J|A|C|S
COMMUNICATIONS

Published on Web 03/22/2006

Synthesis of Substituted Pyridine Derivatives via the Ruthenium-Catalyzed Cycloisomerization of 3-Azadienynes

Mohammad Movassaghi* and Matthew D. Hill

Massachusetts Institute of Technology, Department of Chemistry, Cambridge, Massachusetts 02139

Received January 26, 2006; E-mail: movassag@mit.edu

Due to the prominence of azaheterocycles in natural products, pharmaceuticals, and functional materials, efficient methods for the synthesis of these compounds are of great value.[1,2] The majority of synthetic routes to pyridine and quinoline derivatives rely on condensation reactions of amines and carbonyl compounds.[3,4] The convergent synthesis of *N*-vinyl and *N*-aryl amides readily provides valuable precursors for the preparation of azaheterocycles (Scheme 1).[5] Herein we report a mild and efficient two-step procedure for the conversion of *N*-vinyl and *N*-aryl amides to the corresponding substituted pyridines.

The metal-catalyzed cycloisomerization of dienynes via catalytically generated metal−vinylidene intermediates represents a highly effective method for the synthesis of aromatic compounds.[6] We sought to explore the use of 3-azadienynes as substrates for a metal-catalyzed cycloisomerization reaction, providing a general approach to a broad range of substituted pyridine derivatives **1** (Scheme 1).[7] To take full advantage of the wide range of *N*-vinyl amides available by metal-catalyzed *C*−*N* bond formation,[5] we required a mild and efficient procedure for the direct conversion of amides **2** to the corresponding 3-azadienynes **3** (Table 1).[8] Inspired by recent reports on the electrophilic activation of amides[9] we developed a single-step process for the conversion of *N*-vinyl/aryl amides **2** to the corresponding alkynyl imines **3**. Under our optimum conditions, a cold solution of the *N*-phenyl benzamide (**2a**, Scheme 2) in dichloromethane is treated sequentially with 2-chloropyridine (2-ClPyr, 4.0 equiv) and trifluoromethanesulfonic anhydride (Tf_2O, 1.2 equiv), followed by copper trimethylsilylacetylide (2.7 equiv), which affords the desired trimethylsilyl alkynyl imine **3a** in 97% yield (Table 1, entry 1, 2.5-g scale).[10] The use of 2-chloropyridine as the base[11] was found to be critical in obtaining the desired alkynyl imines.[10] Significantly, this single-step and mild procedure provides access to new alkynyl imines, in particular, those derived from *N*-vinyl amides. For comparison, the use of existing methods[8] for the synthesis of *N*-2-thienyl and *N*-dihydropyranyl alkynyl imines **3** (Table 1, entries 13 and 15) gave none and <10% yield of the desired product, respectively.

Early in our studies we identified the readily available chlorocyclopentadienyl bis(triphenylphosphine) ruthenium complex (CpRu(PPh$_3$)$_2$Cl, **5**)[12] as an effective catalyst for cycloisomerization of terminal alkynyl imine **4a** to product **1a** (Scheme 2).[13] While imine **4a** could be prepared by protodesilylation of the corresponding trimethylsilyl derivative **3a** (Scheme 2), this required an additional step and resulted in decreased stability of the substrate and yield of the cycloisomerization reaction. These considerations prompted the development of a process for the direct use of trimethylsilyl alkynyl imine **3a** as substrate. The trimethylsilyl alkynyl imine **3a**, was used to survey a series of metal complexes, supporting ligands, additives, and solvents.[10] The combination of ruthenium complex **5** (10 mol %), 2-dicyclohexyl-phosphino-2′,6′-dimethoxy-1,1′-biphenyl (SPhos,[14] 10 mol %), and ammonium hexafluorophosphate (1 equiv) in toluene (0.2 M) at 105 °C was identified as the optimal

Scheme 1

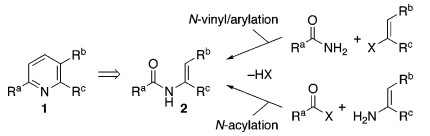
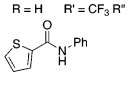
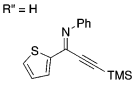
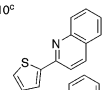
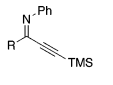
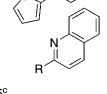
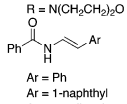
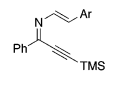
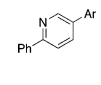
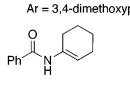
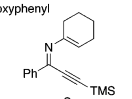
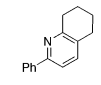
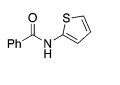
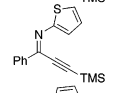
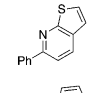
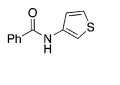
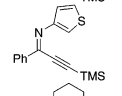
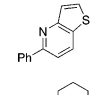
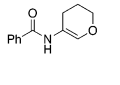
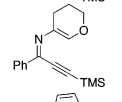
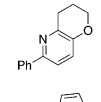
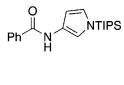
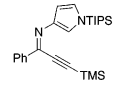
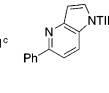


