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Oxidative coupling of alkynes mediated by nitroxyl radicals under Sonogashira conditions and Pd-free catalytic approach to stable radicals of 3-imidazoline family with triple bonds

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Abstract—In the presence of Pd catalyst, 3-imidazoline nitroxyl radicals promote oxidative coupling (dimerization) of terminal alkynes even in the absence of Cu(II) additives. On the other hand, the Pd-free CuI–PPh_3–K_2CO_3–DMF catalytic system leads to the efficient cross-coupling of 1-hydroxy-4-[2-(*p*-iodophenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-3-oxide with terminal aryl- and hetarylacetylenes with the formation of 4-[2-(aryl/hetarylethynyl)phenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyls in 70–75% yields.

High stability of 3-imidazoline nitroxyl radicals and sensitivity of their EPR spectra to the environment account for rapidly emerging applications of these molecules in analytical chemistry, molecular biology, and biophysics.[1,2] In particular, 3-imidazolyl nitroxyls are instrumental for studies of exchange interaction in three-spin systems (cation-radical/anion-radical/stable radical)[3] because of the substantial decrease in the interaction between the nitroxyl radical center and the newly formed ion-radical in the aromatic part of these molecules. This decrease improves the detection of recombination of spin-correlated pairs by shifting the timescale for this effect to a convenient 10–100 ns range.

The alkyne moiety is a particularly suitable rigid structural scaffold for the assembly of paramagnetic molecules with designed magnetic, electronic, and geometric parameters. The triple bond is not only capable of transmitting electronic interactions but also assures rigid and controlled spatial arrangement of the spin-bearing moieties necessary for fundamental studies of intricate chemical phenomena and for the construction of molecular devices for practical applications.

Despite the large body of work dedicated to the chemistry of 3-imidazoline radicals including several monographs,[1,2] information about paramagnetic acetylenic derivatives of 3-imidazoline nitroxyls was absent until recently when we discovered that this previously unknown class of compounds can be prepared through the acetylide synthesis.[4]

However, the requirement of potentially explosive copper acetylides not only remains a significant safety drawback but it also presents a potential limitation because not every terminal alkyne is capable of forming the copper salt (e.g., 3-(*N*-morpholino)propyn-1-yne or 2-methyl-3-butyn-2-ol).

These circumstances motivated us to continue our search of a more general, practical, and *catalytic* approach to acetylenic 3-imidazoline nitroxyl radicals. Even though originally we envisioned this approach to be based on the catalytic version of cross-coupling, only traces of the cross-coupling product were found in the Pd-catalyzed reaction of 4-[2-(*p*-bromophenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyl **1** with phenyl acetylene under the classic Sonogashira conditions.[5] Instead, the reaction affords 90% of diphenyl-

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Keywords: Cross-coupling; Aryl- and hetarylacetylenes; 3-Imidazoline-nitroxyles; Oxidative coupling; Stable radicals.

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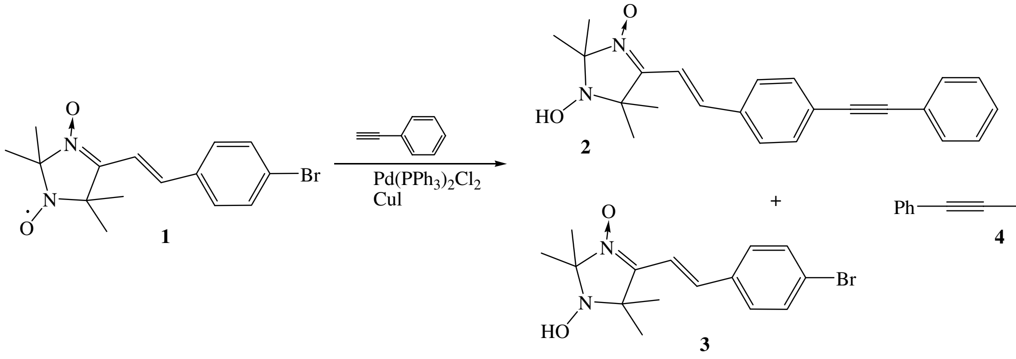


buta-1,3-dyne **4**, the product of oxidative alkyne homocoupling along with 50% of diamagnetic hydroxylamine **3**.

