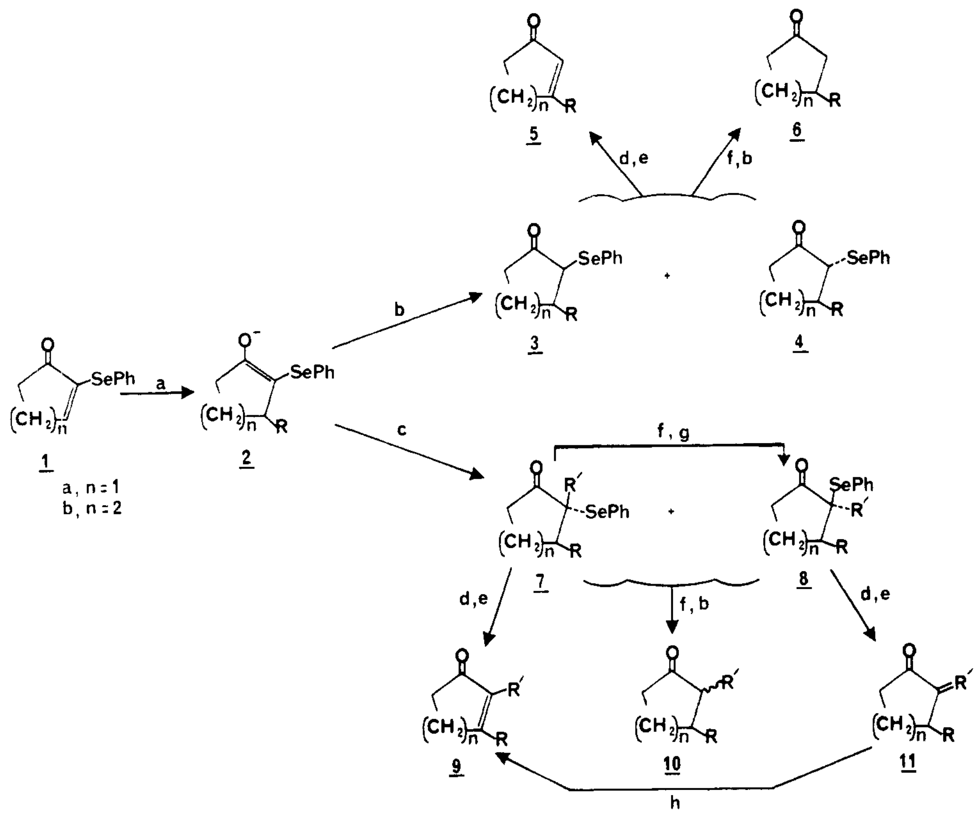
Scheme I[a]



[a] (a) LiR$_2$Cu, Et$_2$O, -20 °C; (b) satd NH$_4$Cl; (c) R'X, Et$_2$O, THF, HMPA, 25 °C; (d) O$_3$; (e) Et$_2$NH, CH$_2$Cl$_2$, Δ; (f) LiSePh, THF; (g) PhSeCl; (h) HCl, *n*-BuOH, 90 °C.

8 entirely to 8, prior to the oxidation/elimination process. We envisioned effecting this isomerization in a relatively straightforward, two-step process: first, a nucleophilic cleavage of the carbon-selenium bond, followed by reselenation of the resulting enolate from the less hindered side yielding the trans isomer 8. In practice, the nucleophilic cleavage of the carbon-selenium bonds in 7 and 8 is readily accomplished by exposing a mixture of these compounds to lithium phenyl selenide in THF at -78 °C.[9] The resulting enolate can then be protonated (saturated NH$_4$Cl solution) to give 10 or directly selenated.[10] The use of this method (LiSePh, then PhSeCl)[11] produces mixtures of 7 and 8 in which 8 is by far the major component. In fact, in three of the cases reported here, the epimerized mixtures contain only trace amounts of 7. Even in the worst case studied, a mixture of **7b** and **8b** which was originally 7:3 is transformed by this method to a 1:4 mixture of **7b** and **8b**, respectively. Once isomerized, these mixtures can then be oxidized and eliminated under standard conditions to give excellent overall yields of 11.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, Research Corporation, and the National Institutes of Health for financial support. We also thank the National Science Foundation for providing funds for the purchase of our Finnigan 4000 GC-MS system.

