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# Palladium-Catalyzed Cleavage of O/N-Propargyl Protecting Groups in Aqueous Media under a Copper-Free Condition[1]

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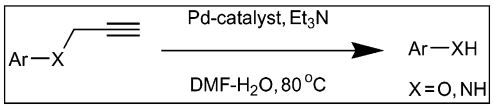
## ABSTRACT




**A copper-free palladium-mediated cleavage of O/N-propargyl bonds in aqueous media has been investigated, affording a mild and convenient method for the deprotection of phenols and anilines. The methodology could be utilized for the selective removal of propargyl groups from aryl ethers and amines without affecting a variety of unprotected functional groups present in the substrates. The mechanism and scope of the reaction is discussed.**

Protecting groups often play a crucial role in many complex synthetic strategies. Therefore, proper selection and cleavage of efficient protecting groups is invariably a prerequisite in such processes especially in the synthesis of natural products and polyfunctional molecules.[2a] The protection of aromatic amino or hydroxyl groups as appropriate amine derivatives or ethers and their subsequent cleavage constitute a useful chemical transformation in organic synthesis. The propargyl group is attractive due to the presence of two orthogonal $\pi$-bonds, which perhaps help in its facile cleavage in the presence of transition metal complexes.[2b,c] Besides, depropargylation has considerable biological significance as is exemplified by its role in aldehyde dehydrogenase (AlDH) inhibitory activity in vivo.[2d]

A number of reports are available in the literature for the cleavage of the carbon−oxygen[3]/carbon−nitrogen[4] bond in a variety of compounds such as allyl, vinyl, and benzyl ethers/amines. Although the cleavage of C−O bonds in allyl ethers/esters has been thoroughly investigated, only a few examples are known dealing with the cleavage of the C−X (X = O, N) bond in propargyl ethers/esters or amines. These include the use of low-valent titanium,[5] hydrogenolysis of propargyl esters with formic acid or formates,[6] nickel-catalyzed electroreductive cleavage of propargyl compounds,[7] palladium-catalyzed reductive cleavage of propargyl esters mediated by $Bu_3SnH$ or by $SmI_2$,[8a−c] and cleavage of propargyl ethers or propargyloxy carbonyl protected amines with tetrathiomolybdate.[8d,e] All these methods involve mild

(1) DRL Publication No 278.

(2) (a) Schelhaas, M.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2056. (b) Nandi, B.; Das, K.; Kundu, N. G. *Tetrahedron Lett.* **2000**, *41*, 7259. (c) Kandikere, R. P.; Naduthambi, D.; Chandrasekaran, S. *Synlett* **2002**, 1762. (d) Shirota, F. N.; DeMaster, E. G.; Elberling, J. A.; Nagasawa, H. T. *J. Med. Chem.* **1980**, *23*, 669.

(3) (a) Deelman, B.-J.; Booij, M.; Meetsma, A.; Teuben, J. H.; Kooijman, H.; Spek, A. L. *Organometallics* **1995**, *14* (5), 2306. (b) Takaki, K.; Kusodo, T.; Uebori, S.; Makioka, Y.; Taniguchi, Y.; Fujiwara, Y. *Tetrahedron Lett.* **1995**, *36* (9), 1505. (c) Takaki, K.; Maruo, M.; Kamata, T.; Makioka, Y.; Fujiwara, Y. *J. Org. Chem.* **1996**, *61* (23), 8332. (d) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, Germany, 1994; p 61−68. (e) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley: New York, 1991; p 42−43. (f) Gigg, R. *J. Chem. Soc., Perkin Trans. 1* **1979**, 712. (g) Gigg, J.; Gigg, R. *J. Chem. Soc. C* **1966**, 8286. (h) Corey, E. J.; Suggs, W. J. *J. Org. Chem.* **1973**, *38*, 3224.

(4) (a) Talukdar, S.; Banerji, A. *Synth. Commun.* **1996**, *26*, 1051. (b) Talukdar, S.; Nayak, S. K.; Banerji, A. *J. Org. Chem.* **1998**, *63*, 4925.

(5) (a) Kadam, S. M.; Nayak, S. K.; Banerji, A. *Tetrahedron Lett.* **1992**, *33*, 5129. (b) Nayak, S. K.; Kadam, S. M.; Banerji, A. *Synlett.* **1993**, 581. (c) Rele, S.; Talukdar, T.; Banerji, A. *Tetrahedron Lett.* **1999**, *40*, 767.

(6) (a) Tsuji, J.; Mandai, T. *Synthesis* **1996**, *1*, 1. (b) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.

