Cu and Ag catalyzed oxidative arylthiation of terminal acetylenes†

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Received 12th April 2010, Accepted 29th June 2010 DOI: 10.1039/c0cc00885k

A mild Cu or Ag catalyzed oxidative arylthiation of terminal acetylenes is introduced. The process, featuring metal catalyzed C-H bond activation as a key step, leads to the formation of highly substituted mercaptoacetylenes under unprecedented neutral conditions.

Synthetic reactions utilizing a metal catalyzed C-H bond activation have secured, deservingly, a prominent place in the organic chemistry toolbox. Obviating the reaction importance is its inherent gain in atomic economy, as the formal leaving group is the simplest possible entity—the hydrogen atom. The general reaction scheme typically includes formation of an organometallic intermediate from the substrates and suitable metal-based catalyst, with the intermediate further undergoing a final transformation after interacting with the reaction partner.¹ Conditions of the reaction greatly differ, depending on the nature of the transition metal catalyst and the type of substrate. The variety of suitable compounds includes heterocyclic, aromatic, aliphatic or other molecules containing a reactive C-H bond.¹ Some of the synthetically most important species falling into this reactivity bracket are terminal acetylenes; thanks to the metal catalyzed C-H activation resulting in facile formation of metal acetylides, they have become over the last several decades an indispensable building block for synthetic chemistry.² The acetylene interactions with Ag^{2a-d} and, particularly, with Cu salts, $2^{2a,e,f}$ have been extensively utilized, leading, for example, to such a fundamental synthetic tool as the Sonogashira cross-coupling protocol, which has currently become the foremost choice for substituted acetylene synthesis.³ The easy formation of the above metal acetylides also attracted our attention and prompted us to investigate their reactivity towards soft metallophilic species. The soft metal acetylides interaction with disulfides and their analogues has been particularly intriguing: The intended synthetic targets-alkyl or aryl mercapto acetylenes-were previously introduced as the substrates for the "inverse-Sonogashira process"-complementary Pd and Cu catalyzed mirror-like cross-coupling protocol.⁴ The key substrates—the alkyl or aryl mercaptoacetylenes-were prepared the traditional way by using BuLi to form lithium acetylides, followed by the treatment of disulfides or their analogs.4a While the reaction conditions of the "inverse-Sonogashira" cross-coupling are very mild and forgiving, the strong base involvement in the substrate synthesis was, unquestionably, troublesome and needed some rectification for its wider synthetic applicability.

Having had a tangible incentive in the synthetically valuable synthon, we focused our research on the investigation of the copper acetylide interaction with disulfides and their analogs.

Although the intrinsic reactivity of organocopper, and less so, of organosilver compounds, with thioorganic moieties is well known, the related chemistry of organic disulfides, abundant and arguably very important naturally occurring moieties,⁵ has still uncharted reactivity territory yet to be discovered. To overcome the problematic chemistry of the sulfur–sulfur bond where, inherent to a common mechanism, the unconsumed sacrificial half of the disulfide forms a detrimentally strong bond with the catalytic metal,⁶ we turned our attention to the analogs of disulfides featuring the sulfur–nitrogen bond instead. Rudiments of the above concept were previously validated with thioimides as the substrates.⁷ Adding their accessibility and stability, they have become the reagents of our choice.

In the pilot part of the investigation Cu phenylacetylide 1 was preformed *via* the common protocol⁸ and treated with thioimides to evaluate the reaction conditions. Unlike the cyclic *N*-thioamide 2d, which reacted smoothly, providing the mercapto acetylene 3d in good yield, acyclic analog 2g did not lead to the desired results. Diphenyl disulfide brought in for comparison did not show, to our surprise, any significant reactivity either (Scheme 1).

Having established the general reactivity pattern, we moved our focus to the corresponding Cu(1) *catalyzed* protocol. Several possible catalyst candidates, Cu(1) 3-methylsalicylate and CuI were examined. While the reaction in the presence of CuI did not proceed beyond mere traces of the products, Cu(1) 3-methylsalicylate catalyzed transformation led cleanly to the desired mercaptoacetylene. Although more exotic than Cu, other metals known for their thiophilicity⁹ such as Ag, Hg, and Pd were also examined as the potential reaction catalysts. Whereas Hg(OAc)₂ and Pd(OAc)₂ were virtually ineffective, AgOAc catalysed reactions showed an efficiency matching the copper catalyzed protocol. While the reactivity of the Cu and Ag acetylides towards *N*-thioamides is, in certain aspects,



Scheme 1 Reaction of N-thioimides with Cu acetylide.

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[†] Electronic supplementary information (ESI) available: Details of the preparative experiments. See DOI: 10.1039/c0cc00885k



Scheme 2 Ag or Cu catalyzed reaction of terminal acetylenes and N-thioamides.

