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Copper-Catalyzed Homo-Dimerization of Nitronates and Enolates under Oxygen Atmosphere

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Abstract

A method for copper-catalyzed oxidative dimerization of nitronates and enolates using oxygen as terminal oxidant has been developed. Cyclization through oxidative intramolecular coupling is also feasible for both nitronates and enolates. The mild reaction conditions lead to good functional group tolerance.

Oxidative dimerization is a useful transformation for the construction of many symmetric organic molecules such as biaryls,^{1a} vicinal dinitroalkanes,^{1b} and 1,4-dicarbonyl compounds.^{1c} In general, the presence of a stoichiometric oxidant is essential for achieving good conversions. Both organic and inorganic oxidants such as 1,2-dihaloethanes,^{2a-b} benzoquinones,^{2c-d} silver salts,^{2e-f} copper salts,^{2e,g-j,t} ceric ammonium nitrate,^{2k,u-v} persulfates,^{2e-f} hydrogen peroxide,^{2e} iron salts,^{2e,m-n} titanium salts,^{2o-p} and halogens^{2p-s} have been used in these transformations (Scheme 1). However, from both environmental and economic reasons, it is advantageous if those stoichiometric oxidants can be replaced by readily accessible oxygen. Although the involvement of oxygen in oxidative dimerization of aromatic compounds has recently witnessed significant progress,³ the oxidative homocoupling of aliphatic anions such as nitronates and enolates utilizing oxygen as terminal oxidant still remains challenging.^{4a}

Vicinal dinitroalkanes are useful intermediates for the synthesis of vicinal diamines that are employed as ligands for transition metal-catalyzed reactions and can be found in many biologically active compounds.⁵ Moreover, the nitro group can also be converted to a wide range of important functionalities such as amine, carbonyl, nitrile, oxime, hydroxylamine, and thiol.⁶

Similarly, the 1,4-dicarbonyl moiety is ubiquitous in organic molecules including natural products and numerous medicinal remedies.^{2t} Therefore, the synthesis of vicinal dinitroalkanes and 1,4-dicarbonyl compounds is still attracting attention. We have recently developed a method for copper-catalyzed dimerization of aromatic compounds employing oxygen as the terminal oxidant.^{3h} We speculated that the strategy should be applicable for oxidative dimerization of nitronates and enolates. Our speculation was based on the fact that Cu(II)-promoted enolate dimerization as well as the oxidation of low-valent copper species to Cu(II) is well-precedented.^{2e-g,j,t,3h} Therefore, we set out to develop conditions for this transformation employing copper catalysis and oxygen as a terminal oxidant.

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SUPPORTING INFORMATION AVAILABLE: Experimental details, data and spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The dimerization of nitroalkanes has been intensively studied in terms of both method development and mechanism. It can be performed by both electrochemical and chemical methods.^{2e,f,k,l,m,r,s,7} In the latter case, several equivalents of chemical oxidants are employed. Sello and Morin have recently published an elegant work on the synthesis of pimarinic-inducing factor.^{2k} The authors have developed a general procedure for oxidative dimerization of various nitroalkanes using 2.2 equivalents of CAN oxidant and NaH base. However, the use of NaH base requires 15-crown-5 to decomplex the sodium counterion from nitronate and ensure a good yield of the product. We reasoned that since nitroalkanes are fairly acidic ($pK_a < 16-17$),⁸ milder bases could be used to generate nitronates. In addition, higher compatibility of base with copper catalyst and oxygen should result in a one-step reaction. A number of bases and solvents were screened for the dimerization of 2-nitropropane under oxygen atmosphere with 10 mol % of copper(II) chloride catalyst. Interestingly, when DBU was employed as a base, the dimerization proceeds smoothly at room temperature in most common solvents such as DMF, THF, dioxane, DCM, acetonitrile, and methanol to afford product in good conversion.⁹ The best results were obtained in DMF and the products were isolated in excellent yields (Table 1). In addition, mild reaction conditions allow for high tolerance of functional groups. The optimized conditions were applied to dimerization of nitroalkanes bearing various functionalities. Functional groups such as ether (entry 5), ester (entry 6), and ketone (entry 7) are tolerated. The reaction was then extended to cyclization of dinitroalkanes through intramolecular oxidative coupling reaction. A mixture of 2,6-dinitroheptane diastereomers underwent cyclization to afford *cis*-1,2-dimethyl-1,2-dinitrocyclopentane as the sole product (entry 8). In contrast, nearly equal amounts (6/4) of *cis*- and *trans*-1,2-dimethyl-1,2-dinitrocyclopentane were observed by Jackson and Bowman in the cyclization of the same substrate.^{2m}

The Nef reaction is a competing process under these conditions and is responsible for diminished yield of some substrates by unproductive consumption of starting material.⁴ The contribution of side reaction becomes significant for substrates containing at least one large alkyl group (entries 2–7). About 8% of cyclohexanone was formed in the dimerization of nitrocyclohexane (analysis by GC). In some cases, an increase of catalyst amount to 15 mol % improves the yield (entries 2, 3, 4, 8).¹⁰

If two diastereoisomers can be produced, for acyclic cases they are usually generated in equal amounts (*dr* = 1:1, entries 3–7). The control experiments reveal that copper catalyst is essential for the formation of product. Only trace of dimerization product was detected if copper(II) chloride is omitted. Additionally, the reactions can be run in open vials under air; however, substantially longer reaction times are required.¹¹ Unfortunately, all attempts to expand the reaction to dimerization of primary nitroalkanes led to disappointing conversions.

