as a colorless liquid. The reagent **1** could be stored in a refrigerator for several weeks without any decomposition.

The preparation of α-keto esters was conveniently carried out by the addition of Grignard reagents to an equimolar amount of **1** in a one-step. For instance, the treatment of **1** with 1 equiv of *p*-methoxyphenylmagnesium bromide at -78 ℃ over 45 min afforded ethyl 2-oxo-2-(*p*-methoxyphenyl) acetate (**4d**) in 69% yield. Although ethyl 2-hydroxy-2,2-di(*p*-methoxyphenyl)acetate was formed by the overaddition of *p*-methoxyphenylmagnesium bromide as a side product (7%) during the reaction, it was easily separated by vacuum distillation. The success of this reaction is presumably due to the fact that 6-membered chelate between magnesium of Grignard reagent and oxygen/ring nitrogen atom of **1** is partially formed by the preferential attack of Grignard reagent to the carbon atom of carbopyridyloxy group even in the presence of electron-withdrawing carboethoxy group.

As shown in *Table* 1, various α-keto esters were conveniently prepared by this method in high yields. Especially, the reaction worked well with aromatic Grignard reagents and the presence of electron-donating (**4b-4d**) or electron-withdrawing group (**4e**) in substituted phenylmagnesium bromide didn't affect the efficiency of the reaction

Table 1. Preparation of α-keto esters from ethyl 2-pyridyl oxalate and Grignard reagents[a]

Entry 4	RMgBr R	Product	Isolated yield, %
a	C_6H_5		65
b	*o*-CH_3-C_6H_4		70
c	*p*-CH_3-C_6H_4		72
d	*p*-CH_3O-C_6H_4		69
e	*p*-Cl-C_6H_4		67
f	2,6-$(CH_3)_2C_6H_3$		78
g	α-Naphthyl		72
h	$C_6H_5(CH_2)_2$[b]		54
i	$CH_3(CH_2)_7$[c]		56
j	*c*-C_6H_{11}[c]		68

[a]The Grignard reagents were added over 45 min at -78 ℃ and stirred for 0.5 h. [b]$C_6H_5(CH_2)_2MgBr \cdot CuBr \cdot 2LiBr$ was used. [c]The corresponding $RMgCl \cdot CuBr \cdot 2LiBr$ was used.

under the present reaction conditions. Furthermore, the reaction of **1** with sterically hindered 2,6-dimethylphenylmagnesium bromide afforded **4f** in 78% yield without a significant side product. The aliphatic α-keto ester was prepared by a modified procedure, treating Grignard reagent (**4h-4j**) with lithium bromide/copper(I) bromide. Thus, the addition of cyclohexyl magnesium chloride to a greenish solution of lithium bromide (2 equiv) and copper (I) bromide in tetrahydrofuran provided a light brownish solution, which was slowly added to **1** at -78 °C to afford **4j** in 68% yield.

In conclusion, the present method provides an efficient synthesis of α-keto esters using **1** in connection with high yields of aromatic α-keto esters, availability of starting material, and the convenience of one-step operation.

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