

HETEROCYCLES, Vol. 65, No. 2, 2005, pp. 273 - 277

Received, 10th November, 2004, Accepted, 22nd December, 2004, Published online, December, 24, 2004

PALLADIUM(0)-CATALYZED AMINO-HECK REACTION OF γ,δ -UNSATURATED KETONE *N,N,N*-TRIMETHYLHYDRAZONIUM SALTS

Mitsuru Kitamura, Hideyuki Yanagisawa, Motoki Yamane, and Koichi Narasaka*

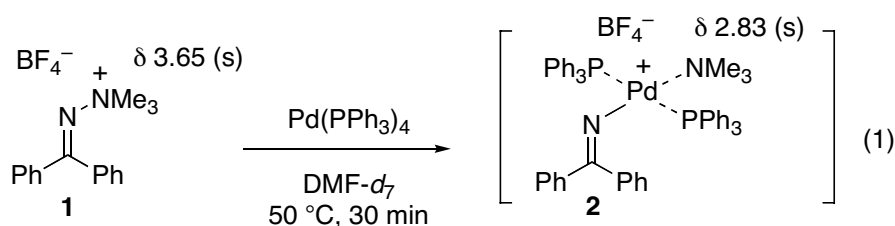
Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033; narasaka@chem.s.u-tokyo.ac.jp

Abstract – Oxidative addition of *N,N,N*-trialkylhydrazonium salts takes place to a palladium(0) complex, resulting the formation of alkylideneaminopalladium(II) species. This N–N bond scission process is applied to the transformation of γ,δ -unsaturated ketone hydrazonium salts to pyrroles by amino-Heck reaction.

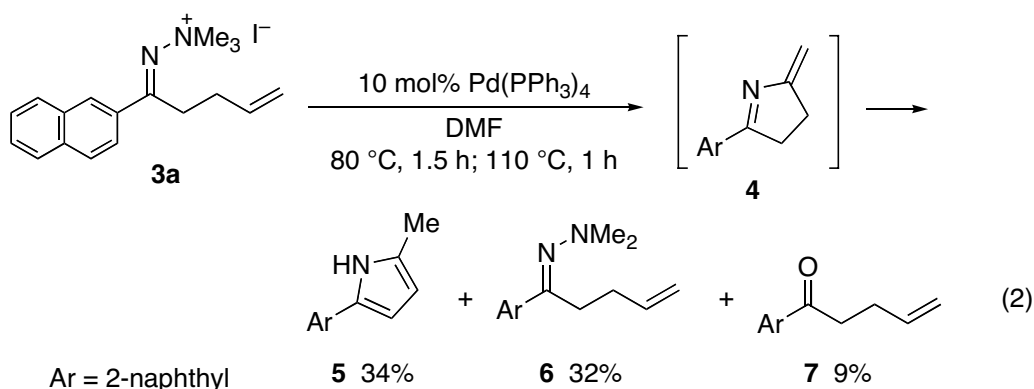
Recently, we reported that N–O bonds of oxime derivatives is cleaved by the oxidative addition to Pd(0) complexes to generate alkylideneaminopalladium(II) species.^{1,2} When olefinic *O*-pentafluorobenzoyloximes are treated with a catalytic amount of Pd(PPh₃)₄ in the presence of Et₃N, Mizoroki-Heck-type cyclization (amino-Heck reaction) proceeds *via* the amino-palladium intermediates, affording various azaarenes such as pyrroles,^{2a,b} pyridines,^{2c} isoquinolines,^{2c} spiroimines,^{2d,e} and azaazulenes.^{2f,g}

Concerning of N–N bond cleavage with transition metal complexes, the oxidative addition of azines to metal complexes has been reported, whereas there has been no example on the oxidative addition of hydrazone or hydrazonium salt to our knowledge.³ We expected that *N,N,N*-trialkylhydrazonium salt would react with Pd(0) complexes like oxime derivative because trialkylammonio group is regarded as a leaving group.⁴

