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AN EFFICIENT SYNTHESIS OF α-KETO AMIDES VIA REACTION OF α-(N-METHYLANILINO)-ACETONITRILE WITH ESTERS FOLLOWED BY HYDROLYSIS USING COPPER (II) ACETATE

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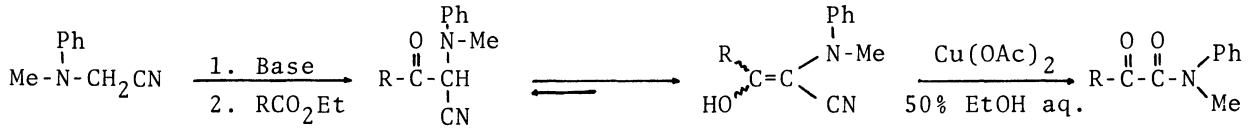
An efficient sequence proposed for the conversion of esters to α-keto amides involves the reaction of α-(N-methylanilino)-acetonitrile with esters to afford β-hydroxy-α-cyanoenamines of which hydrolysis using copper (II) acetate gives the corresponding α-keto amides in good yields.

The utility of α-keto amides has been well-known as important intermediates for synthesis of amino acids[1] and penicillin analogs.[2] Accordingly, many synthetic methods of α-keto amides have been studied heretofore as follows: (a) the oxidation of α-hydroxy amides;[3] (b) the epoxidation of ethyl alkylidenecyanoacetate;[4] (c) the carbonylation of amides;[5] (d) the reaction of the carbamoyl-lithium with esters;[6] (e) the hydrolysis of acrylcyanates;[7] (f) the reaction of the organo lithium compounds with tetramethyloxamide;[8] (g) the reaction of the pyridine salt of hydroxymaleic anhydride with amines;[9] (h) the reaction of alkyloxalylacetate anhydrides with amine;[10] (i) the reaction of Grignard reagents with thiocyanates.[11] Many of these methods, however, lack effective procedures for synthesis of the intermediates in each step or require starting materials which are difficulty to synthesize. We wish to report here an efficient sequence for the synthesis of α-keto amides. The present method has been established by employing reactions of α-(N-methylanilino)-acetonitrile[12] (1) with aromatic esters to form β-hydroxy-α-cyanoenamines (2), which could be easily converted into the corresponding α-keto amides by hydrolysis using copper (II) acetate in good yields.

Scheme 1.



1 (Keto-type) 2 (E- and Z-isomers) 3

The typical procedure is as follows: To a mixture of potassium hydride (KH) (0.59 g, 14.7 mmol) and ethyl benzoate (1.18 g, 7.9 mmol) dissolved in dry tetrahydrofuran (THF) (30 ml) was added 0.98 g (6.7 mmol) of 1 dissolved in dry THF (10 ml) under a dry nitrogen atmosphere at 0 °C. The reaction mixture was stirred at room temperature for 3 h, and then poured into a saturated solution (20 ml) of ammonium

Table 1. Formation of β-hydroxy-α-cyanoenamines (2)

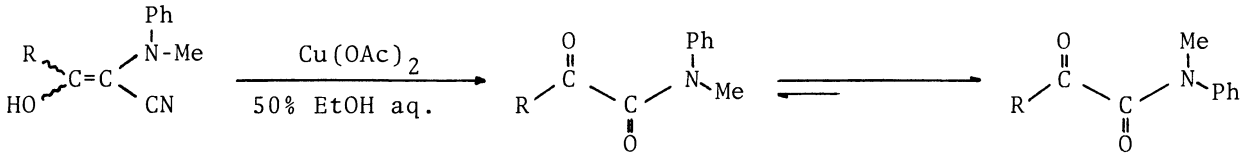
Entry No	R of Esters[a]	Base[b]	Solvent	Conditions		Yield (%) of 2	
1	Ph	NaH	THF	room temp	1 day and reflux 4 h	2a	68%
2	Ph	NaH	DMF	room temp	6 h	2a	76%
3	Ph	KH	THF	room temp	3 h	2a	87%
4	p-MeC_6H_4	KH	THF	room temp	3 h	2b	74%
5	p-$MeOC_6H_4$	KH	THF	room temp	3 h	2c	91%
6	p-ClC_6H_4	KH	THF	room temp	3 h	2d	82%
7	p-$O_2NC_6H_4$	KH	THF	room temp	22 h and reflux 22 h	2e	0%

a) 1.2 mol-equiv. based on 1. b) 2.2 mol-equiv. based on 1.