Table 1 Ag or Cu catalyzed reaction of terminal acetylenes and N-thioamides. The reaction scope

| Product | Х | R | R′ | Method ^a | Yield $(\%)^b$ |
|---------|-----------------|-------------|--|---------------------|----------------|
| 3a | Н | benzyl | Ph | A, (C) | 90, (88) |
| 3b | NO_2 | 2,4-diMeOPh | (COOEt) ₂ (CH ₃)C-CH ₂ - | A | 92 |
| 3c | NO_2 | 2,6-diMePh | 4-(MeO)-2-(Me)Ph | A, (D) | 86, (90) |
| 3d | NO ₂ | allyl | Ph | B | 93 |
| 3e | NO_2 | allyl | pyridin-3-yl | В | 96 |
| 3f | NO_2 | 2,6-diMePh | 2-BrPh | А | 83 |
| 3g | NO_2 | allyl | n-Bu | В | 73 |
| 3h | NO_2 | 2,4-diMeOPh | cyclopropyl | B, (D) | 89, (93) |
| 3i | NO ₂ | 2-HOPh | (1,3-dioxoisoindolin-2-yl)methyl | В | 92 |
| 3i | Η | benzyl | pyridin-3-yl | А | 71 |
| 3k | NO_2 | allyl | 2-(Cl)-5-(NO ₂)PhCOOCH ₂ - | B, (D) | 85, (91) |
| 31 | PhCONH | i-Pr | 3-cyanoprop-1-yl | A, (C) | $88, (22^{c})$ |
| 3m | Н | benzyl | cyclopropyl | (D) | (97) |
| 3n | NO_2 | allyl | 4-fluorophenyl | (D) | (94) |

^{*a*} General procedures: Method A: A mixture of *N*-thioamide **2** (0.50–1.00 mmol), acetylene **1** (1.3–2.0 eq.) and CuMeSal (1–3%) in degassed DMF (1–2 mL) was irradiated in a microwave reactor. Method B: A mixture of *N*-thioamide **2** (1.00–4.00 mmol), acetylene **1** (1.3–2.0 eq.) and CuMeSal (1–3%) in degassed DMF (2–3 mL) was heated under argon at 50–80 °C. Method C: A mixture of *N*-thioamide **2** (0.70–2.00 mmol), acetylene **1** (1.2–2.0 eq.) and AgOAc (1–3%) in DMF (1–2 mL) was irradiated in a microwave reactor. Method D: A mixture of *N*-thioamide **2** (1.00–1.50 mmol), acetylene **1** (1.2–2.0 eq.) and AgOAc (1–3%) in DMF (1.5–3 mL) was heated at 50–70 °C. ^{*b*} The yields in parentheses represent the Ag catalyzed protocol. ^{*c*} Conversion.

comparable, there are still the reactions facets which clearly distinguish between the two. The synthetically most significant difference is the reaction sensitivity to air. Whereas the Cu catalyzed protocol needs to strictly adhere to inert atmosphere requirements to avoid the excessive formation of the diacetylene homocoupling by-product, the quality of the atmosphere in the silver catalyzed version is not critical.

Not surprisingly, the reactivity of the *N*-thioamides was, to some extent, influenced by the substitution pattern; while *p*-nitro substituted substrates reacted smoothly under mild conditions, elevated temperatures or prolonged times were needed for a successful reaction outcome when an electron donating substituent was present. In the latter case the excessive reaction times were successfully remedied by using a microwave reactor. Out of the solvents examined as the possible reaction media, DMF was selected on the basis of the isolated yields.

The results, which summarize the reaction scope, are depicted in Scheme 2 and Table 1.

The likely mechanism of the reaction starts, as probed in the stoichiometric mode, with the formation of metal acetylide, which further reacts with the sulfur–nitrogen bond of *N*-thioamides. While the nature of the latter step can have, in general, multiple explanations, the selection of metals and their similar reactivity let us propose a nucleophilic attack of metal acetylide on the sulfur atom of *N*-thioamide, accompanied by SN bond activation by thiophilic metal as the tentative reaction mechanism. The other path, starting with the oxidative addition of metal into the SN bond, which could be justified in the Cu

catalyzed protocol,⁷ and which is highly unlikely in the silver catalyzed reaction, can be, given the mirror-like reaction outcome in both respective cases, discounted (Scheme 3).

To validate one of the purposes behind the new synthetic protocol, the "inverse-Sonogashira" cross-coupling reaction was demonstrated on several of the formed mercaptoacetylenes (Scheme 4, Table 2).¹⁰



Scheme 3 Tentative mechanism of the reaction.



Scheme 4 Cross-coupling reaction of the mercaptoacetylenes.

