Tetrahedron Vol. 39, No 20, pp 3279 to 3282, 1983
Printed in Great Britain

0040-4020/83 $3.00+.00

EFFICIENT COPPER-CATALYZED OXIDATION OF DIHYDRAZONES OF α-DIKETONES TO DISUBSTITUTED ACETYLENES

JIRO TSUJI,* HIROAKI KEZUKA, YOMISHI TOSHIDA, HIROSHI TAKAYANAGI and KEIJI YAMAMOTO
Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

(*Received in Japan* 7 *March* 1983)

Abstract—Dihydrazones of α-diketones were oxidized by using Cu_2Cl_2/O_2/pyridine system in dichloromethane at room temp to give disubstituted acetylenes. Although the dihydrazones were found to be oxidized with four equivalents of Cu(II) salt without oxygen, efficient oxidation of the dihydrazones proceeded smoothly in the presence of a catalytic amount of Cu(I) chloride under oxygen, thus providing a convenient preparative method of distributed acetylenes.

We have reported that oxygen-treated copper(I) chloride in pyridine is a useful system for efficient oxidation of various N-containing organic compounds under very mild conditions. Oxidative ring cleavage of *o*-phenylenediamine gives *cis, cis*-muconolnitrile in a high yield.[1] Substituted indoles are oxidatively cleaved to give 2-formylaminoacetophenone derivatives.[2] Dihydrazones of α-diketones can be converted into disubstituted acetylenes.[3] Hydrazides of carboxylic acids are also transformed to the corresponding acids, esters, and amides under oxygen atmosphere by using Cu(I) chloride or Cu(II) acetate as an oxidizing agent.[4] The latter two reactions are useful for organic synthesis, because usually they are carried out with stoichiometric amounts of rather expensive and toxic Hg(II)[5] or Pb(IV)[6] compounds as an oxidizing agent, or a Co(II) complex as a catalyst.[7]

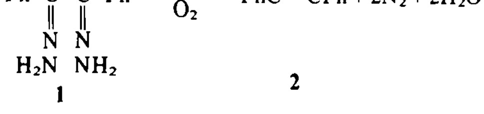
In the above-mentioned reactions, it is assumed that the real oxidizing agent is Cu(II) state generated *in situ* from Cu(I) chloride by absorbing oxygen, and stoichiometric amounts of the Cu(I) chloride were, in some cases, used for the oxidation. In order to make the reactions more useful, we have tried to carry out the oxidation as a catalytic process with regard to the Cu(II) salts by taking advantage of the fact that reduced Cu(I) can readily be converted into Cu(II) state by oxygen under selected conditions.

Preliminary accounts of the oxidation of dihydrazones of α-diketones to disubstituted acetylenes have already been reported [3b] and details of the catalytic oxidation procedures typically by using Cu_2Cl_2/O_2/pyridine system in dichloromethane are presented in this paper.

RESULTS AND DISCUSSION

(a) *Stoichiometric oxidation of benzil dihydrazone* (1)

We have found that oxidation of benzil dihydrazone (1) takes place smoothly to give diphenylacetylene (2) by using various Cu(II) salts as an oxidizing agent (eqn 1). At first is was confirmed that the dihydrazone 1 dissolved in dry pyridine was



$$\underset{\substack{\| \\ N \\ H_2N}}{\text{Ph-C}}-\underset{\substack{\| \\ N \\ NH_2}}{\text{C-Ph}} \xrightarrow[O_2]{\text{Cu(II) salt}} PhC\equiv CPh + 2N_2 + 2H_2O \qquad (1)$$

1 2

oxidized readily with 4 equiv of $Cu(OAc)_2 \cdot H_2O$ with evolution of quantitative amount of N_2 to give 2 in 86% yield under a N_2 atmosphere.