chloride. The aqueous layer was extracted with isopropyl ether (2 x 100 ml). The combined ether layer was washed with brine, and dried with anhydrous magnesium sulfate. After distilling the ether, the residue was purified by means of column chromatography and/or recrystallization. Thus, α-(N-methylanilino)-β-hydroxy-cinnamonitrile (2a) was obtained in 87% yield as a mixture of two enol-types (E- and Z-isomers). Likewise, p-methyl-, p-methoxy- and p-chloro-α-(N-methylanilino)-β-hydroxy-cinnamonitriles (*i.e.*, 2b, 2c, and 2d) were obtained in good yields. However, treatment of 1 with ethyl p-nitrobenzoate did not give the corresponding β-hydroxy-α-cyanoenamine (2e) at all, but many kinds of by-products. The component ratio of enol-keto for 2 obtained was estimated by means of ^{1}H-NMR spectroscopy as follows: 2a = 100:0; 2b = 100:0; 2c = 70:30; 2d = 95:5. Within two enol-types, the component of Z-form is presumed to be predominant. This is probably due to a hydrogen bonding in contrast with general enamines having no OH group.[13] Thus, β-hydroxy-α-cyanoenamines (2) as precusors of α-keto amides (3) were simply synthesized under usual conditions such as NaH-DMF and KH-THF systems (see Table 1). These structures were confirmed by IR, mass and ^{1}H-NMR spectroscopy.[14]

Conversion of β-hydroxy-α-cyanoenamines (2) to α-keto amides (3) was easily established by treating 2 with 2 mol-equivalent of copper (II) acetate dissolved in ethanolic aqueous solution at 50 °C (see Scheme 2). The typical procedure is as follows: A mixture of 2a (0.50 g, 2.0 mmol), copper (II) acetate (0.74 g, 4.1 mmol) and 50% ethanolic aqueous solution (20 ml) was gently warmed to 50 °C for 4 h, and then cooled to room temperature. After inorganic salt was filtered off, the alcoholic aqueous layer was extracted with dichloromethane (2 x 50 ml). The combined organic layer was washed with water, and dried over anhydrous magnesium sulfate. After filtering magnesium sulfate and distilling the solvent, the residue was purified by means of column chromatography and/or recrystallization from benzene. Thus, benzoylformic N-methylanilide[15] (3a) was obtained in 79% yield. Likewise, p-toluoyl, p-anisoyl- and p-chlorobenzoyl-formic N-methylanilides (*i.e.*, 3b, 3c, and 3d) were obtained in 73%, 41%,and 80% yields, respectively. In the case of 2c constituting more favorable keto-form, the reaction of 2c and EtOH used as a co-

Scheme 2. Conversion of β-hydroxy-α-cyanoenamines (2) to α-keto amides (3).



2 3 s-cis (major) 3 s-trans (minor)

2a: R = Ph — 4 h at 50 C → 3a 79%

2b: R = p-MeC_6H_4 — 3 h at 50 C → 3b 73% + p-$MeC_6H_4CO_2Et$ (9%)

2c: R = p-$MeOC_6H_4$ — 3 h at 50 C → 3c 41% + p-$MeOC_6H_4CO_2Et$ (21%)