(7) Olivero, S.; Dunach, E. *Tetrahedron Lett.* **1997**, *38*, 6193.

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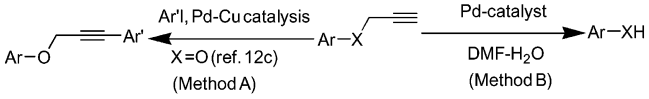
reaction conditions but most of them require either the use of multiple reagents or prior preparation of the actual reagent.[5,8] Moreover, a few of them were found to be incompatible with several functional groups especially halogens[7] where dehalogenation was observed frequently. Thus there is a continuing demand for the development of alternative methods which depropargylate amines/ethers more efficiently under mild conditions.

In connection with our studies on the development of various diaryl heterocycles for biological testing in different therapeutic areas, we have reported the synthesis of 3,4-diaryl furanones,[9] 3,4-diarylmaleic anhydrides,[10] and pyrrolo[1,2-*b*]pyridazines.[11] In further pursuance of our research under the new drug discovery program a wide variety of appropriately functionalized phenols and anilines were needed for the synthesis of compounds of potential biological interest. Therefore a general and straightforward method was required for the cleavage of the C−X (X = O, N) bond in propargyl ethers/amines toward the synthesis of such compounds. We have a long-term interest on palladium-catalyzed reactions[12] and now wish to present here our exploratory work on the development of novel palladium-mediated depropargylation of aromatic ethers and amines under mild conditions.

The palladium-catalyzed coupling (Sonogashira coupling) reaction of aryl halides with terminal alkynes provides a powerful tool for the C−C bond formation reaction.[12,13] This reaction is usually carried out in the presence of catalytic amounts of a palladium(II) complex as well as copper(I) iodide in an amine as solvent under inert atmosphere and the methodology has been extended well for the coupling of propargyl ether with aryl halides (Method A, Scheme 1).[13c]

**Scheme 1**




On the other hand, this palladium−copper-catalyzed reaction led to the dimerization of the terminal alkynes in the presence of oxygen or other reagents.[14] Since CuI in the presence of excess amine base seemed to have a significant role in such oxidative homocoupling of terminal acetylenes, copper-free palladium-catalyzed reactions have been developed[12a,15] for the coupling of aryl halides with terminal alkyne. However, we have observed that cleavage of the C−X (where X = O, N) bond[16] occurs when the reaction was performed employing propargyl ether or amine as the terminal acetylene in the absence of aryl halide in dimethylformamide (DMF) in the presence of water (Method B, Scheme 1). Thus when propargyl ethers/amines[17] (**I**) were treated with $(PPh_3)_2PdCl_2$ in aqueous DMF in the presence of triethylamine at 80 °C for 2 to 3 h corresponding phenols/amines (**II**) were isolated in good yields. The results of this study are summarized in Table 1.

By use of this palladium-catalyzed depropargylation reaction a wide variety of aryl propargyl ethers and amines were cleaved to the corresponding phenols and amines (Table 1). Various substituents on the phenyl ring of the starting ether or amine (**I**) are well tolerated during the course of the reaction. Ethers afforded good yields of products irrespective of the presence of an electron-withdrawing group such as aldehyde, ketone, nitro (entry 1−4, Table 1), or electron donating group, e.g. chloro and methoxy (entries 7 and 9, Table 1), on the phenyl ring. However, yields were satisfactory in the case of amines (entries 14−16, Table 1). Halogens were found to be well tolerated in this palladium-mediated reaction, as no dehalogenated products were detected in theses cases (entries 5, 8, 9, 11, and 16, Table 1). Also, reducible functional groups present in the substrate remained unaffected (entries 1−6, 8, and 14−15, Table 1).

The palladium-catalyzed C−X bond cleavage was found to be regioselective as alkoxy groups such as methoxy remained unaffected during the course of the reaction (entries 5−7, Table 1). However, propargylic ester along with the ether was cleaved under the conditions employed in the reaction (entry 13, Table 1).

The depropargylation reaction of ether/amine was usually carried out in DMF−$H_2O$ (2:1) with use of triethylamine as a base. The advantage in the use of DMF as solvent is its ability to solubilize a wide variety of substrates and palladium catalyst as well as its miscibility with water, which therefore facilitates the cleavage of the C−X bond. Nevertheless, the

(8) (a) Zhang, H. X.; Guibe, F.; Balavoine, G. *Tetrahedron Lett.* **1988**, *29*, 619. (b) Inanaga, J.; Sugimoto, Y.; Hanamoto, T. *Tetrahedron Lett.* **1992**, *33*, 7035. (c) Aurrecoechea, J. M.; Anton, R. F. *J. Org. Chem.* **1994**, *59*, 702. (d) Swamy, V. M.; Ilankumaran, P.; Chandrasekaran, S. *Synlett* **1997**, 513. (e) Sinha, S.; Ilankumaran, P.; Chandrasekaran, S. *Tetrahedron Lett.* **1999**, *40*, 771.

