Construction of 1,2,5-Tricarbonyl Compounds using Methyl Cyanoacetate as a Glyoxylate Anion Synthon Combined with Copper(I) Iodide-Catalyzed Aerobic Oxidation

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Abstract: A practical and efficient synthesis of various 1,2,5-tricarbonyl compounds is described. The synthesis has been carried out by a conjugate addition of methyl cyanoacetate to the β -position of α , β -unsaturated carbonyl compounds and a subsequent copper(I) iodide-catalyzed aerobic oxidation. In addition, various α -aryl- and α -alkyl- α -keto esters have been synthesized using a similar approach.

Keywords: aerobic oxidation; copper(I) iodide; glyoxylate anion synthon; methyl cyanoacetate; 1,2,5-tricarbonyl compounds; umpolung

The construction of a 1,4-dicarbonyl functionality is important in organic synthesis.^[1–4] However, such a synthesis through the bond formation either at 1,2- or 2,3-bonds required one part to have an unusual polarity (umpolung synthon). Since Corey and Seebach introduced the concept of umpolung extensive progress has been achieved.^[2] Although numerous methods have been developed for the preparation of 1,4-dicarbonyl compounds,^[1] the most widely used approach is a conjugate addition reaction of masked acyl anions and their equivalents to α , β -unsaturated carbonyl compoundss. The construction of 1,4-dicarbonyl compounds by 1,2-bond formation using an acyl anion equivalent is depicted in Scheme 1.

However, the reported methods for valuable 2,5diketo esters (1,2,5-tricarbonyl compounds) are highly limited.^[3] Reetz and co-workers have used 1,2-diethoxy-1,2-disilyloxyethylene as a glyoxylate anion synthon,^[3a] while Flores-Parra and Khuong-Huu used methyl dimethoxyacetate during their synthesis of 2,5diketo esters.^[3c] An extension of the acyl anion to a glyoxylate anion synthon could provide an efficient



Scheme 1. Umpolung strategy for 1,4-dicarbonyl compounds.

way to 2,5-diketo esters theoretically, as shown in Scheme 1. Very recently, a conjugate addition of a glyoxylate anion equivalent to nitroalkenes^[4a] and a Stetter reaction of glyoxamide anion synthon to α,β unsaturated carbonyl compounds^[4b–d] have been successfully achieved to synthesize α -keto esters and α keto amides. However, the Stetter reaction between ethyl glyoxylate and an α,β -enone was not studied in depth except for only one entry in the report of Rovis,^[4b] to the best of our knowledge. The reason might be ascribed to a difficult accessibility for pure ethyl glyoxylate.^[5] Ethyl glyoxylate mostly exists in its hydrate^[5a,b] or polymeric forms,^[5c] and this renders the Stetter reaction difficult in the presence of an N-heterocyclic carbene catalyst.

Thus, we envisioned that a two-step synthesis of 2,5-diketo esters (1,2,5-tricarbonyl compounds) could be carried out from a α,β -enone and ethyl cyanoace-tate *via* a conjugate addition and a subsequent aerobic oxidation, as shown in Scheme 2. To our delight, we found that a conjugate addition product, the α -cyano- δ -keto ester, can be converted to the 2,5-diketo ester in high yield by copper-catalyzed aerobic oxida-





Scheme 2. Synthetic strategy for 2,5-diketo esters.

tion. Ethyl cyanoacetate was used as an efficient ethyl glyoxylate anion equivalent in the reaction, and we wish to report herein the preliminary results.

Copper- or base-mediated oxidations of benzylic^[6a,b] or secondary nitriles^[6c,d] to ketones, α -cyano esters to α -keto esters,^[7] α -cyano amides^[8a] or α -amino nitriles^[8b,c] to α-keto amides have been reported. The oxidations were effected using molecular oxygen,^[6,7] peracetic acid,^[8a] NaOCl^[8b] or Oxone.^[8b] Although the yields were moderate, a variety of precedent reports implied that our synthetic approach could be realizable. With this confidence in mind, we decided to use O_2 as an oxidant and examined the optimum reaction conditions with ethyl 2-cyano-5-oxo-3,5-diphenylpentanoate (1a) which was prepared from ethyl cyanoacetate and chalcone (LiClO₄/Et₃N/room temperature, 10 min, 92% yield).^[9a] A base-mediated aerobic oxidation of **1a** was not fruitful. The reaction of **1a** in DMF in the presence of Cs₂CO₃ under an O₂ balloon atmosphere produced 4-oxo-2,4-diphenylbutyronitrile in moderate yield (45%) instead of the desired product, ethyl 2,5-dioxo-3,5-diphenylpentanoate (2a). The mechanism is not clear at this stage.