First, we monitored the reaction of 2-diphenylmethylene-1,1,1-trimethylhydrazonium tetrafluoroborate (**1**)⁵ with an equimolar amount of Pd(PPh₃)₄ in DMF-*d*₇ by ¹H NMR spectrum (eq. 1). After 0.5 h at 50 °C, the singlet peak of methyl groups of **1** at 3.65 ppm disappeared and a new singlet peak was observed at 2.83 ppm. The methyl groups of Me₃N•HCl, PdCl₂(NMe₃)₂, and trimethylamine are observed at 2.83 ppm (CDCl₃, DMSO-*d*₆),⁶ 2.58 ppm (CCl₄),⁷ and 2.12 ppm (CCl₄),⁸ respectively. Accordingly, it was suggested that the N–N bond of hydrazonium salt (**1**) was cleaved to form alkylideneaminopalladium species (**2**) coordinated with Me₃N.



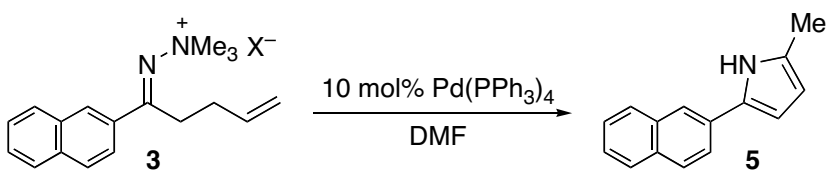
Then, the catalytic amino-Heck cyclization¹ was tried by treating γ,δ -unsaturated ketone hydrazone iodide (**3a**) with a catalytic amount of Pd(PPh₃)₄ in DMF (eq. 2). The reaction did not proceed at 80 °C, while hydrazone salt (**3a**) was consumed after 1 h at 110 °C to give pyrrole (**5**) in 34% yield, which was the isomerization product of the initially formed methylidenedihydropyrrole (**4**), along with dimethylhydrazone (**6**) (32%) and ketone (**7**) (9%).



Hydrazone (**6**) was formed presumably by demethylation by the attack of iodide anion. To prevent this side reaction, hydrazone salts (**3**) having other counter anions⁵ were subjected to the amino-Heck reaction (Table 1). In the reaction of **3b** ($X^- = p\text{-MeC}_6\text{H}_4\text{SO}_3^-$) at 110 °C, the yield of pyrrole **5** increased to 48% (run 2). The reaction of **3c** ($X^- = \text{BF}_4^-$) was completed at 80 °C to afford **5** in 81% yield (run 3). In the case of hydrazone hexafluorophosphate (**3d**), pyrrole (**5**) was obtained in 69% yield at 80 °C (run 4), and the yield was increased up to 85% by performing the reaction in *N,N*-dimethylacetamide (DMA) at 120 °C (run 5). Thus, hydrazone salts having the counter anions with low nucleophilicity are favorable for the cyclization, probably due to 1) the suppression of the demethylation of hydrazone salts and 2) the acceleration of the olefinic part insertion to the more cationic alkylideneaminopalladium(II) complexes.⁹

Furthermore, we investigated the effect of ligands, and PPh₃ was found to be suitable for the reaction among PPh₃, P(*c*-Hex)₃, P(*t*-Bu)₃, P[3,5-(CF₃)₂C₆H₃], and Ph₂P(CH₂)₄PPh₂.