(9) (a) Pal, M.; Rao, Y. K.; Rajagopalan, R.; Misra, P.; Kumar, P. M.; Rao, C. S. World Patent WO 01/90097, 29 Nov 2001; *Chem. Abstr*. **2002**, *136*, 5893. (b) Padakanti, S.; Veeramaneni, V. R.; Pattabiraman, V. R.; Pal, M.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2002**, *43*, 8715. (c) Pal, M.; Rao, V. V.; Srinivas, P.; Murali, N.; Akhila, V.; Premkumar, M.; Rao, C. S.; Misra, P.; Ramesh, M.; Rao Y. K. *Indian J. Chem.* **2003**, in press.

(10) Pattabiraman, V. R.; Padakanti, P. S.; Veeramaneni, V. R.; Pal, M.; Yeleswarapu, K. R. *Synlett* **2002**, 947.

(11) Pal, M.; Batchu, V. R.; Khanna, S.; Yeleswarapu, K. R. *Tetrahedron* **2002**, 9933.

(12) (a) Pal, M.; Parasuraman, K.; Gupta, S.; Yeleswarapu, K. R. *Synlett* **2002**, 1976. (b) Pal, M.; Kundu, N. G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 449. (c) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.* **1993**, 86. (d) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc., Chem. Commun.* **1992,** 41.

(13) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, p 521. (c) Nguyen, B. V.; Yang, Z. Y.; Burton, D. J. *J. Org. Chem*. **1993**, *58* (26), 7368−76.

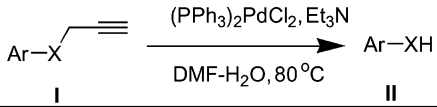
(14) (a) Rossi, R.; Carpita, A.; Bigelli, C. *Tetrahedron Lett.* **1985**, *26*, 523. (b) Kundu, N. G.; Pal, M.; Chowdhury, C. *J. Chem. Res. Synop.* **1993**, 432. (c) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969 and references therein.

(15) (a) Fu, X.; Zhang, S.; Yin, J.; Schumacher, D. P. *Tetrahedron Lett.* **2002**, *43*, 6673. (b) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691. (c) Wu, M.-J.; Wei, L.-M.; Lin, C.-F.; Leou, S.-P.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7839.

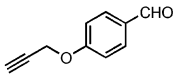
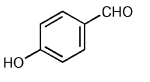
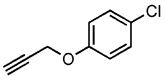
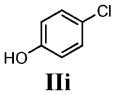
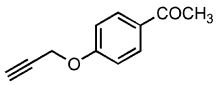
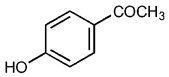
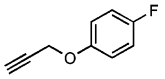
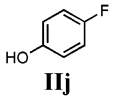
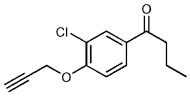
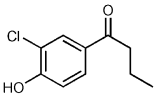
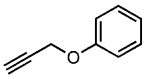
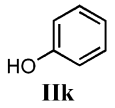
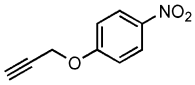
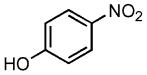
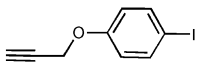
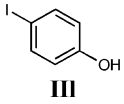
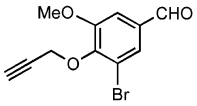
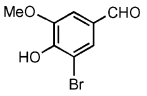
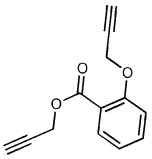
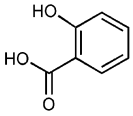
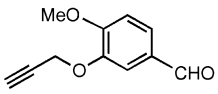
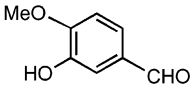
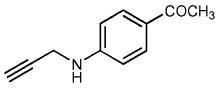
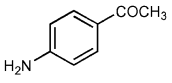
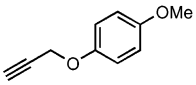
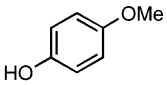
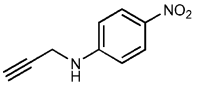
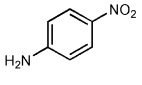
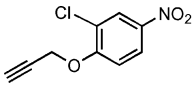
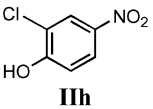
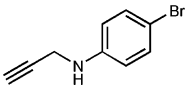
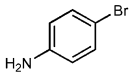
(16) For the cleavage of the C−S bond with concurrent *S*-arylation under palladium−copper catalysis see: Kundu, N. G.; Nandi, B. *Tetrahedron* **2001**, *57*, 5885 and references therein.