Thus we examined the conversion of **1a** to **2a** under various copper-catalyzed oxidation conditions, and the results are summarized in Table 1. From the results the use of CuI (1.1 equiv.) in CH₃CN at 25 °C was selected as the optimum conditions (entry 2). The use of a catalytic amount of CuI (entry 1) or other solvents such as DMF, toluene, CH₂Cl₂ and aqueous EtOH (entries 3–6) was less efficient. Among the copper salts, CuI was the reagent of choice. With other copper catalysts (entries 7–11) a sluggish reaction was observed and/or the amounts of side products increased including cyanohydrin **3a** and halogenated compounds (see Table 1).

Then we turned our attention to a catalytic version in combination with a suitable ligand. As shown in Table 2, the use of DMEDA (L1), TMEDA (L2), and ethylenediamine (L3) showed low to moderate yields of 2a (entries 1–3). The use of 1,10-phenanthroline (L4) gave a reasonable yield of 2a (entry 4) while 8quinolinol (L5) and L-proline (L6) were totally ineffective (entries 5 and 6). Reducing the amounts of CuI and 1,10-phenanthroline lowered the yield of 2a(entries 7–9). Overall, the conditions using 1,10-phenanthroline were the best, albeit the yield of 2a was slightly lower than that of the conditions employing an equivalent amount of CuI (entry 2 in Table 1).

Table 1	I. C	opper-m	ediated	aerobic	oxidation	of	1a . ^{la}	aj
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Entry	Catalyst ^[b]	Solvent	Time [h]	2a [%] ^[c]
1	CuI	CH ₃ CN	40	57 ^[d]
2	CuI	CH ₃ CN	3	89 ^[e]
3	CuI	DMF	4	75
4	CuI	toluene	4	0
5	CuI	CH_2Cl_2	4	0
6	CuI	aq. EtOH	10	66
7	CuCl	CH ₃ CN	6	33 ^[f]
8	CuBr	CH ₃ CN	40	39 ^[g]
9	CuCN	CH ₃ CN	4	62 ^[h]
10	$Cu(OAc)_2$	CH ₃ CN	40	13 ^[i]
11	$CuCl_2$	CH ₃ CN	5	0

^[a] Carried out under O₂ balloon atmosphere at 25 °C.

^[b] 1.1 equiv. of copper salt were used except for entry 1 (0.2 equiv.).

^[c] Isolated yield.

^[d] **3a** (15%).

- ^[e] Selected as conditions A.
- [f] 1a (15%), 3a (5%) and ethyl 2-chloro-2-cyano-5-oxo-3,5diphenylpentanoate (27%).
- ^[g] **1a** (28%), **3a** (5%) and ethyl 2-bromo-2-cyano-5-oxo-3,5diphenylpentanoate (8%).

^[h] **3a** (17%).

^[i] **1a** (17%) and **3a** (25%).

Table 2. CuI-catalyzed aerobic oxidation of 1a in the presence of a ligand.^[a]

Entry	CuI (equiv.)	Ligand (equiv.) ^[b]	Time [h]	2a [%] ^[c]
1	0.2	L1 (0.3)	3	58
2	0.2	L2(0.3)	3	27
3	0.2	L3(0.3)	3	53
4	0.2	L4 (0.3)	5	78 ^[d]
5	0.2	L5 (0.3)	24	0
6	0.2	L6(0.3)	24	0
7	0.05	L4(0.1)	24	14
8	0.1	L4 (0.2)	24	34
9 ^[e]	0.05	L4 (0.1)	5	53

^[a] CH₃CN/O₂ balloon/25 °C is common.

[b] Ligands: L1, N,N-dimethylethylenediamine; L2, N,N,N',N'-tetramethylethylenediamine; L3, ethylenediamine; L4, 1,10-phenanthroline; L5, 8-quinolinol; L6, Lproline.

^[c] Isolated yield.

^[d] Selected as conditions B.

^[e] Carried out at 45 °C.

In order to show the generality, we examined various substrates under the selected optimized conditions: conditions A (entry 2 in Table 1) and conditions



^[a] Isolated yield (conditions A/conditions B, and NT means not tried). ^[b] Methyl and α -keto esters are *trans*.

Scheme 3. Synthesis of 1,2,5-tricarbonyl compounds.

B (entry 4 in Table 2). Some representative starting materials **1a–1** were prepared from various α ,β-enones *via* a conjugate addition of methyl cyanoacetate, ethyl cyanoacetate, allyl cyanoacetate, and 2-cyanoacetamide according to the reported methods.^[9a,b] The results for the synthesis of 1,2,5-tricarbonyl compounds **2a–1** are summarized in Scheme 3. Various cyclic and acyclic 1,2,5-tricarbonyl compounds were prepared in moderate to good yields (72–93%). Usually, conditions A showed better results than conditions B; however, the yield of amide derivative **2f** was quite low under conditions A.