Table 1. Effect of Counter Anions



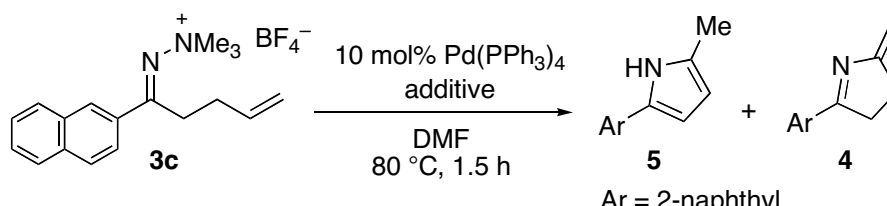
run	X ⁻	3	conditions	yield/%
1	I ⁻	3a	80 °C, 1.5 h; 110 °C, 1.0 h	34
2	<i>p</i> -MeC ₆ H ₄ SO ₃ ⁻	3b^a	80 °C, 0.5 h; 110 °C, 1.5 h	48
3	BF ₄ ⁻	3c	80 °C, 1.5 h	81
4	PF ₆ ⁻	3d	80 °C, 1.5 h	69
5 ^b	PF ₆ ⁻	3d	120 °C, 1.0 h	85

a) Prepared by the reaction of **3a** with *p*-MeC₆H₄SO₃Ag and the successive removal of AgI.

b) *N,N*-Dimethylacetamide (DMA) was used as solvent.

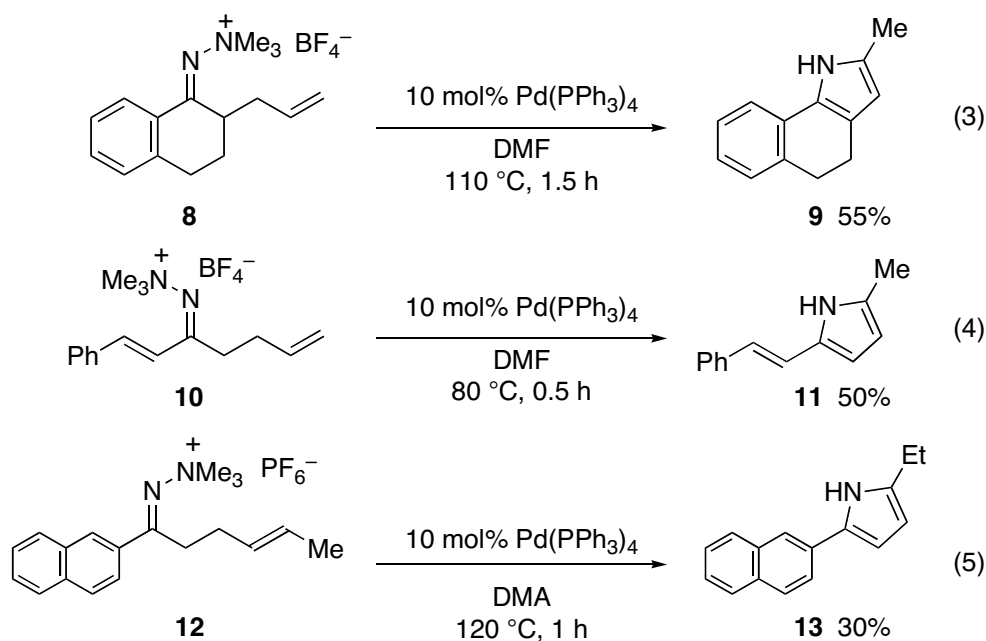
Although Heck reaction is performed in the presence of bases, no base was added to the present amino-Heck reaction because trimethylamine was formed during the course of the reaction. Then the influence of bases was examined (Table 2). Addition of Et₃N considerably disturbed the reaction (run 2), whereas bulkier *i*-Pr₂NEt did not interfere the reaction (run 3). Methyl transfer from hydrazone salt (**3c**) to Et₃N may be the main reason of the low yield. Interestingly, addition of MS 4A prevented the preliminary cyclization product (**4**) from the isomerization to pyrrole (**5**), yielding methylenedihydropyrrole (**4**) as a major product (run 4). The abstraction of the generating acid with molecular sieve reduced the isomerization of **4**.

Table 2 Effect of Additives



run	additive (mol amt.)	5	4
1	none	81%	—
2	Et ₃ N (3.0)	18%	—
3	<i>i</i> -Pr ₂ NEt (3.0)	77%	—
4	MS 4A (4.0 wt/wt)	5% ^a	61%

As shown in eqs. 3-5, some aryl ketones and α,β -unsaturated ketone hydrazone salts were transformed to substituted pyrroles by the present amino-Heck reaction. Internal olefin was found to be less reactive than terminal olefin (eq. 5).