(17) Aryl propargyl ethers were prepared according to the procedure described in the literature, see for example: Ishikawa, T.; Mizutani, A.; Miwa, C.; Oku, Y.; Komano, N.; Takami, A.; Watanabe, T. *Heterocycles* **1997**, *45*, 2261.

**Table 1.** Deprotection of Aryl Propargyl Ethers/Amines in the Presence of Palladium Catalyst[a]




I II

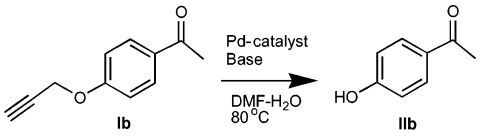
| Entry | Substrate (**I**) | Products[b] (**II**) | Yield (%)[c] | Entry | Substrate (**I**) | Products[b] (**II**) | Yield (%)[c] |
|---|---|---|---|---|---|---|---|
| 1. |  **Ia** |  **IIa** | 75 | 9. |  **Ii** |  **IIi** | 71 |
| 2. |  **Ib** |  **IIb** | 78 | 10. |  **Ij** |  **IIj** | 67 |
| 3. |  **Ic** |  **IIc** | 65 | 11. |  **Ik** |  **IIk** | 75 |
| 4. |  **Id** |  **IId** | 74 | 12. |  **Il** |  **IIl** | 51 |
| 5. |  **Ie** |  **IIe** | 68 | 13. |  **Im** |  **IIm** | 45 |
| 6. |  **If** |  **IIf** | 55 | 14. |  **In** |  **IIn** | 57 |
| 7. |  **Ig** |  **IIg** | 63 | 15. |  **Io** |  **IIo** | 52 |
| 8. |  **Ih** |  **IIh** | 77 | 16. |  **Ip** |  **IIp** | 53 |

[a] Reactions were carried out by using **I** (1.0 equiv), $PdCl_2(PPh_3)_2$ (0.04 equiv), $Et_3N$ (8 equiv) in DMF−$H_2O$ (2:1) for 2 h (entries 1−3) or 3 h (entries 4−16). [b] Identified by $^1H$ NMR, IR, mass. [c] Isolated yields.

use of other solvents such as acetonitrile and dioxane is under investigation. The role of triethylamine was also investigated and the reaction did not proceed in the absence of base (entry 2, Table 2). The reactions were usually carried out at 80 °C for 2−3 h. Lowering the temperature was found to be ineffective in terms of the yield of products. The presence of water seemed to have a crucial role in the depropargylation reaction [the minimum amount of water required for the successful depropargylation reaction was found to be DMF: $H_2O$ = 43:1(entry 1, Table 2)] and therefore further study on the influence of water on the rate of the reaction as well as product yields is in progress.

The depropargylation reaction proceeds well in the presence of $(PPh_3)_2PdCl_2$ and no reaction was observed in the absence of this catalyst (entry 3, Table 2). Use of other catalysts such as $(PPh_3)_4Pd$ was also investigated and was

**Table 2.** Effect of Reaction Conditions on Depropargylation reaction[a]



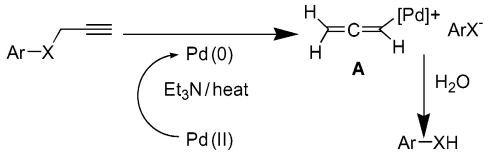

| entry | catalyst | base (reaction time) | yield (%)[b] |
|---|---|---|---|
| 1 | $(PPh_3)_2PdCl_2$ | $Et_3N$ (4 h) | 75[c] |
| 2 | $(PPh_3)_2PdCl_2$ | no $Et_3N$ (12 h) | n.d. |
| 3 | No $(PPh_3)_2PdCl_2$ | $Et_3N$ (48 h) | n.d. |
| 4 | $(PPh_3)_4Pd$ | $Et_3N$ (2 h) | 80 |
| 5 | $(PPh_3)_4Pd$ | $NaHCO_3$ (12 h) | 49 |
| 6 | No $(PPh_3)_4Pd$ | $NaHCO_3$ (24 h) | n.d. |