Supplementary Material Available: Experimental details for the preparation of representative compounds (3 pages). Ordering information is given on any current masthead page.

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Received December 20, 1979

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[9] Cleavage of the carbon-selenium bond of α-(phenylselenenyl)-propiophenone by lithium phenyl selenide has been previously noted; see: Reich, H. J.; Renza, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

[10] Although not specifically listed in tabular form, these protonation reactions in all cases lead to deselenated ketones 6 and 10 in essentially quantitative yields.

[11] This transformation may also be accomplished by using LiSePh, followed by CH$_3$I.

[12] Fellow of the Alfred P. Sloan Foundation, 1980-1982.

Copper(II)-Induced Cleavage of Carbon-Carbon Bonds. Mononitriles of Muconic Acids from *o*-Benzoquinones, Catechols, and Phenols by Reaction with Copper(II) in the Presence of Ammonia

Summary: *o*-Benzoquinones, catechols, and phenols react with certain copper(II) reagents to give, in one step, mononitriles of muconic acids.

Sir: Recently we reported on the oxidative cleavage of *o*-benzoquinones, catechols, and phenols to the corresponding monoesters of muconic acids.[1-3] In discussing the nature of the active copper(II) species responsible for the carbon-carbon bond cleavage, we suggested that in pyridine solution the active component of the reagent was dimeric cupric methoxy hydroxide complexed with pyridine.[2,3] We demonstrated[2,3] that this active component

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[1] M. M. Rogić, T. R. Demmin, and W. B. Hammond, *J. Am. Chem. Soc.*, **98**, 7441 (1976).

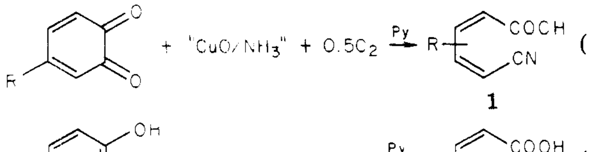
[2] M. M. Rogić and T. R. Demmin, *J. Am. Chem. Soc.*, **100**, 5472 (1978).

[3] M. M. Rogić and T. R. Demmin, "Aspects of Mechanism and Organometallic Chemistry", J. H. Brewster, Ed., Plenum Press, New York, 1978, p 141.

could be generated by reacting methanol with the "copper(II)–oxygen" species[4] that is obtained by oxidizing copper(I) chloride in pyridine.

We now report that the reaction of ammonia with the same "copper(II)–oxygen" species (generated as before)[4] produces a new copper reagent, "CuO/NH$_3$" (eq 1),[5] which reacts with *o*-benzoquinones, catechols, and phenols in the presence of oxygen[6] to afford the corresponding mononitriles of muconic acids **1a–d** (eq 2–4, R = *t*-Bu; eq 3 and 4, R = H).

$$4CuCl + O_2 \xrightarrow{Py} [\quad] \xrightarrow[Py]{NH_3} \text{"CuO/NH}_3\text{"} \qquad (1)$$



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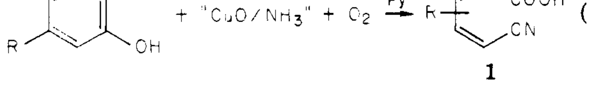

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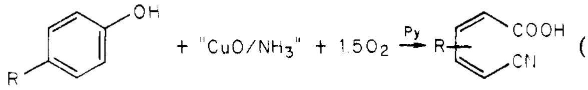

(4)

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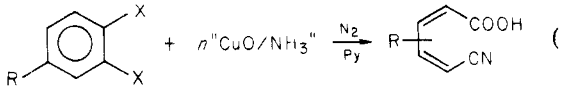
As in the cleavage to muconic acid esters,[1-3] the oxidation of *o*-benzoquinones and catechols to muconic acid mononitriles can also be effectively carried out with the "CuO/NH$_3$" reagent[6] *in the absence of oxygen* (eq 5, R = *t*-Bu, X = O, *n* = 0.5; X = OH, *n* = 1). The reaction with 4-*tert*-butylcatechol is representative. A solution of purified cuprous chloride (5.93 g, 60 mmol) in 60 mL of dry pyridine was exposed to dry oxygen with stirring at room temperature.[7] After complete oxidation (15 mmol of O$_2$), the resulting reaction mixture was degassed and then placed in an ice–water bath and saturated with dry ammonia gas. A solution of 4-*tert*-butylcatechol (1.66 g, 10 mmol) in pyridine (20 mL) was then added dropwise at 0 °C with stirring under a nitrogen atmosphere. After 30 min at 0 °C and 30 min at room temperature, the volatiles were evaporated and the dark residue was hydrolyzed at 0 °C with dilute hydrochloric acid in chloroform under nitrogen. Drying and evaporation of the chloroform solution afforded a mixture of isomeric muconic acid mononitriles **1b**, **1c**, and **1d** a ratio of 5:4:1 in approximately 60–70% crude yield.[8] Similar reaction with the 4-*tert*-butyl-1,2-benzoquinone (eq 5) gave the same products in a comparable yield.