The oxidation of 1 was also carried out under O_2 in a pyridine solution of Cu_2Cl_2 (4 equiv) which was treated with O_2 prior to the reaction to generate Cu(II) species: $Cu_2Cl_2 + 1/2O_2 \rightarrow CuCl_2 \cdot CuO$[8].

In both cases, however, pyridine appeared to be essential only for supporting ligands of Cu(II) species and methanol-benzene mixed solvent was also satisfactory. Finally, dichloromethane with added pyridine was found to be convenient for all oxidative conversion of 1 into 2 in an excellent yield. All results thus obtained are summarized in Table 1. Homogeneity of the reaction mixture is of primary importance for the smooth oxidation of 1 rather than variation of ligands as far as two Cu(II) species are concerned. This is not the case for the oxidation of acid hydrazides to the corresponding acids.[4]

It should be mentioned that acetylenes substituted with aliphatic groups are similarly prepared, being exemplified by the preparation of dehydrocivetone in 82% yield.[9]

(b) *Catalytic oxidation of benzil dihydrazone* (1) *and* 6,7-*dodecanedione dihydrazone* (3)

The oxidation as a catalytic process with regard to Cu(II) salts is most feasible for preparative purpose. It is well-known that Cu(I) salts are readily oxidized with O_2. The possibility of catalytic oxidation of α-diketone dihydrazones to disubstituted acetylenes using a catalytic amount of Cu(II) salts under O_2 was herein examined and we found the reaction proceeded catalytically under proper conditions.

Both $Cu(OAc)_2 \cdot H_2O$ and Cu_2Cl_2 with added pyridine, pretreated with O_2, in dichloromethane were found to be the most convenient reagents for the catalytic oxidation of 1. The reaction was carried out by adding slowly a dichloromethane solution of 1 to a stirred solution of Cu(II)-pyridine complex dissolved in the same solvent with concomitant bubbling of O_2 through the mixture at room temperature.

As shown in Table 2, the catalytic oxidation of 1 was carried out with four different Cu(II) species at 1/8 equivalent level in dichloromethane and then with different amounts of Cu_2Cl_2-pyridine in the same solvent (Entries 3–5). As was confirmed in the stoichiometric reaction, four moles of Cu(II) salts are equivalent to one mole of dihydrazone 1.

Table 1. Stoichiometric oxidation of benzil dihydrazone (1) to diphenylacetylene (2) with Cu(II) salts[a]

Entry	Cu(II) Salt	Solvent (mL)	2, Yield(%)[b]
1	$Cu(OAc)_2.H_2O$[c]	pyridine (30)	86
2		CH_2Cl_2 (30)-pyridine (2)	97
3		MeOH (30)-benzene (10)	94
4	Cu_2Cl_2/O_2/pyridine[d]	pyridine (30)	81
5		CH_2Cl_2 (30)-pyridine (2)	97
6		CH_2Cl_2 (30)	30
7		MeOH (30)-benzene (10)	82

[a] 1 (1.0 mmol)/solvent (10 mL) was added dropwise to Cu(II) (4.0 mmol)/solvent (ca. 20 mL) (see, Experimental).

[b] Isolated by column chromatography.

[c] Under nitrogen.

[d] Under oxygen: $Cu_2Cl_2 + 1/2.\ O_2 \xrightarrow{\text{pyridine}} CuCl_2.CuO$ (ref. 8 and see the text).

Table 2. Catalytic oxidation of benzil dihydrazone (1) to diphenylacetylene (2) with Cu(II) salts in CH_2Cl_2[a]

Entry	Cu(II) Salt (mmol)	Pyridine (mL)	2, Yield(%)[b]
1	$Cu(OAc)_2.H_2O$ (1.0)	1.0	91
2	(0.25)	0.25	- (78)
3	Cu_2Cl_2/O_2/pyridine[c] (1.0)	1.0	90
4	(0.5)	0.5	55 (69)
5	(0.25)	0.25	53 (70)
6	$Cu(OMe)_2$[d] (1.0)	1.0	53
7	$CuCl_2$ (1.0)	1.0	trace[e]

[a] Dihydrazone 1 (2.0 mmol) dissolved in CH_2Cl_2 (10 mL) was added to Cu(II)-pyridine in CH_2Cl_2 (10 mL) with bubbling oxygen.