[a] Reactions were carried out by using **Ib** (1.0 equiv), Pd catalyst (0.04 equiv), base (8 equiv) in DMF−$H_2O$ (2:1). [b] Isolated yields. [c] DMF−$H_2O$ (43:1). n.d. = not detected.

found to be equally effective (entry 4, Table 2), implying the participation of Pd(0) in the C−X bond cleavage.[18] Use of a mild inorganic base such as $NaHCO_3$ along with $(PPh_3)_4Pd$ was also found to be satisfactory when applied for a longer period of time (entry 5, Table 2). Since the procedure does not involve the use of copper salts, no oxidative homocoupled product of terminal alkynes was detected in these cases. This is in sharp contrast to the result disclosed for the depropargylation of thioether earlier where CuI was found to be essential along with the palladium catalyst and no depropargylation took place in the absence of either of the catalysts.[2b,16]

While the precise mechanism of the palladium-catalyzed depropargylation reaction is not clear at this stage, presumably the C−X bond cleavage proceeds via generation of an allenylpalladium intermediate **A** (Scheme 2).[19] Thus the aryl

**Scheme 2.** Proposed Mechanism for the Palladium-Catalyzed Depropargylation Reaction




propargylamine or ether reacts with palladium(0), generated from palladium(II) complex,[20] leading to the formation of intermediate **A** with the cleavage of the C−X bond. This allenylpalladium intermediate then undergoes nucleophilic attack on the central sp carbon by a water molecule thereby releasing the desired aniline or phenol with the regeneration of Pd(0) species which then completes the catalytic cycle. Further investigation on this $S_N2'$-type reaction of the Pd complex with the propargyl derivatives is in progress.

We have shown that a variety of aryl propargyl ethers and amines (**I**) can be deprotected in the presence of palladium catalyst under a copper-free condition without affecting the other functional groups. To demonstrate the generality and scope of this approach an azole derivative, i.e., 1-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}-1-ethanone required for the synthesis of doxadiazolidine-dione of biological interest[21a,b] was prepared with **IIb** and commercially available 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethan-1-ol according by the procedure[21b] described in the literature. Also, ketones **III** ($RCOC_6H_4OH$-*p*; R = Et, n-Pr), prepared via *O*-propargylation[17] of phenol followed by Friedel−Crafts acylation and finally deprotection according to the method B (Scheme 1), have been utilized for the synthesis of potent and selective $H_3$ recepter antagonists.[21c]

In conclusion, we have described a palladium-mediated facile and mild procedure for the deprotection of aryl propargylamines and ethers in aqueous media. To the best of our knowledge this is the first example of the cleavage of propargylamines/ethers under palladium catalysis. The procedure does not involve the use of copper salt as co-catalyst and therefore precludes the dimerization of the acetylene moiety of the propargyl group. The present deprotection methodology certainly has advantages over the existing methods in terms of operational simplicity and functional group tolerability and therefore holds promise in protecting group chemistry. Further research is ongoing to investigate the mechanism of the reaction and applications of this methodology to other systems.

**Acknowledgment.** We thank Dr. A. Venkateswarlu, Dr. R. Rajagopalan, and Prof. J. Iqbal for their constant encouragement and the Analytical Department for spectral support.

**Supporting Information Available:** Experimental procedures and spectral data for all new compounds described in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Participation of Pd(0) is supported further by the appearance of a palladium black on the wall of the reaction flask in a few cases.

(19) For a similar mechanistic sequences, see: (a) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025. (b) Monteiro, N.; Arnold, A.; Blame, G. *Synlett* **1998**, 1111.

(20) For a discussion on the generation of Pd(0) from Pd(II) salts in $Et_3N$, see: (a) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113. (b) Jeevanandam, A.; Narkunan, K.; Ling, Y.-C. *J. Org. Chem.* **2001**, *66*, 6014.

(21) (a) Malamas, M. S.; Sredy, J.; Gunawan, I.; Mihan, B.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Flam, B. R. *J. Med. Chem.* **2000**, *43*, 995. (b) Malamas, M. S.; Sredy, J.; McCaleb, M.; Gunawan, I.; Mihan, B.; Sullivan, D. *Eur. J. Med. Chem. Chim. Ther.* **2001**, *36*, 31. (c) Faghih, R.; Dwight, W.; Gentles, R.; Phelan, K.; Esbenshade, T. A.; Ireland, L.; Miller, T. R.; Kang, C.-H.; Fox, G. B.; Gopalakrishnan, S. M.; Hancock, A. A.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2031.