N,N-Dimethylhydrazones are widely employed as carbonyl equivalents in organic synthesis, particularly as aza-enolate. It has been hardly used hydrazones as nitrogen sources except hydrogenation to amino group due to the difficulty in the N-N bond cleavage.¹⁰ The presented process would provide a possibility that hydrazone moiety can be used not only as a carbonyl equivalent but also as imino moiety. The reaction of alkyl ketone hydrazone salts was not examined yet, since these salts are susceptible to be hydrolyzed. Efficient preparative method of alkyl ketone hydrazone salts is now under investigation.

ACKNOWLEDGEMENTS

This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" and a Grant-in-Aid for The 21st Century COE Program for Frontiers in Fundamental Chemistry from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We are grateful to Kanto Denka Kogyo Co., Ltd. for a generous gift of PF₅.

REFERENCES AND NOTES

- For review, see: M. Kitamura and K. Narasaka, *Chem. Rec.*, 2002, **2**, 268.
- a) H. Tsutsui and K. Narasaka, *Chem. Lett.*, 1999, 45. b) H. Tsutsui, M. Kitamura, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1451. c) H. Tsutsui and K. Narasaka, *Chem. Lett.*, 2001, 526. d) M. Kitamura, S. Zaman, and K. Narasaka, *Synlett*, 2001, 974. e) S. Zaman, M. Kitamura, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 1055. f) M. Kitamura, S. Chiba, O. Saku, and K.

- Narasaka, *Chem. Lett.*, 2002, 606. g) S. Chiba, M. Kitamura, O. Saku, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 785.
3. a) G. Erker, W. Frömberg, C. Krüger, and E. Raabe, *J. Am. Chem. Soc.*, 1988, **110**, 2400. b) T. Zippel, P. Arndt, A. Ohff, A. Spannenberg, R. Kempe, and U. Rosenthal, *Organometallics*, 1998, **17**, 4429. c) A. Zimniak and G. Bakalarski, *J. Mol. Struct.*, 2001, **597**, 211. d) J. L. Kiplinger, D. E. Morris, B. L. Scott, and C. J. Burns, *Organometallics*, 2002, **21**, 3073.
4. Recently, MacMillan *et al.* reported the oxidative addition of sp^2C-N bond of aryltrimethylammonium salt. S. B. Blakey and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 6046.
5. *N,N,N*-Trimethylhydrazonium salts are prepared by the reaction of corresponding dimethylhydrazones with methylating reagents such as MeI, $Me_3O \cdot BF_4$ and $Me_3O \cdot PF_6$. a) A. Eddaïf, A. Laurent, P. Mison, N. Pellissier, P.-A. Carrupt, and P. Vogel, *J. Org. Chem.*, 1987, **52**, 5548. b) P. A. S. Smith and C. R. Messing, *J. Org. Chem.*, 1988, **53**, 2959.
6. C. J. Pouchert and J. Behnke, "The Aldrich Library of ^{13}C and 1H FT-NMR Spectra," Aldrich Chemical, Milwaukee, 1992.
7. P. L. Goggin, R. J. Goodfell, and F. J. S. Reed, *J. Chem. Soc., Dalton Trans.*, 1972, 1298.
8. M. J. Lacey, C. G. Macdonald, A. Pross, J. S. Shannon, and S. Sternhell, *Aust. J. Chem.*, 1970, **23**, 1421.
9. a) C. Amatore, E. Carré, A. Jutand, M. A. M'Barki, and G. Meyer, *Organometallics*, 1995, **14**, 5605. b) A. Yamamoto, Y. Kayaki, K. Nagayama, and I. Shimizu, *Synlett*, 2000, 925.
10. E. J. Corey and D. Enders, *Tetrahedron Lett.*, 1976, 3.