[b] Yields of isolated 2 after 2 h reaction. In parentheses are those after 6 h.

[c] Static atmosphere of oxygen retards the oxidation.

[c] Prepared *in situ* from $CuCl_2$ and LiOMe.

[e] Intractable materials formed.

Table 3. Catalytic oxidation of 6,7-dodecanedione dihydrazone (3) to 6-dodecyne (4) with Cu(II) salts[a]

Entry	Cu(II) Salt (1.0 mmol)	Solvent (mL)	4, Yield(%)[b]
1	Cu_2Cl_2/O_2/pyridine	CH_2Cl_2 (20)-pyridine (1.0)	88[c]
2		CH_2Cl_2 (20)-DBU (2.0)	78
3	$Cu(OAc)_2.H_2O$	CH_2Cl_2 (20)-pyridine (1.0)	46
4	$Cu(OMe)_2$		29
5	$CuCl_2$		–[d]

[a] Dihydrazone 3 (2.0 mmol) dissolved in CH_2Cl_2 (10 mL) was added to Cu(II) salt plus added amine in CH_2Cl_2 (10 mL) with bubbling oxygen.

[b] Isolated yield after 2 h reaction.

[c] Slow addition of 3 was essential.

[d] Intractable materials formed.

It is seen that $Cu(OMe)_2$ is inferior in catalytic activity to $Cu(OAc)_2$ or Cu_2Cl_2-pyridine at 1/8 equiv level, whereas $CuCl_2$ is almost inactive for the reaction under O_2, causing undesired reaction to form intractable materials. The reaction proceeded satisfactorily even when the amount of Cu_2Cl_2-pyridine was 1/16 equivalent. By further decrease to 1/32, the yield of 2 was somewhat deteriorated even after prolonged reaction.

The catalytic reaction is also applicable to aliphatic α-diketone dihydrazones. We have already shown that 4-octyne was obtained from dihydrazone of 4,5-octanedione in 89% yield using Cu_2Cl_2 at 1/2 equivalent level under O_2.[3a] Here is given the catalytic oxidation of 6,7-dodecanedione dihydrazone (3) in detail.[3b]

Preparation of 3 was carried out in a similar manner to that for benzil dihydrazone (1).[5] The reaction of 6,7-dodecanedione (5) with excess hydrazine hydrate seemed to proceed much slowly than that of benzil, being accompanied by some contamination with monohydrazone. However, the mixture may be used for synthetic purposes.

Oxidation of 6,7-dodecanedione dihydrazone (3) to 6-dodecyne (4) was carried out with four different Cu(II) catalysts at 1/8 equivalent level and the results are given in Table 3. It is of interest that catalytic activity of four Cu(II) species employed is evaluated in terms of the yield of 4 in the following order: Cu_2Cl_2/O_2/pyridine > $Cu(OAc)_2 \cdot H_2O > Cu(OMe)_2$. The fact that $CuCl_2$ dissolved with added pyridine in dichloromethane is again inactive as a catalyst for oxidation suggests an intriguing feature of the active species generated from Cu_2Cl_2-pyridine complex pretreated with O_2. It is very likely that oxidation of Cu(I) chloride in pyridine provides a mixture of bispyridine Cu(II) chloride and an oxido-Cu(II)-pyridine complex presumably existing as a soluble di-μ-oxo-bridged one[10] on the thermodynamic basis.

Therefore, in the oxidation of dihydrazones, the active Cu(II) species which act as one-electron acceptors from the dihydrazone are reasonably assumed to be the oxido-Cu(II)-complexes solvated with pyridine.