The dimerization of enolates is well-established and has been widely applied in organic synthesis. However, no copper-catalyzed process has been developed yet.^{2g-i,n,p,t} We were interested in establishing the conditions for copper-catalyzed enolate dimerization using oxygen as the terminal oxidant. Propiophenone was chosen as the model substrate. The lithium enolate was prepared by treatment of ketone with LDA in THF at $-78\text{ }^{\circ}\text{C}$. The resulting enolate solution was reacted with oxygen in the presence of 10% of copper(II) chloride. Only 10% conversion to the dimerization product was observed. We assumed that lithium enolate is unstable under the reaction conditions. Consequently, the enolate anion should be stabilized in the presence of oxygen. A feasible solution for this issue is the introduction of a more electrophilic zinc or magnesium salt. We were gratified to find that treatment of lithium enolate solution with 0.3 equivalents of zinc chloride improves the conversion from 10% to 70%. Increasing the amount of zinc chloride additive to 1

equivalent decreases the conversion. Further optimization led to the use of copper(II) acetylacetonate catalyst. The optimized conditions involve 10 mol % Cu(acac)₂ catalyst, 0.3–0.5 equivalents of ZnCl₂ additive, and 1 atm of oxygen affording the desired product in 68% isolated yield. The conditions work well for a variety of carbonyl compounds such as ketones (entries 1–4, 7), esters (entry 5), and amides (entry 6).

Good results can be obtained for both primary and secondary ketones (entries 1–3), although tertiary ketone afforded diminished yield, presumably due to steric effects (entry 4). For chiral or *pro*-chiral secondary ketones, two diastereoisomers are produced with preferential formation of *syn* (*dl*) diastereoisomer (entries 2–3). Analogous outcome have also been observed in stoichiometric dimerizations.^{2i,n,t} The cyclization through intramolecular oxidative coupling is also successful and a mixture *cis*- and *trans*-1,2-dibenzoylcyclohexane was obtained if 1,8-diphenyloctane-1,8-dione was subjected to the general conditions. As expected, *trans*-isomer was formed predominantly (entry 7). In general, the yields in the catalytic reactions parallel the ones previously described in stoichiometric reactions.^{2g-i}

In conclusion, we have developed two copper-catalyzed methods for oxidative dimerization of nitroalkanes and carbonyl compounds that employ oxygen as the terminal oxidant. Mild reaction conditions in the homocoupling of nitroalkanes lead to good functional group tolerance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 9. Please see Supporting Information for optimization data.
 10. Increase of CuCl₂ loading increases the dimerization product yield; however, the effect becomes smaller with higher Cu(II) loading. Please see Supporting Information for details.
 11. Dimerization of nitrocyclohexane under air led to 52% conversion to product in 5 hours. If reaction was run under nitrogen, 9% conversion to product was observed (15 mol% CuCl₂ used). Please see Supporting Information for details..

A. Known Dimerization of Nitronates

Oxidants: $\text{Na}_2\text{S}_2\text{O}_8$, $\text{K}_3[\text{Fe}(\text{CN})_6]$, AgNO_3 , H_2O_2 , halogens, CAN

B. Known Dimerization of Enolates

Oxidants: CuCl_2 , FeCl_3 , TiCl_4 , halogens

C. This Work

Scheme 1.
Dimerization of Nitronates and Enolates

Table 1

Dimerization of Nitroalkanes^a

$ \begin{array}{c} R_1 \quad R_2 \\ \diagdown \quad / \\ C \\ \\ NO_2 \end{array} \xrightarrow[\text{DBU (2 equiv)}]{\text{CuCl}_2 (10\%)} \begin{array}{c} R_1 R_2 \\ \diagdown \quad / \\ C \quad C \\ \quad \\ NO_2 \quad NO_2 \end{array} $ DMF, O ₂ , rt, 1-2 h			
entry	nitroalkane	product	yield
1			80%
2 ^b			55%
3 ^b			73%
4 ^b			60%
5			62%
6			63%
7			46%
8 ^{b,c}			53%

^aNitroalkane (1.0 mmol), DBU (2.0 mmol), CuCl₂ (0.1 mmol), DMF (0.8 mL), room temperature, 1–2 h. Yields are isolated yields.^bCuCl₂ (0.15 mmol) was used.^cDBU (4 mmol) was employed.

Table 2

Dimerization of Carbonyl Compounds^a

$ \begin{array}{c} \text{R}_1\text{---C(=O)---CH}_2\text{---R}_2 \\ \xrightarrow[2. \text{ Cu(acac)}_2 (10\%), \text{ THF, O}_2, \text{ rt, 10 min}]{1. \text{ LDA (1.1 equiv), ZnCl}_2 (0.3 \text{ equiv})} \\ \text{R}_1\text{---C(=O)---CH(R}_2\text{)---CH(R}_2\text{)---C(=O)---R}_1 \end{array} $			
entry	carbonyl compound	product	yield
1 ^c			69%
2			68%
		<i>dr</i> = 4:1	
3			64%
		<i>dr</i> = 1.9:1	
4 ^b			31%
5 ^c			52%
6 ^{c,b}			58%
7 ^b			55%
		<i>trans:cis</i> = 2:1	

^a Carbonyl compound (1.0 mmol), LDA (1.1 mmol), ZnCl₂ (0.3 mmol), Cu(acac)₂ (0.1 mmol), THF (1.0 mL), room temperature, 10 minutes. Yields are isolated yields of a diastereomer mixture if applicable.

^b Cu(acac)₂ (0.15 equiv) was used.

^c 0.5 mmol of ZnCl₂ was employed.