Table 1

Entry	Amide Substrate (**2**)	3-Azadienyne (**3**)	Yield (%)[a]	Product (**1**)	Yield (%)[a]
1	**2a**, R = H R′ = H R″ = H	**3a**	97[b]	**1a**	91[b]
2	R = H R′ = H R″ = OMe		89		92
3	R = OMe R′ = H R″ = H		96		91
4	R = H R′ = CF_3 R″ = H		73, <10[c]		89
5			81		75
6	R = $^cC_6H_{11}$		85		69
7	R = ^{t}Bu		83, 95[c]		69
8	R = N($CH_2CH_2)_2$O		80		62
9	 Ar = Ph		78		77
10	Ar = 1-naphthyl		86		83
11	Ar = 3,4-dimethoxyphenyl		92		78
12			75		73
13			63[d]		99
14			98		97
15			99		70
16			82, 91[c]		64[e]

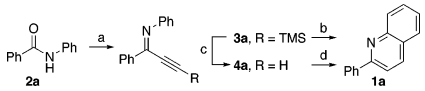
[a] Isolated yields: all entries are an average of two experiments. Optimum conditions used uniformly. [b] Gram-scale experiments. [c] Yield of the corresponding desilylated imine.[10] [d] Kept at −78 °C.[10] [e] 5 mol % of catalyst system used.

set of conditions, as illustrated by the clean conversion of imine **3a** to quinoline **1a** in 90% yield (Table 1, entry 1, 1.0-g scale).[10]

Interestingly, neither SPhos nor PPh_3 alone were ideal ligands when used independently with chlorocyclopentadienyl cycloocta-1,5-diene ruthenium complex (CpRuCODCl, **6**)[15] for cycloisomerization of 3-azadienyne **3a**.[10] However, the combination of these ligands in conjunction with ruthenium complex **6** provided a catalyst system with activity equal to that of the optimal system.[10] While the exact role of SPhos is unclear at this time,[16] ^{31}P NMR

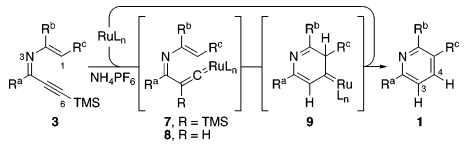
10.1021/ja060626a CCC: $33.50

Scheme 2 [a]



[a] Reagents and conditions: a) Tf_2O, 2-ClPyr, CH_2Cl_2; TMSC≡CCu, THF, −78→0 °C. b) **5**, SPhos, NH_4PF_6, toluene, 105 °C. c) K_2CO_3, MeOH. d) **5**, toluene, 105 °C.

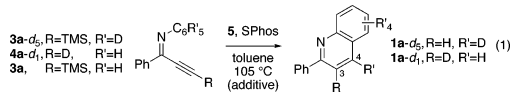
Scheme 3



experiments confirm that PPh_3 outcompetes SPhos in displacement of COD from **6**, providing complex **5** and remaining SPhos—similar to the optimal precatalyst mixture. Also, ^{1}H NMR monitoring of the cycloisomerization reaction of azadienyne **3a**, employing complex **6** and SPhos alone, revealed the formation of the inactive CpRu(η_6-C_6H_5Me)PF_6 complex.[17]

The optimal reaction conditions proved to be compatible with a variety of *C*-silyl alkynyl imines (Table 1). In particular, we found even highly sensitive *N*-vinyl/heterocyclic imines to be excellent substrates (Table 1, entries 9−16), providing a convergent and versatile azaheterocycle synthesis. Importantly, the direct conversion of *C*-silyl alkynyl imines **3** to the corresponding azaheterocycles **1** with this Ru-catalyst system avoids the isolation of the more sensitive terminal alkynyl imines (i.e., Table 1, entry 4). In only two cases (entries 7 and 16) in situ desilylation was found to be exceedingly slow, prompting the use of the corresponding terminal alkyne derivatives as the substrates for cycloisomerization. In the synthesis of the acid-sensitive *N*-triisopropylsilylazaindole (entry 16), lowering the catalyst loading (5 mol %) from our standard conditions was beneficial.