EXPERIMENTAL

Materials. Cu_2Cl_2, $CuCl_2$, and $Cu(OAc)_2 \cdot H_2O$ were commercial reagents and used without purification. $Cu(OMe)_2$ was prepared *in situ* by treatment of $CuCl_2$ with 2 equiv of LiOMe in THF for 1 hr. The green-colored mixture was evaporated *in vacuo* to dryness and the residue was dissolved in dry CH_2Cl_2 containing an appropriate amount of pyridine.

Benzil dihydrazone (1) was prepared according to a standard method[5] and recrystallized from abs EtOH, m.p. 147° (lit.[5] m.p. 150°).

Preparation of 6,7-dodecanedione dihydrazone (3). 5 was prepared by Br-oxidation of 6,7-bis(trimethylsiloxy)-6-dodecene in 60–80% yield,[11] the latter being prepared by Rühlmann's modified acyloin condensation[12] of ethyl hexanoate as an *E*/*Z* mixture, b.p. 118–120°/4 Torr in 75% yield: 5: b.p. 83–85°/3 Torr (a yellow semi-solid) (lit.[13] b.p. 110–120°/10 Torr). ^1H NMR (60 MHz, $CDCl_3$, TMS) δ 0.87 (*t*, 6H), 1.42 (*br peak*, 12H), and 2.75 ppm (*t*, *J* = 7 Hz, 4H). ^{13}C NMR (22.5 MHz, $CDCl_3$, TMS) δ 13.9, 22.4, 22.9, 31.4, 36.1 and 200.2 ppm. IR (neat) 1710 cm^{-1}.

To a soln of 5 (13.5 g, 0.07 mol) dissolved in PrOH (70 mL) was added 80% hydrazine hydrate (23.0 g, 0.36 mol) in one portion. The mixture was refluxed for 60 hr and then cooled in an ice-water to precipitate yellowish-white crystals. The ppts were collected by filtration, washed with little cold EtOH, and dried *in vacuo* to afford crude 3 (9.33 g, 59% yield), which was contaminated with monohydrazone. TLC (ether-hexane, 3:1) R_f 0.60 for **5** and 0.73 for monohydrazone. Prolonged column chromatography (silica gel, hexane-ether eluent) caused some decomposition of crude **3**. Analytical sample of **3** was obtained by preparative TLC. **3**: m.p. 79–80° (hexane). ^{1}H NMR (90 MHz, $CDCl_3$, TMS) δ 0.89 (*t*, 6H), 1.35 (*br pk*, 12H), 2.48 (*t*, $J = 8$ Hz, 4H), and 5.34 ppm (*br s*, 4H). ^{13}C NMR (22.5 MHz, $CDCl_3$, TMS) δ 14.0, 22.5, 22.6, 25.1, 32.2, and 151.6 ppm. (Found C, 63.93; H, 11.87; N, 24.35%. Calc for $C_{12}H_{26}N_4$ C, 63.67; H, 11.58; N, 24.75%).

Oxidation procedures. All stoichiometric and catalytic oxidations of α-diketone dihydrazones were carried out in a similar manner and two typical examples are given.

Stoichiometric oxidation of benzil dihydrazone (**1**) *to diphenylacetylene* (**2**) (Entry 5, Table 1.) Reagent grade Cu(I) chloride (0.403 g, 4.0 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and pyridine (2 mL) to give an yellow-green clear soln. O_2 from a gas buret was introduced to the soln with vigorous stirring. Rapid absorption of O_2 (about 20 mL) ceased in 15 min, the mixture becoming a dark green suspension. To this mixture was added dropwise a soln of **1** (0.237 g, 1.0 mmol) in CH_2Cl_2 (10 mL) over a period of 10 min at room temp with stirring. Slightly exothermic reaction proceeded smoothly with N_2 evolution. Stirring was continued for 1 hr under an O_2 atmosphere to ensure the completion of oxidation. The mixture was hydrolyzed with 3 N HCl (40 mL), the organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer and extracts were washed with brine, dried over $MgSO_4$, and evaporated to leave crude **2**, which was purified by column chromatography (silica gel, hexane) to give 0.173 g (97%) of crystals of **2** and identified by mixed m.p. (59–60°) with an authentic sample (m.p. 59–61°).