As a next trial, methyl (or ethyl) 2-arylcyanoacetates **1m–r** were prepared *via* a base-mediated S_NAr reaction or a palladium-catalyzed α -arylation from the corresponding aryl halides according to the reported methods.^[9c-h] As shown in Scheme 4, CuImediated aerobic oxidation of **1m–r** provided the corresponding α -keto esters **2m–r** in reasonable yields (56–76%) under the conditions A. Usually, a Friedel– Crafts acylation of electron-rich arenes with oxalyl chloride and subsequent treatment with MeOH pro-



^[b] Carried out at 50 °C.

Scheme 4. Synthesis of α -aryl- α -keto esters.

vided the corresponding α -keto esters in good yields. However, the method cannot be applied for arenes bearing an electron-withdrawing group. Thus, our two-step protocol can be used efficiently in such cases.

In addition, some α -alkyl- α -keto esters were also synthesized *via* a similar strategy, as summarized in Scheme 5. Starting materials **1s–w** were prepared by alkylation of the corresponding alkyl bromides or chlorides (K₂CO₃, CH₃CN, room temperature).^[9] The CuI-mediated aerobic oxidation of these α -cyano esters provided the corresponding alkyl-substituted α keto esters **2s–u** in good yields (76–84%). However, the reaction of **1v** produced benzil as the major prod-



^[a] Carried out under conditions A (2 h).

^[b] Benzil was formed in 69% yield.

^[C] Intractable complex mixtures with some benzaldehyde.

Scheme 5. Synthesis of α -alkyl- α -keto esters.



Scheme 6. Plausible reaction mechanism.

uct (69%) instead of the desired product. In addition, the reaction of **1w** also failed and produced appreciable amounts of benzaldehyde. The results of **1v** and **1w** might be ascribed to the preferential oxidation at the benzylic position rather than the α -position of a cyano group.

A plausible reaction mechanism of Cu-mediated aerobic oxidation of 1 was proposed tentatively, as shown in Scheme 6. The key radical intermediate I was generated by hydrogen atom abstraction from 1 with molecular oxygen, meanwhile, Cu(I) was oxidized to Cu(II) and oxygen was transformed to hydroperoxide anion.^[10] Subsequently, the intermediate I reacted with the hydroperoxide anion to form the hydroperoxide II. In addition, Cu(II) was reduced to Cu(I) which could enter to the next catalytic cycle (vide infra). As reported in a similar case, an elimination of isocyanic acid (HNCO) from hydroperoxide II via a dioxetane intermediate III afforded the α -keto ester 2.^[11] In one part, the hydroperoxide II was reduced to a cyanohydrin 3 and eventually to 2. As proposed in the mechanism, a catalytic amount of CuI could catalyze the reaction; however, CuI might be destroyed to a certain unidentified copper salt by the reaction with liberated HNCO.^[12] Thus, an equimolar amount of CuI was required for the efficient conversion of 1 to 2. However, further studies must be performed for a detailed reaction mechanism in order to explain the results in a catalytic version (conditions **B**).

In summary, an efficient synthesis of various 1,2,5tricarbonyl compounds has been carried out by a conjugate addition of methyl cyanoacetate to the β -position of α , β -unsaturated carbonyl compounds and a subsequent CuI-catalyzed aerobic oxidation. In addition, various α -aryl- and α -alkyl- α -keto esters have been synthesized using a similar approach.

Experimental Section

Typical Experimental Procedure for CuI-Mediated Aerobic Oxidation of Ethyl 2-Cyano-5-oxo-3,5-diphenylpentanoate (1a)

A mixture of **1a** (321 mg, 1.0 mmol) and CuI (210 mg, 1.1 mmol) in CH₃CN (3.0 mL) was stirred at 25 °C for 3 h under an O₂ balloon atmosphere. Then the mixture was filtered through a pad of Celite and washed with CH₂Cl₂. The organic solvents were removed by evaporation, and the residue was purified by flash column chromatography (hexanes/ EtOAc, 10:1) to afford ethyl 2,5-dioxo-3,5-diphenylpentanoate (2a) as a colorless oil; yield: 276 mg (89%). IR (film): v = 1729, 1681, 1246 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 1.29$ (t, J = 7.2 Hz, 3H), 3.43 (dd, J = 18.3 and 3.9 Hz, 1 H), 4.03 (dd, J=18.3 and 10.5 Hz, 1 H), 4.28 (q, J= 7.2 Hz, 2H), 5.15 (dd, J=10.5 and 3.6 Hz, 1H), 7.26–7.60 (m, 8H), 7.93–7.98 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): $\delta\!=\!13.89,\;43.12,\;48.42,\;62.49,\;127.95,\;128.16,\;128.63,\;128.87,$ 129.13, 133.49, 135.35, 135.93, 160.34, 192.17, 197.37; ESI-MS: $m/z = 333 [M + Na]^+$; anal. calcd. for C₁₉H₁₈O₄: C 73.53, H 5.85; found: C 73.67, H 5.98.

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