Although the focus of this work is on the development of an efficient catalytic cross-coupling process, it is worth pointing out that 1,3-dynes find a number of interesting applications[6] and it has been suggested[7] that Pd-catalyzed processes provide a more 'mild, efficient and selective' approach to such oxidative homocoupling products relative to the traditional Eglington, Hay and Glaser couplings.[8]

However, in most of such processes oxidative homocoupling of terminal alkynes in the presence of $Pd(PPh_3)_2Cl_2$ only proceeds in the presence of a suitable *external* oxidant such as chloroacetone,[9a] *p*-chloranil,[9b] bromoacetate,[9c] I_2,[9d] trimethyl amine oxide[9e] or air.[7,9f] All of these scenarios are different from the present case where no *external* oxidant was present. To the best of our knowledge, our work presents a first report of *oxidative cross-coupling caused by the substrate itself* in the absence of an external oxidant. Interestingly, recently reported Pd-catalyzed reactions in the presence of more delocalized and less oxidizing[1] 2-imidazoline nitronyl moiety as part of ether alkyne or aryl halide components proceed through a normal cross-coupling pathway.[10]

Although the role of an oxidant is believed to be in the transformation of Pd(0) to Pd(II) species, several mechanistic scenarios are consistent with the zero-order dependence of reaction rate on alkyne concentration observed by Fairlamb, Marder, and co-workers.[7] Although this dependence suggests that reoxidation of Pd(0) to Pd(II) may be a slow, rate-limiting step, this reoxidation can either proceed directly through the interaction of Pd(0) with the oxidant or be mediated by a copper species through a redox sequence, which is reminiscent of that in the Wacker process for the aerobic oxidation of alkenes to aldehydes and is summarized in the two equations below:

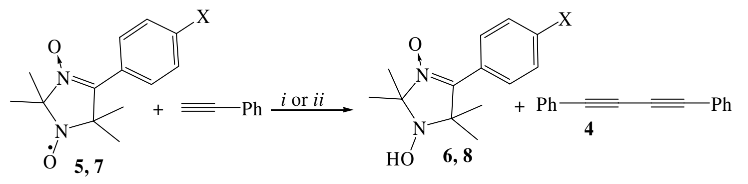
$$\mathrm{Cu(I)} + \text{oxidant} \rightarrow \mathrm{Cu(II)}$$

$$2\mathrm{Cu(II)} + \mathrm{Pd(0)} \rightarrow 2\mathrm{Cu(I)} + \mathrm{Pd(II)}$$

In order to test the ability of nitroxyl radicals to promote oxidative coupling of alkynes and investigated the possible involvement of Cu species, we studied reactivity of phenyl acetylene under copper-free conditions using two Pd-based catalytic systems under inert atmosphere. In order to simplify the interpretation of these results, we used starting materials without bromine substitution in the aromatic moiety. These substrates were chosen to decrease the number of possible products and identify functional groups responsible for the formation of hydroxylamines and dehydrodimer **4**.

Interestingly, we found that homocoupling is efficient even in the absence of Cu salts.[11] However, the presence of Pd is essential. No changes occurred when nitroxides **5** and **7** were stirred with phenyl acetylene and Et_3N in refluxing benzene under an inert atmosphere for 2–5 h in the absence of $Pd(PPh_3)_2Cl_2$. However, once $Pd(PPh_3)_2Cl_2$ was added to the reaction mixture, products **6** and **8** (28–94%) along with dehydrodimer **4** (66–90%) were formed after 5–7 h. Formation of diamagnetic hydroxylamine proceeded more efficiently from the more electron deficient nitro-substituted substrate **7**.