Catalytic oxidation of dihydrazone of 6,7-*dodecanedione* (**3**) *to* 6-*dodecyne* (**4**) (Entry 1, Table 3). A soln of Cu(I) chloride (0.100 g, 1.0 mmol) in dry CH_2Cl_2 (10 mL) and pyridine (1 mL) was placed in a flask equipped with a gas inlet tube for constant introduction of O_2. To the soln which had been oxidized by O_2 stream prior to the reaction was added dropwise a soln of **3** (0.453 g, 2.0 mmol) in CH_2Cl_2 (10 mL) through a Hirshberg funnel over a period of 1 hr under constant bubbling of O_2 with stirring. The mixture was stirred at room temp for additional 2 hr, and hydrolyzed with dil HCl. After the usual work-up and short column chromatography, **4** (0.293 g, 88%) was obtained by distillation, b.p. 110–115°/30 Torr (Kugelrohr) (lit.[14] b.p. 115°/30 Torr). GLC (silicone DC-550 3m, at 140°, H_2 40 mL/min) T_R4.2 min. ^{1}H NMR (60 MHz, CCl_4, TMS) δ 0.89 (*t*, 6H), 1.48 (*br pk*, 12H), and 2.15 ppm (*br t*, 4H).

REFERENCES

[1] T. Kajimoto, H. Takahashi and J. Tsuji, *J. Org. Chem.* **41**, 1389 (1976); H. Takahashi, T. Kajimoto and J. Tsuji, *Synth. Commun.* **2**, 181 (1972); J. Tsuji and H. Takayanagi, *Org. Syntheses* **57**, 33 (1977).

[2] J. Tsuji and H. Takayanagi, *Chem. Letters* 65 (1980); J. Tsuji, H. Kezuka, H. Takayanagi and K. Yamamoto, *Bull. Chem. Soc. Jpn* **54**, 2369 (1981).

[3a] J. Tsuji, H. Takahashi and T. Kajimoto, *Tetrahedron Letters* 4573 (1973); [b] J. Tsuji, H. Takayanagi and Y. Toshida, *Chem. Letters* 147 (1976).

[4] J. Tsuji, T. Nagashima, N. T. Qui and H. Takayanagi, *Tetrahedron* **36**, 1311 (1980); J. Tsuji, S. Hayakawa and H. Takayanagi, *Chem. Letters* 437 (1975).

[5] A. C. Cope, D. S. Smith and R. J. Cotler, *Org. Syntheses Coll.* Vol. 4, 377 (1963).

[6] K. Nakagawa, and H. Onoue, *Chem. Commun.* 396 (1978).

[7] A. Inada, Y. Kakamura, and Y. Morita, *Chem. Pharm. Bull.* **30**, 1041 (1982).

[8] J. Tsuki and H. Takayanagi, *Tetrahedron* **34**, 641 (1978).

[9] J. Tsuji and T. Mandai, *Tetrahedron Letters* 3285 (1977).

[10] M. M. Rogić and T. R. Demnin, *J. Am. Chem. Soc.* **100**, 5472 (1978).

[11] J. Starting, S. Reiffers, and H. Wynberg, *Synthesis* 209 (1971).

[12] U. Schräpler and K. Rühlmann, *Chem. Ber.* **97**, 1383 (1964).

[13] L. Bouveault and R. Locquin, *Bull. Soc. Chim. Fr.* [3] **35**, 652 (1906).

[14] E. A. Bried and G. F. Hennion, *J. Am. Chem. Soc.* **59**, 1310 (1937).