2d: R = p-ClC_6H_4 — 5 h at 50 C → 3d 80%

solvent in the hydrolysis occurred to give ethyl p-anisate in 21% yield. α-Keto amides (3) have been reported to exist as a mixture of two rotational isomers, s-cis and s-trans.[16] The presence of s-cis (90%) and s-trans (10%) isomers was also confirmed by means of ^{1}H-NMR spectroscopy. Hydrolysis of dialkylated aminoacetonitriles using copper (II) acetate has been reported to give the corresponding ketones in our previous paper.[17] There is, however, no information about the hydrolysis of α-cyanoenamines like 2 using copper (II). Copper (II) acetate has oxidative ability and can form stable complexes with cyanide ion: Copper (II) ion removes the cyanide group from 2, precipitating as $[Cu(CN)_4]^{3-}$ salts. The resulting copper (II) ion is reduced to copper (I) ion. On the other hand, nickel (II) acetate has the ability forming stable complexes with cyanide ion, but can not oxidize 2. The hydrolysis using nickel (II) did not proceed at all. However, nickel (II) ion in the presence of hydrogen peroxide can hydrolyze 2 to give 3. An usual acid-hydrolysis used for aminoacetonitriles and enamines failed for 2 in this work.

The conversion of esters to α-keto amides has the advantage of simplicity of the reaction procedure, and ready availability of α-aminoacetonitriles.

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12) α-(N-Methylanilino)-acetonitrile was easily synthesized according to procedure described in the literature [N. Itoh, Chem. Pharm. Bull., 10, 55 (1962)].
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14) All β-hydroxy-α-cyanoenamines (2) were new compounds, and gave satisfactory microanalyses. Their physical properties are for a mixture of two enol-forms (E- and Z-isomers) and keto-form as follows:
2a: mp 136-139 °C; IR(KBr): ν_{OH} 3250 cm^{-1}, ν_{CN} 2190 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ: 3.09(s, N-Me of Z), 3.32(s, N-Me of E), 6.8-8.2(m, Phenyl H and OH); MS(70eV) m/e: 250(M^+), 105(100).
2b: mp 114 °C; IR(KBr): ν_{OH} 3230 cm^{-1}, ν_{CN} 2200 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ: 2.42(s, Ph-Me), 3.09(s, N-Me of Z), 3.31(s, N-Me of E), 6.7-8.1(m, ArH and OH); MS (70eV) m/e: 264(M^+), 119(100).
2c: mp 92-94 °C; IR(KBr): ν_{OH} 3240 cm^{-1}, ν_{CN} 2200 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ: 2.90 (s, N-Me of Keto), 3.13(s, N-Me of Z), 3.35(s, N-Me of E), 3.85(s, OMe of Keto), 3.88(s, OMe of E and Z), 5.91(s, CH of Keto), 6.7-8.2(m, Phenyl H and OH); MS (70eV) m/e: 280(M^+), 135(100).
2d: mp 131-132 °C; IR(KBr): ν_{OH} 3230 cm^{-1}, ν_{CN} 2210 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ: 2.86(s, N-Me of Keto), 3.09(s, N-Me of Z), 3.33(s, N-Me of E), 5.83(s, CH of Keto), 6.7-8.1(m, Phenyl H and OH); MS (70eV) m/e: 286(M^+ + 1), 284(M^+ - 1), 139(100).
15) Within α-keto anilides (3) obtained in this work, 3a and 3b are known compounds. Melting point (130-131.5 °C) of 3b agreed with that (128-129 °C) reported in the literature.[11a] However, that (63 °C) of 3a did not agree with that (83-84 °C) reported.[11b] Physical properties of 3a together with new compounds (3c and 3d) are described below. They gave satisfactory microanalyses.
3a: mp 63 °C; IR(KBr): $\nu_{C=O}$ 1672, 1644 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ: 3.33(s, N-Me of s-trans), 3.48(s, N-Me of s-cis), 7.0-8.1(m, Phenyl H); MS (70eV) m/e: 239 (M^+), 105(100).
3c: mp 102-103 °C; IR(KBr): $\nu_{C=O}$ 1660, 1644 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ: 3.32(s, N-Me of s-trans), 3.47(s, N-Me of s-cis), 3.84(s, OMe), 6.7-8.1(m, Phenyl H); MS (70eV) m/e: 269(M^+), 135(100).
3d: mp 101 °C; IR(KBr): $\nu_{C=O}$ 1676, 1648 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ: 3.34(s, N-Me of s-trans), 3.48(s, N-Me of s-cis), 7.0-8.0(m, Phenyl H); MS (70eV) m/e: 275(M^+ + 1), 273(M^+ - 1), 139(100).
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