Subjecting the alkynyl imine **3a**-d_5 (eq 1) to our standard conditions gave the quinoline **1a**-d_5 (eq 1) with C4-deuterium



incorporation (68%).[10] The use of terminal alkynyl imine **4a**-d_1 (eq 1, without NH_4PF_6) as substrate provided quinoline **1a**-d_1 (eq 1) with C3-deuterium incorporation (72%).[10] Furthermore, employing ammonium hexafluorophospate-d_4 in the cycloisomerization of alkynyl imine **3a** (eq 1), provided the quinoline **1a**-d_1 (eq 1) with C3-deuterium incorporation (68%).[10] The protodesilylated imine **4a** (Scheme 2) was not detected as a persistent intermediate by TLC or ^{1}H NMR monitoring experiments (Table 1, entry 1), and the silyl alkynyl imine **3a** was recovered unchanged from the reaction mixture in the absence of Ru-complex **5**. Additionally, only a trace amount of the desired desilylated and cycloisomerized product was detected when the ammonium hexafluorophosphate was omitted, returning the starting material as the mass balance. These observations suggest the direct conversion of the silyl alkynyl imine **3a** to the *C*-silyl metal vinylidene[18] **7** (Scheme 3) followed by protodesilylation and cycloisomerization to give **1a**.

The chemistry described here provides a two-step process for the synthesis of substituted pyridine derivatives from readily available *N*-vinyl/-aryl amides (Scheme 2, steps a and b). Noteworthy features of this chemistry include the single-step conversion of a wide range of readily available amides, including sensitive *N*-vinyl amides, to the corresponding *C*-silyl alkynyl imines and their direct Ru-catalyzed protodesilylation and cycloisomerization to the corresponding azaheterocycles. This Ru-catalyzed conversion of C6-trimethylsilyl 3-azadienynes to azaheterocycles, not only reduces a three-step sequence[4c] to a single-step but also does not require the isolation of sensitive and/or inaccessible terminal alkynyl imines as substrates.

Acknowledgment. M.M. is a Dale F. and Betty Ann Frey Damon Runyon Scholar supported by the Damon Runyon Cancer Research Foundation (DRS-39-04). M.M. is a Firmenich Assistant Professor of Chemistry. We acknowledge ACS-PRF (40631G1), NSF (547905), Amgen Inc., and MIT for funding.

Supporting Information Available: Experimental procedures and spectroscopic data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews, see: (a) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. (c) Abass, M. *Heterocycles* **2005**, *65*, 901.
(2) (a) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., McKillop, A., Eds; Pergamon: Oxford, 1996; Vol. 5; p 167. (b) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; Wiley-VCH: New York, 1999.
(3) For reviews on metal-catalyzed heterocycle synthesis, see: (a) Bönnemann, H.; Brijoux, W. *Adv. Heterocycl. Chem.* **1990**, *48*, 177. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (c) Zeni G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (d) Varela, J. A.; Saá, C. *Chem. Rev.* **2004**, *104*, 3787.
(4) For related recent metal-catalyzed azaheterocycle syntheses, see: (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553, (b) Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **2003**, *68*, 8595, (c) Sangu, K.; Fuchibe, K.; Akiyama, T. *Org. Lett.* **2004**, *6*, 353, (d) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763, (e) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030 and references therein.
(5) (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973.
(6) For related reviews, see: (a) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311. (b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (c) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. For related representative reports, see: (d) Trost, B. M.; Dyker, G.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 7809. (e) Wang, Y.; Finn, M. G. *J. Am. Chem. Soc.* **1995**, *117*, 8045. (f) Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319. (g) Ohe, K.; Kojima, M.; Yonehara, K.; Uemura, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1823. (h) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928.
(7) (a) Boger, D. L. *J. Heterocycl. Chem.* **1998**, *35*, 1003. (b) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379.
(8) For reports on the synthesis of alkynyl imines via a two-step procedure involving imidoyl chlorides, see: (a) Ried, W.; Erle, H.-E. *Chem. Ber.* **1979**, *112*, 640. (b) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280. (c) Lin, S.-Y.; Sheng, H.-Y.; Huang, Y.-Z. *Synthesis* **1991**, 235. For related reports, see: (d) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (e) Van den Hoven, B. G.; Alper, H. *J. Am. Chem. Soc.* **2001**, *123*, 10214.
(9) (a) Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077. (b) Charette, A. B.; Grenon, M. *Can. J. Chem.* **2001**, *79*, 1694.
(10) See the Supporting Information for details.
(11) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072.
(12) (a) Gilbert, J. D.; Wilkinson, G. *J. Chem. Soc. (A)* **1969**, 1749. (b) Blackmore, T.; Bruce, M. I.; Stone, F. G. A. *J. Chem. Soc. (A)* **1971**, 2376. (c) Bruce, M. I.; Windsor, N. J. *Aust. J. Chem.* **1977**, *30*, 1601.
(13) (a) For a related report on metal-catalyzed isomerization of *N*-aryl benzamide derived terminal alkynes (i.e., **4a**) using $W(CO)_5$·THF (20−100 mol %) to afford 2-arylquinolines after treatment with NMO, see ref 4c. (b) For a report on Ru-catalyzed C2-vinylation of pyridines, see: Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2003**, *125*, 4720.
(14) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.
(15) Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199.
(16) For related discussions on the steric and electronic effects of phosphines used with complex **6** in Ru−vinylidene formation, see: Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680.
(17) McNair, A. M.; Schrenk, J. L.; Mann, K. R. *Inorg. Chem.* **1984**, *23*, 2633.
(18) Schneider, D.; Werner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 700.

JA060626A