Although the mechanism of dimerization is still unclear, direct H-atom abstraction of alkyne C–H bond with the nitroxyl radical followed by dimerization of the concomitantly formed phenylethynyl radical is unlikely because of the high bond dissociation energy of sp-hybridized C–H bonds. The role of Pd salt may be in the formation of a π-complex[12] where the C–H bond is weakened.

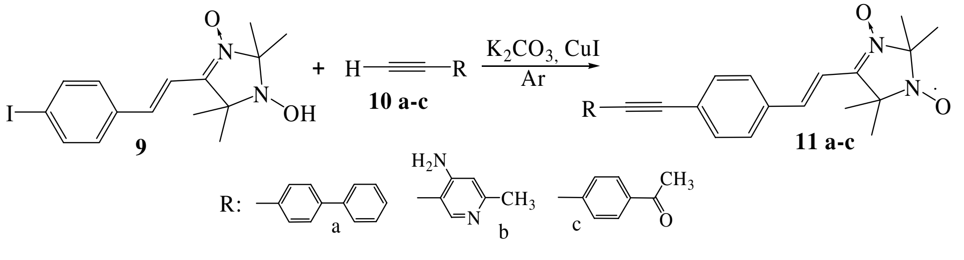


X = H (5, 6)
NO_2 (7, 8)

i: $Pd(PPh_3)_2Cl_2$, Et_3N, C_6H_6, Ar, 80 °C
6 66%, **4** 66%;
8 91%, **4** 74%.

ii: $PdCl_2$, AcONa*3aq, CuI, CH_3CN, Ar
6 28%, **4** 90%;
8 94%, **4** 66%.

Since Cu-free Pd catalysis led to the oxidative homocoupling, we investigated the viability of Pd-free Cu-catalyzed version of cross-coupling[13] in the next step. We also utilized the ca. 800-fold greater reactivity of aryl iodides relative to the respective bromides in cross-couplings with alkynes.[14,15] Gratifyingly, we found that the target acetylenic nitroxyl radicals **11a–c** are indeed formed in 70–75% yields in the reactions of hydroxylamine **9** with terminal aryl- and hetarylacetylenes **10a–c** mediated by the catalytic system CuI–PPh$_3$–K$_2$CO$_3$–DMF.[16,17]



It is noteworthy that, under these conditions, the diamagnetic iodide can be used as a starting material, thus eliminating the need for the additional step of preparation of the spin-labeled product. Although the mechanism for the transformation of diamagnetic compound to the paramagnetic product is so far unknown, it has been observed that the diamagnetic derivatives are slowly oxidized to their respective radicals even in the solid state when stored at room temperature.

In summary, we developed a catalytic Pd-free synthetic approach to the family of nitroxyls with 3-imidazoline core and alkyne substituents including aryl and hetaryl moieties as well as functional groups of both donor and acceptor character. This approach is likely to be useful when classic Sonogashira-type cross-coupling fails due to reoxidation of the catalytic Pd(0) species by the substrate.

