Ascorbate mediated copper catalyzed reductive cross–coupling of disulfides with aryl iodides†

Marek Martinek, Michal Korf and Jiri Srogl*

Received 8th February 2010, Accepted 13th April 2010
First published as an Advance Article on the web 12th May 2010
DOI: 10.1039/c002725a

The concept of using ascorbic acid as a mediator/ reducing agent in a Cu(I) catalyzed process is introduced and further demonstrated on a cross–coupling reaction of aryl iodides with disulfides.

One of the foremost examples of modern synthetic method is the chemistry that helps connect two often highly functionalized entities, while forming a new bond between two atoms of respective subunits in the process. The presence of a transition metal, which facilitates chemistry through consequent oxidative addition/reductive elimination steps, is often required.[1] In this scenario, the reaction partners must possess respective, formally electrophilic and nucleophilic properties in order to keep the catalyst in the reduced form and thus maintain its activity. Although far less used, the opposite circumstances, in which both of the coupling partners show the electrophilic attributes, have been recently the center of intensive research.[2] Setting aside the selectivity issues ensuing inevitably from the presence of two moieties belonging to the same reactivity bracket, the rising challenge in such a reductive cross–coupling to keep the catalyst in an active reduced form has been met by employing a variety of reducing reagents. Unlike a working line of oxidants used in organic synthesis, which is virtually limitless, the selection of reducing agents is, despite great progress in the last few decades, somehow narrow.[3] Complex hydrides of aluminium, boron, tin and silicon commonly added to supplement a variety of traditional reducing agents, alkali metals, Mg, Zn, Mn *etc.* cannot fully remedy the situation due to their high reactivity and toxicity, accompanied by, in some cases, rather prohibitive cost.

Trying to amend the situation above, we want to present a mild and selective reductive cross–coupling reaction of disulfides with aryl iodides, which leads to thioethers as the desired reaction product. There are a great number of methods for the preparation of thioethers in the toolbox of the modern organic chemist.[4] The number is justified by the importance of this functionality in various areas of chemistry.[5] The methods for thioether preparation have been traditionally based on chemistry utilizing a high nucleophilicity of thiolate moieties in non–catalyzed or transition metal catalyzed coupling reactions with organic halides.[6]‡ The method employing disulfides as the source of a thioorganic group has also been introduced, employing Mg and Zn as the reducing agents.[7]§ Elevated temperatures together with a stoichiometric amount of highly reactive metals in the latter case rendered the method rather harsh and consequently unfit for a variety of functional groups.

Addressing those issues while seeking a mild replacement for the reducing agents traditionally used in reductive coupling protocols, we proposed ascorbic acid or its salts to be viable substitutes for its general availability and chemical tolerance.

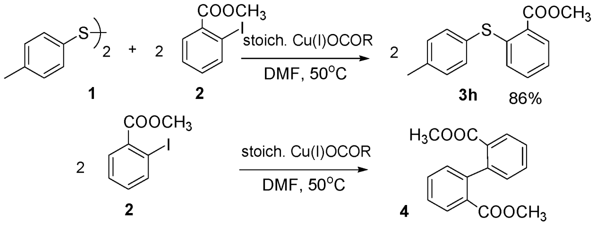
The reducing ability of ascorbic acid, particularly when coupled with the Cu catalyst is well known.[8] Equally well documented is the involvement of Cu complexes in coupling chemistry of arylhalides and thiols.[6b–d,9] Linking both of the reactivity patterns, we have followed on the proposal and centered our investigation on the development of a new mild, synthetically useful protocol.

In order to map the reactivity of disulfides with aryl iodides in the presence of copper, disulfide **1** was treated with aryl iodide **2** and an equimolar amount of Cu(I)3-methylsalicilate. The experiment resulted in an exclusive formation of cross–coupling product **3h** in high yield. (Scheme 1) When disulfide was omitted from the reaction mixture in the control experiment, Ullmann homocoupling product **4** was formed quantitatively, fully in accordance with the published account.[10]

Validating the concept by reducing the amount of the Cu catalyst, the same experiment was carried out with 5% of the CuMeSal and 1.5 equivalents of sodium ascorbate. This, again, led to an exclusive formation of the desired thioether **3** (Scheme 2).