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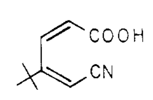
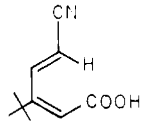
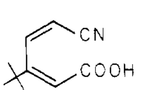


1b



1c



1d

The reaction with catechol provided previously unknown *cis,cis*-muconic acid mononitrile **1a**, mp 136–138 °C, in 40–50% yield (eq 5, X = OH, R = H, *n* = 1).[8] The same mononitrile **1a** is also obtained by reaction with phenol. However, this particular transformation takes place only in the presence of oxygen (eq 4, R = H) and is very much slower (complete oxygen uptake required about 16 h at atmospheric pressure of O$_2$).

A reactive "CuO/NH$_3$" reagent[5] can also be generated by oxidizing copper(I) chloride in ammonium hydroxide solution. Moreover, the conversion of phenol and catechol to the acid nitrile **1a** (eq 3 and 4, R = H) was also possible in this aqueous solvent system. (The work in progress will establish the optimal reaction conditions and the most advantageous solvent system.)

The "CuO/NH$_3$" reagent can be prepared and *isolated* by oxidizing copper(I) chloride in pyridine solution at room temperature, followed by saturation with anhydrous ammonia at 0 °C (eq 1) and filtration of the totally insoluble dark green solid under an inert atmosphere. After being washed with ether and dried at 0 °C in vacuo, the solid can be stored in a refrigerator under a dry inert atmosphere over an extended period of time. The isolated solid is amorphous as shown by X-ray diffractometry and the IR spectrum showed absorptions at 3330, 3210, 3160, 1610, 1230, and 735 cm^{-1}. The elemental analysis suggested the empirical formula $CuClO_{0.5}N_2H_6$.[9]

That this isolated solid is chemically equivalent to the "CuO/NH$_3$" reagent generated in situ is illustrated by the following experiment. To a suspension of the "CuO/NH$_3$" reagent[10] (7.0 g, 50 mmol) in dry pyridine under an inert atmosphere, a solution of 4-*tert*-butylcatechol (0.83 g, 5 mmol) in the same solvent was added with stirring over a period of 1 h at 0 °C. After an additional 30 min at 0 °C and 30 min at room temperature, the usual workup provided the same mixture of isomeric acid nitriles **1b–d** in ca. 50% yield.

At this time a discussion of the mechanism for this novel reaction would be premature. Nevertheless, several observations are notable. First, as in the related carbon–carbon bond cleavages[1,3] with the "copper–oxygen" reagents,[2,4] the overall four-electron oxidation of catechol to the muconic acid mononitrile does not require oxygen. Second, the paucity of coupling products, typically formed by one-electron oxidations in the presence of cupric chloride,[11] suggests that acid nitrile formation may involve

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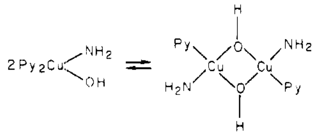
[4] The reaction of oxygen with cuprous chloride provides a mixture of bis(pyridine) cupric chloride and what appears to be dimeric or oligomeric cupric oxide ("copper–oxygen" species) complexed with pyridine.[2,3]

[5] Formally, "CuO/NH$_3$" reagent is a mixture consisting of either bis(pyridine) cupric chloride or cupric chloride complexed with ammonia, or both, and the product(s) of the reaction of the monomeric, dimeric, or oligomeric cupric oxide with ammonia. By analogy with the active component of the "CuO" reagent in the previous work,[1-3] the active component of this reagent may be viewed as a dimeric copper(II) amide hydroxide present in equilibrium with the corresponding monomeric and oligomeric species complexed with pyridine or ammonia.