 Table 2 Cross-coupling reaction of the mercaptoacetylenes^a

| Product | 3 | R'' | R′ | Yield (%) |
|---------|----|----------------------|--|--------------|
| 5a | 3d | 4-tolyl | Ph | 85 |
| 5b | 3k | 4-MeOPh | 2-(Cl)-5-(NO ₂)- PhCOOCH ₂ - | 83 |
| 5c | 3g | 4-dibenzothienyl | n-Bu | 69 |
| 5d | 3k | 3-NO ₂ Ph | 2-(Cl)-5-(NO ₂) PhCOOCH ₂ - | 66 |
| 5e | 3n | 2,6-diMePh | 4-fluorophenyl | 58 |
| 5f | 3n | 2-MeOPh | 4-fluorophenyl | 76 |
| | | | | |

^{*a*} General procedure: Thioacetylene (1.00 mmol), arylboronic acid (1.30 mmol), Cu(1) 3-methylsalicylate (1.20 mmol) and Pd(PPh₃)₄ (5 mol%) were stirred in DME (8 mL) under argon at 40–45 °C for 16 h.

Setting aside their excellent synthetic accessibility, there is an interesting advantage in utilizing the cyclic *N*-thioamides as the reaction substrates. The present structural motif reveals a unique intrinsic reactivity pattern further obviating the substrate selection; Cu thiolates, the obligatory byproducts of the cross-coupling reaction,^{4a} can be turned back into the starting *N*-thioamide substrates under exceptionally mild conditions, releasing copper in due course.¹¹

Overall, we have introduced a metal catalyzed oxidative arylthiation of terminal alkynes. The tentative reaction mechanism was proposed, which starts with a C–H bond activation step and involves the intermediate formation of metal acetylides. The synthetic utility of the resulting mercaptoacetylenes is illustrated by several cross-coupling reactions and the concept of the byproduct recycling is demonstrated by way of a novel oxidative method. The work was supported by IOCB (Z40550506), and the Czech Academy of Sciences (M200550907).

Notes and references

- (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (b) I. V. Seregin and V. Gevorgian, *Chem. Soc. Rev.*, 2007, **36**, 1173; (c) Y. J. Park, J.-W. Park and C.-H. Jun, *Acc. Chem. Res.*, 2008, **41**, 222; (d) L. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013; (e) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (f) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (g) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624.
- (a) A. M. Sladkov and L. Y. Ukhin, Russ. Chem. Rev., 1968, 37, 748; (b) U. Halbes-Letinois, J.-M. Weibel and P. Pale, Chem. Soc. Rev., 2007, 36, 759; (c) Y. Yamamoto, Chem. Rev., 2008, 108, 3199; (d) S. P. Shahi and K. Koide, Angew. Chem., Int. Ed., 2004, 43, 2525; (e) M. P. Cassidy, J. Rauschel and V. V. Fokin, Angew. Chem., Int. Ed., 2006, 45, 3154; (f) F. Himo, T. Lowel, R. Hilgraf, V. V. Rostovtsev, L. Noodelman, K. B. Sharpless and V. V. Fokin, J. Am. Chem. Soc., 2005, 127, 210.
- 3 (a) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 16, 4467; (b) E. Negishi and L. Anastasia, *Chem. Rev.*, 2003, 103, 1979; (c) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, 107, 874.
- 4 (a) C. Savarin, J. Srogl and L. S. Liebeskind, Org. Lett., 2001, 3, 91. For a haloacetylene version of the chemistry see:
 (b) N. Miyaura, K. Yamada and A. Suzuki, Tetrahedron Lett., 1979, 20, 3437; (c) X. Yang, L. Zhu, Y. Zhou, Z. Li and H. Zhai, Synthesis, 2008, 11, 1729; (d) C.-M. Yu, J.-H. Kweon, P.-S. Ho, S.-C. Kang and G. Y. Lee, Synlett, 2005, 2631.
- 5 S. Oae and T. Okuyama, Organic Sulfur Chemistry: Biochemical Aspects, CRC Press, Boca Raton, 1992.
- 6 (a) For Rh catalyzed version see: M. Arisawa, M. Fujimoto, S. Morinaka and M. Yamaguchi, J. Am. Chem. Soc., 2005, 127, 12226; (b) For stoichiometric Cu(1)OTf and trimethylsilyl acetylene see: N. Miyachi and M. Shibasaki, J. Org. Chem., 1990, 55, 1975.
- 7 C. Savarin, J. Srogl and L. S. Liebeskind, Org. Lett., 2002, 4, 4309.
- 8 W. Shi, Y. Luo, X. Luo, L. Chao, H. Zhang, J. Wang and A. Lei, J. Am. Chem. Soc., 2008, 130, 14713.
- 9 R. G. Pearson, J. Am. Chem. Soc., 1963, 85, 3533; R. G. Pearson, Chemical Hardness, Wiley-VCH, Weinheim, 1997.
- 10 The general reactivity pattern of the present thioacetylenes in the cross-coupling reaction is the same as the one published previously.^{4a} When n-hexyl boronic acid was used as the coupling partner no desired productwas detected.
- 11 While it is clearly not the main topic of the paper, the Cu releasing reaction was experimentally demonstrated. For the details see the supplementary materials.