Looking for the best reaction conditions, a series of solvents was examined (THF, AcOH, DMF, H_2O). The best results were obtained when water with a catalytic amount of Brij^R micellar catalyst was used as the reaction media. The superiority of the latter condition can be reasoned by solubility factors (sodium ascorbate) and the issues connected to the product isolation.

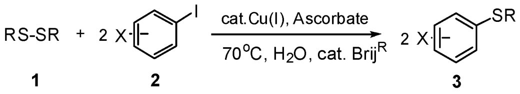
To demonstrate the synthetic scope, various reaction partners¶ were examined under the reaction conditions with the results depicted below (Table 1).



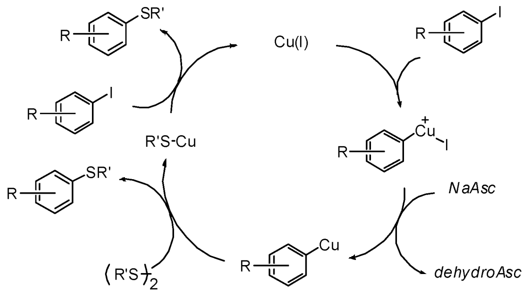
Scheme 1 Cu(I) mediated transformation of aryl iodide.

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Praha 6, Czech Republic. E-mail: jsrogl@uochb.cas.cz

† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/c002725a



Scheme 2 Cu (I) catalyzed, ascorbic acid mediated cross–coupling reaction of aryl iodides with disulfides.

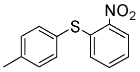
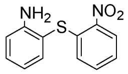
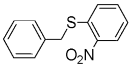
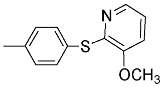
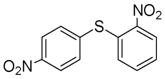
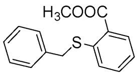
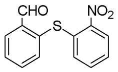
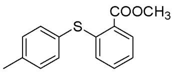
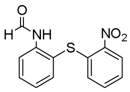


Scheme 3 Tentative mechanism of Cu catalyzed, ascorbate mediated reaction.

There are multiple possibilities of how to view the reaction from the mechanistic standpoint. The first possible path is based on the extensively discussed oxidative addition of Cu(I) into the carbon iodine bond of the aryl halides in the first step,[9b] the alternative way is based on prior reductive generation of Cu(I)thiolate, which further reacts with aryliodide. In order to distinguish between the two routes *p*-tolyldisulfide and 2-formanilidedisulfide respectively were treated in separate experiments with sodium ascorbate in the presence of catalytic Cu. Neither experiment led to any significant amount of the reduction product. When, in the complementary set of experiments, the disulfides were omitted from the reaction mixture, various amounts of dehalogenated product were formed. As a result, we tentatively propose the mechanism involving the formation of oraganocopper species in the first step, which further interact, after the reduction by ascorbate, with the present disulfide moiety, forming the desired thioether (Scheme 3).‖

Overall, we presented here the concept of using a mild and environmentally benign reducing agent, sodium ascorbate, to keep the catalyst in the metal catalyzed reaction in its reduced, active form. The concept has been illustrated on the reductive

Table 1 Investigation of the reaction scope

Entry	Disulfide **1 R** =	Aryliodide **2**	Thioether **3**	Yield
a	*p*-Tolyl	2-Nitrophenyl		83%
b	2-Aminophenyl	2-Nitrophenyl		71%
c	Benzyl	2-Nitrophenyl		64%
d	*p*-Tolyl	2-(3-Methoxy)pyridne		70%
e	4-Nitrophenyl	2-Nitrophenyl		51%
f	Benzyl	2-(Carboxymethyl)phenyl		39%
g	2-Phenylcaronyl	2-Nitrophenyl		65%
h	*p*-Tolyl	2-(Carboxymethyl)phenyl		66%
i	2-Formanilide	2-Nitrophenyl		89%

cross–coupling of aryl iodides with disulfides leading to synthetically desirable products in good to excellent yields. To demonstrate the chemical tolerance of the reaction conditions, substrates containing easily reducible groups have been selected.