[6] It should be noted that the "CuO/NH$_3$" reagent refers to a mixture of several copper species[5] resulting from the reaction whose stoichiometry is indicated in eq 1, assuming a minimum ratio of Cu/NH$_3$ of two. The "stoichiometries" in eq 2–4 indicate the ratios of reagents used in the experiments; the "stoichiometries" in eq 5 indicate amounts of the "CuO/NH$_3$" reagent that would be required for the appropriate oxidations; however, in the actual experiment an excess of the reagent was used.

[7] The same reaction system as described in ref 2 was used.

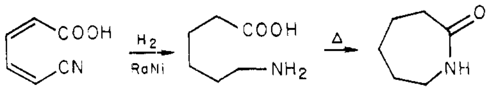
[8] All new compounds are fully characterized. The stereochemistry of nitrile acids **1a–d** was assigned from their NMR spectra.

[9] Use of 4 molar equiv of concentrated ammonium hydroxide in place of excess anhydrous ammonia yielded a lighter green complex, elemental composition $CuClO_{0.5}N_2H_6$, which was also active in the carbon–carbon bond cleavage to nitrile acid.

[10] The "CuO/NH$_3$" reagent is insoluble in pyridine saturated with ammonia at 0 °C. However, addition of the reagent to pyridine containing no ammonia provided a light green solution and suspended dark green solid, suggesting a partial solubility.

sequential two-electron processes.[12] Third, the success with both pyridine and aqueous ammonia as solvents indicates that the nature of the solvent system may not be critical,[13] provided that it is capable of effective solvation of both copper(II) and copper(I) species.[14]

Finally, in accordance with our overall objective,[2,3,15] hydrogenation of *cis,cis*-muconic acid mononitrile (**1a**) over Ra/Ni in ethanol at room temperature and under 1000 psi of hydrogen provided the ω-aminocaproic acid, which was readily converted to caprolactam[16] (eq 6).



(6)

1a

Acknowledgment. We thank Messrs. Bruce Van Buskirk, John Rodler, and Francis Ruggiero for their valuable assistance in all phases of this work. We are also indebted to the staff of our Chemical Physics Department for their analytical services.

Registry No. 1a, 73824-86-9; **1b**, 73824-87-0; **1c**, 73824-88-1; **1d**, 73824-89-2; 4-*tert*-butylcatechol, 98-29-3; 4-*tert*-butyl-1,2-benzoquinone, 1129-21-1; catecho, 120-80-9; phenol, 108-95-2; CuO, 1317-38-0; NH_3, 7664-41-7.

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[11] W. Brackman and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 74, 937, 1021, 1070, 1100, 1107 (1955).

[12] For a discussion of the possible single-step two-electron oxidation mechanisms in similar transformations, see ref 2 and 3.

[13] Other solvents including *N,N*-dimethylformamide and *N*-methylpyrrolidone have also been successfully used in the reaction.

[14] For example, both cupric hydroxide and cuprous chloride[2,3] are insoluble in water but are quite soluble in ammonium hydroxide. Similarly, pyridine efficiently stabilizes both copper(II) oxygen species[4] and copper(I) chloride.[2,3]

[15] See, for example, (a) M. M. Rogić, J. Vitrone, and M. D. Swerdloff, *J. Am. Chem. Soc.*, 98, 4756 (1976); (b) K. P. Klein, T. R. Demmin, B. C. Oxenrider, M. M. Rogić, and M. T. Tetenbaum, *J. Org. Chem.*, 44, 275 (1979).

[16] See, for example, F. Mares and D. Sheehan, *Ind. Eng. Chem. Process Des. Dev.*, 17, 9 (1978).

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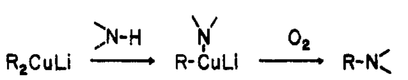
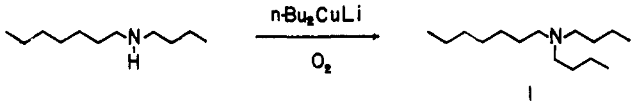
Novel *N*-Alkylation of Amines with Organocopper Reagents

Summary: A mild and efficient method for the *N*-alkylation of amines is described, based on the oxidative coupling of lithium alkylcopper amide, which is derived from lithium dialkylcuprates and primary or secondary amines. The high chemospecificity of the method was demonstrated.