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References and notes

1. *Imidazoline Nitroxides*; Volodarsky, L. B. Ed., CRC: Boca Raton, Florida, *Synthesis and Properties*, 1988; Vol. I, 222 pp *and Applications*, Vol. II, 160 pp.
2. Voldarsky, L. B.; Reznikov, V. A.; Ovcharenko, V. I. *Synthetic Chemistry of Stable Nitroxides*; CRC: Boca Raton, 1994; p 221.
3. Sviridenko, F. B.; Stass, D. V.; Kobzeva, T. V.; Tretyakov, E. V.; Klyatskaya, S. V.; Mshvidobadze, E. V.; Vasilevsky, S. F.; Molin, Yu. N. *J. Am. Chem. Soc.* **2004**, *126*, 2807.
4. (a) Vasilevsky, S. F.; Klyatskaya, S. V.; Korovnikova, O. L.; Stass, D. V.; Amitina, S. A.; Grigor'ev, I. A.; Elguero, J. *Tetrahedron Lett.* **2004**, *45*, 7741; (b) Vasilevsky, V. F.; Klyatskaya, S. V.; Korovnikova, O. L.; Stass, D. V.; Amitina, S. A.; Grigor'ev, I. A.; Elguero, J. *Tetrahedron* **2005**, *62*, 4591.
5. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467.
6. (a) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537; (b) Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1350.
7. Batsanov, A. S.; Collings, J. C.; Fairlamb, I. J. S.; Holland, J. P.; Howard, J. A. K.; Lin, Z.; Marder, T. B.; Parsons, A. C.; Ward, R. M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 703.
8. A recent example: Yin, W.; Srirama Sarma, P. V. V.; Ma, J.; Han, D.; Chen, J. L.; Cook, J. M. *Tetrahedron Lett.* **2005**, *46*, 6363.
9. (a) Rossi, R.; Carpita, A.; Bigelli, C. *Tetrahedron Lett.* **1985**, *26*, 523; (b) Chen, C.; Ai, Z.; Lin, J.; Hong, X.; Xi, C. *Synlett* **2006**, 2454; (c) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969; (d) Liu, Q.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 4371; (e) Li, J.-H.; Liang, Y.; Zhang, X.-D. *Tetrahedron* **2005**, *61*, 1903; (f) Nguyen, P.; Yuan, Z.; Agocs, L.; Lesley, G.; Marder, T. B. *Inorg. Chim. Acta* **1994**, *220*, 289; Takahashi, A.; Endo, T.; Nozoe, S. *Chem. Pharm. Bull.* **1992**, *40*, 3181; Jung, F.; Burger, A.; Biellmann, J. F. *Org. Lett.* **2003**, *5*, 383.
10. (a) Klyatskaya, S. V.; Tretyakov, E. V.; Vasilevsky, S. F. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 128; (b) Stroh, C.; Mayor, M.; von Hänish, C. *Tetrahedron Lett.* **2004**, *45*, 9623.
11. *Method*: (i) An example: Solution of phenyl acetylene (0.05 g, 0.05 ml, 0.47 mmol) in 1 mol of benzene was added to a mixture of **7** (0.11 g, 0.39 mmol), Et$_3$N (3 ml), and Pd(PPh$_3$)$_2$Cl$_2$ (0.02 g) in 7 ml of benzene under inert atmosphere. The mixture is stirred under reflux for 4 h until the disappearance of phenyl acetylene (TLC control). After the reaction mixture is filtered through a small pad of Al$_2$O$_3$, the solvent is removed under reduced pressure. Crude residue is purified with chromatography on Al$_2$O$_3$ using hexane, benzene, and ethyl acetate as eluents to yield 0.10 g of hydroxylamine **8** (91%), mp 85–86 °C (mp$_{\text{lit}}$ 85–87 °C, Volodarskii, L. B.; Grigor'ev, I. A.; Grigor'eva, L. N.; Kirilyuk, I. A.; Amitina, S. A. *Zh. Org. Chem.*, **1985**, *21*, 443) and 0.037 g (74%) of dyne **4**, mp 85–87 °C (mp$_{\text{lit}}$ 87–88 °C, Campbell, I. D.; Eglington G. *Org. Synth. Coll.* **1973**, *5*, 517). *Method:* (ii) An example: Solution of phenyl acetylene (0.03 g, 0.03 ml, 0.28 mmol) in 1 mol of acetonitrile was added to a mixture of **7** (0.16 g, 0.57 mmol),

AcONa·$3H_2I$ (0.12 g, 0.86 mmol), CuI (0.05 mg) and $PdCl_2$ (0.05 mg) in 5 ml of acetonitrile under inert atmosphere. Reaction was stirred at room temperature for 7 h until the full consumption of phenyl acetylene (TLC control). After the reaction mixture is filtered through a small pad of Al_2O_3, the solvent is removed under reduced pressure. Crude residue is dissolved in benzene and refluxed with activated carbon. After hot filtration, the residue is recrystallized from benzene/ethyl acetate mixture to give 0.15 g (94%) of product **8**. The mother liquor was evaporated and chromatographed on Al_2O_3 to yield 0.02 g (67%) of product **4**.

12. Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874.
13. Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716.
14. Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 259.
15. Tretyakov, E. V.; Knight, D. W.; Vasilevsky, S. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3713.

16. *General procedure of Pd-free cross-coupling reaction*: A mixture of iodide **9** (150 mg, 0.39 mmol), PPh_3 (0.04 mmol), CuI (0.02 mmol), potassium carbonate (0.6 mmol), and alkyne **10a**–**c** (0.4 mmol) in 10 ml of DMF was stirred under the stream of argon at 90–100 °C for 3.5–4 h until the full consumption of iodide **9**(TLC-control, 'Silufol'). Then $CHCl_3$ (30 ml) and water (40 ml) were added, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2×25 ml). The combined organic layers were washed with 25% aqueous NH_3 (2×15 ml), dried over K_2CO_3, filtered through Al_2O_3, and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on Al_2O_3 (elution with chloroform). Subsequent recrystallization gave pure compounds **11a**–**c**.
17. Full analytical and spectroscopic data confirm the proposed structures for all compounds reported herein. In all cases the ESR spectra were measured in degassed toluene with 10^{-5}–10^{-4} M concentration of radicals. Selected data: 2,2,5,5-Tetramethyl-4-{2-[*p*-(biphenylethyn-1yl)phenyl]vinyl}-3-imidazoline-3-oxide-1-oxyl (**11a**): yield 115 mg (71.4%), mp 238.5–239.0 °C (from benzene). IR, cm^{-1}: $\nu_{max} = 1255$ (N→O), 1368 (N–O), 2213 (C≡C). HRMS, *m*/*z* (%): 435.2 [M^+] (13.79), 405.2 (29.00), 390.2 (56.62), 389.2 (40.43), 388.2 (100.00), 347.2 (62.17), 291.2 (54.24), 252.2 (19.13), 167.2 (21.17). Found: *m*/*z* 435.20869 [M^+]. $C_{29}H_{27}N_2O_2$ Calcd: M = 435.20724. ESR: $g_{iso} = 2.0060$ ($\Delta H_{DPPH} = 4.05$ G), $A_N = 14.06$ G, $A_{H(CH_3)}$ (12H) = 0.23 G, A (^{13}C) = 5.72 G. The yield of compound **11b** is 75.0%, mp 202.5–203 °C (from benzene). IR, cm^{-1}: $\nu_{max} = 1253$ (N→O), 1364 (N–O), 2206 (C≡C). HRMS, *m*/*z* (%): 389.0 [M^+] (7.90), 359.1 (5.30), 344.1 (11.32), 342.1 (22.28), 286.9 (9.81), 244.9 (10.78). Found: *m*/*z* 389.19693 [M^+]. $C_{23}H_{25}N_4O_2$ Calcd: M = 389.19774. ESR: $g_{iso} = 2.0059$ ($\Delta H_{DPPH} = 3.96$ G), $A_N = 13.86$ G, $A_{H(CH_3)}$ (12H) = 0.23 G, A(^{13}C) = 5.62 G. Compound **11c**: Yield 73.3%, mp 179–180.5 °C (from a mixture of hexane–benzene). IR, cm^{-1}: $\nu_{max} = 1264$ (N→O), 1361 (N–O), 1674 (C=I), 2212 (C≡C). HRMS, *m*/*z* (%): 401.2 [M^+] (5.31), 386.2 (14.34), 371.1 (21.04), 356.1 (32.30), 354.1 (44.52), 312.9 (20.09), 299.0 (32.62), 256.9 (22.17). Found: *m*/*z* 401.18722 [M^+]. $C_{25}H_{25}N_2O_3$ Calcd: M = 401.18650. ESR: $g_{iso} = 2.0062$ ($\Delta H_{DPPH} = 3.98$ G), $A_N = 14.04$ G, $A_{H(CH3)}$(12H) = 0.23 G, A(^{13}C) = 5.88 G.