The work was supported by the Czech Academy of Sciences (Z40550506, M200550907) and GACR (203/08/1318).

Notes and references

‡ Complementary protocols have also been published which utilize disulfides[11a] or their equivalent[11b] as the substrates for a metal catalyzed cross–coupling reaction with arylboronic acid. While the void of detrimentally high nucleophilicity of thiolates can be considered preferable, arylhalides are, compared with organoboron compounds, the reagent of choice due to their general availability.

§ Thiolate intermediates can be the likely reaction culprits under those conditions.

¶ In an attempt to keep the focus on the conceptual part of the study—ascorbate as the mild alternative to the traditionally used coupling reductive mediators—substrates were deliberately selected a) which possess easily reducible groups and/or b) whose reactivity record in Cu(I) catalyzed reaction under Ullman conditions is well known. There has been no intention, however, to map all the synthetic aspects of the reaction for a fear of venturing into the area discussed elsewhere. The corresponding aryl bromides did not show under the reaction conditions any reactivity.

‖ Pre-coordination of disulfides to the Cu catalyst seems to be a fundamental part of the cross–coupling mechanism as no traces of the Ullman or reduction products have been detected when disulfides were present in even the "Cu stoichiometric" reaction mixture.

1 J.-P. Corbet and G. Mignani, *Chem. Rev.*, 2006, **106**, 2651–2710.

2 (*a*) W. M. Czaplik, M. Mayer and A. Jacobi von Wangelin, *Angew. Chem., Int. Ed.*, 2009, **48**, 607; (*b*) A. Krasovskiy, C. Duplais and B. G. Lipshutz, *J. Am. Chem. Soc.*, 2009, **131**, 15592; (*c*) D. A. Everson, R. Shrestha and D. J. Weix, *J. Am. Chem. Soc.*, 2010, **132**, 920; (*d*) M. Amatore and C. Gosmini, *Chem. Commun.*, 2008, 5019.

3 A. Burke, D. Steven, A. Danheiser and L. Rick, *Handbook of Reagents for Organic Synthesis—Oxidizing and Reducing Agents*, John Wiley & Sons,Chichester, 1999.

4 S. Oae, *Organic Sulfur Chemistry: Structure and Mechanism*, CRC Press, Inc., Boca Raton, 1991.

5 S. Oae and T. Okuyama, in *Organic Sulfur Chemistry: Biochemical Aspects*, CRC Press, Inc., Boca Raton, 1992.

6 (*a*) J. F. Hartwig and D. Barranano, *J. Am. Chem. Soc.*, 1995, **117**, 2937–2938; (*b*) F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 3517; (*c*) C. G. Bates, R. K. Gujadhur and D. Venkataraman, *Org. Lett.*, 2002, **4**, 2803; (*d*) C. Palomo, M. Oiarbide, R. Lopez and E. Gomez-Bengoa, *Tetrahedron Lett.*, 2000, **41**, 1283.

7 (*a*) N. Taniguchi, *J. Org. Chem.*, 2004, **69**, 6904; (*b*) S. Chowdhury and S. Roy, *Tetrahedron Lett.*, 1997, **38**, 2149–2152.

8 (*a*) B. Fuger, *Synlett*, 2009, 848–849; (*b*) O. A. Attanasi, G. Favi, P. Filippone, F. Mantellini, G. Moscatelli and F. R. Perrulli, *Org. Lett.*, 2010, **12**, 468; (*c*) J. Srogl and S. Voltrova, *Org. Lett.*, 2009, **11**, 843–845.

9 (*a*) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428; (*b*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400–5449.

10 S. Zhang, D. Zhang and L. S. Liebeskind, *J. Org. Chem.*, 1997, **62**, 2312–2313.

11 (*a*) N. Taniguchi, *Synlett*, 2006, 1351–1354; (*b*) C. Savarin, J. Srogl and L. S. Liebeskind, *Org. Lett.*, 2002, **4**, 4309–4312.