Sir: There is a lack of methodologies which cleanly introduce nitrogen at donor sites.[1] The use of haloamine or hydroxyamine derivatives is a classical solution to this problem.[2] Herein we describe an entirely different approach based on the oxidative coupling of lithium alkylcopper amide,[3] which is derived in situ from lithium dialkylcuprates and primary or secondary amines.[4]


$$R_2CuLi \xrightarrow{>N-H} R-\overset{\diagup N \diagdown}{Cu}Li \xrightarrow{O_2} R-N<$$

In a typical example, butylheptylamine (1 equiv in ether) was added to lithium dibutylcuprate (5 equiv in ether-hexane) at -20 °C. Stirring was continued at -20 °C for 2 h.[5] Excess molecular oxygen was bubbled into the suspension via syringe at -20 °C over 5 min. The mixture was then quenched in concentrated ammonium hydroxide and extracted with ethyl acetate. Purification by column chromatography on silica gel (*i*-$PrNH_2$-MeOH 1:200) gave dibutylheptylamine (1) in 73% yield.[6]



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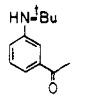
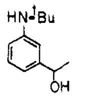
The conditions cited above were crucial for efficient *N*-alkylation of amines. Under similar conditions without oxygen, only a trace amount of **1** was obtained with the recovery of butylheptylamine. Ethereal solvents (diethyl ether or tetrahydrofuran (THF)) were preferable, and less polar solvents (toluene or hexane) decreased the yield.[7] The use of ether as solvent with 3 and 1 equiv of lithium dibutylcuprate afforded **1** in yields of 62 and 54%, respectively.[8]

Representative results obtained on oxidation of other alkylcopper amides are listed in Table I. The method seems to be highly effective for the oxidative coupling of amines with primary alkyl and aryl groups.[9] Furthermore, the bulky *tert*-butyl group can also be introduced by this method. Although introduction of tertiary alkyl groups gave poor yields (23-46%), the conversion yields are usually very high (94% yield[10] for *m*-(*tert*-butylamino)acetophenone (**2**)). In fact, the classical methods are totally ineffective for such transformations. For *tert*-butylation, the polar solvent system, e.g., THF, is preferable and only the starting amine was recovered in the ether solvent. In some cases (entry 1 and 5), Grignard reagents were found to give somewhat higher yields of coupling products than the corresponding organolithium compounds.

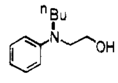
Application of the method to *m*-aminoacetophenone led to the desired *N*-alkylation product **2** without any undesirable complication. Similarly, *N*-alkylation of *m*-(1-hydroxyethyl)aniline and 2-anilinoethanol was achieved successfully without any protection of the hydroxy function.[11] A darkened bond in the formula indicates the bond created by carbon-nitrogen bond forming reactions.



2 (32% (94%)[10])



3 (39%)



4 (37%)

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[1] D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 18, 239 (1979).

[2] For a recent example, see D. I. C. Scopes, A. F. Kluge, and J. A. Edwards, *J. Org. Chem.*, 42, 376 (1977).

[3] For the oxidative coupling of lithium dialkylcuprates, see (a) G. M. Whitesides, J. SanFilippo, Jr., C. P. Casey, and E. J. Panek, *J. Am. Chem. Soc.*, 89, 5302 (1967); (b) G. H. Posner, *Org. React.*, 22, 253 (1975).

[4] Although we have no evidence on the formation of lithium alkylcopper amide, the following reaction infers its existence: The reaction of butylcopper with lithium butylheptylamide in the presence of excess lithium dibutylcuprate at -20 °C for 2 h gave 1 in 78% yield after oxidative workup.

[5] A total of 36.5 mL of solvent was used per millimole of organocopper reagent. All operations were performed under argon atmosphere.

[6] This compound was characterized by IR, mass, and NMR spectra.

[7] Decomposition products were formed at the origin of a TLC plate.

[8] The use of 10 equiv of *n*-Bu_2CuLi gave a yield comparable to that with 5 equiv of *n*-Bu_2CuLi.

[9] Despite much information on organocopper reactions, the available data, in our hands, are not sufficient to allow formulation of a detailed course of this reaction. However, the reactivity of the alkylcopper amide and the yield of the reaction seem to be closely dependent on the type of solvent used and on coordination phenomena of the nitrogen atom.

[10] The yield is based on consumed *m*-aminoacetophenone.

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