Novel Two-Step Stereoselective Synthesis of (*E*)-Enamines and 1-Amino-1,3-dienes from Terminal Alkynes

Henri Doucet, Christian Bruneau,* Pierre H. Dixneuf

Laboratoire de Chimie de Coordination et Catalyse, UMR 6509, CNRS-Université de Rennes, Campus de Beaulieu, F-35042 Rennes, France

Fax : 33 2 99 28 69 39 ; e-mail : bruneau@univ-rennes1.fr

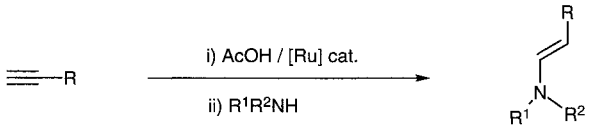
Received 25 March 1997

Abstract : (*E*)-Enamines and 1-amino-1,3-dienes have been prepared by reaction of secondary amines with alk-1-en-1-yl acetates resulting from the ruthenium-catalyzed *anti*-Markovnikov addition of acetic acid to terminal alkynes and enynes.

Enamines are very specific and useful enol equivalents for aldehydes. They react with electrophiles such as propargyl and allyl bromide or carbonyl derivatives, and add to Michael acceptors to give selective C-C bond formation.[1] With imine derivatives, enamines give 1-azabuta-1,3-dienes,[2] pyridines,[3] or diamines,[4] and they have been used for the access to cyclopentadienes *via* [3+2] cycloaddition with chromium and tungsten alkynylcarbenes.[5] As far as unsaturated enamines are concerned, 2-amino-1,3-dienes have found useful applications for the synthesis of functionalized [4+2] cycloaddition products[6] and seven-membered rings upon reaction with vinylchromium carbenes.[7]

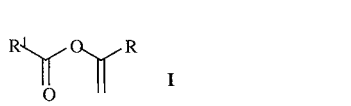
Besides their straightforward preparation from carbonyl compounds and secondary amines, enamines have been obtained *via* the Wittig-Horner reaction,[8] dehydrocyanation of α-aminonitriles,[9] addition of Grignard reagents to dialkyl formamides,[10] zirconium-assisted coupling of butadiene with nitriles,[11] and reaction of lithium amide with 1-methoxybutadiene to give 1-aminobuta-1,3-dienes.[12] Enamines also result from zirconium-catalyzed hydroamination of alkynes,[13] and vinyl amines have been prepared from acetylene in the presence of ruthenium catalysts.[14] However, the most efficient methods involving terminal alkynes are the intramolecular aminopalladation of acetylenic amines followed by cross-coupling with aromatic halides,[15] and the mercury(II)-catalyzed amination of 3-en-1-ynes[16] leading to 2-amino-1,3-dienes *via* the regioselective Markovnikov addition of the amino group to the triple bond.

We now report the two-step stereoselective synthesis of (*E*)-enamines and dienamines from terminal alkynes, based on the regioselective ruthenium-catalyzed *anti*-Markovnikov *trans*-addition of carboxylic acids followed by reaction with secondary amines according to Scheme 1.

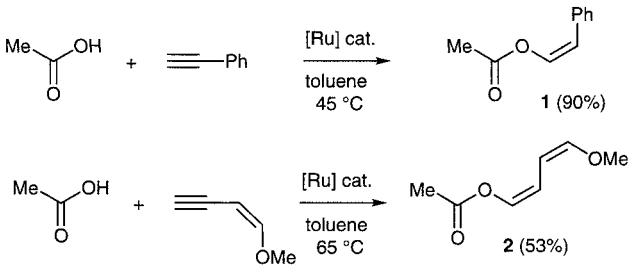


Scheme 1

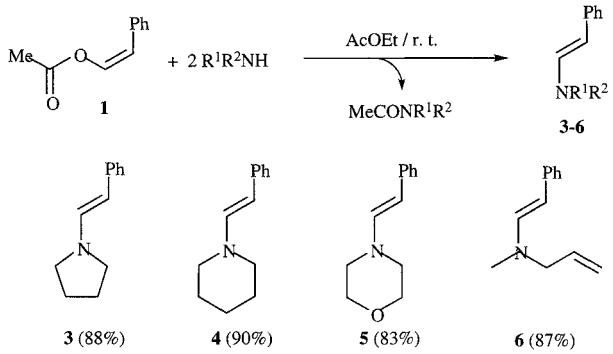
The acylating properties of alk-1-en-2-yl esters **I** under neutral conditions have been used for the formation of amides from amines, esters from alcohols and amido derivatives from primary amides, carbamates and ureas.[17] On the other hand, very little is known about the reactivity of alk-1-en-1-yl esters **II**, probably because of the lack of straightforward preparation methods.



Under experimental conditions related to those of our previous work on ruthenium-catalyzed *anti*-Markovnikov *trans*-addition of carboxylic acids to terminal alkynes,[18,19] in the presence of 1 mol% of (1,4-bis(diphenylphosphino)butane)Ru(CH_2=C(Me)-CH_2)$_2$ catalyst, the addition of 10 mmol of acetic acid to 10 mmol of phenylacetylene in hexane at 45 °C for 4 h led to (*Z*)-β styryl acetate **1** in 90% yield, and the reaction with 10 mmol of (*Z*)-4-methoxybut-3-en-1-yne at 65 °C for 20 h gave the (*Z*, *Z*)-4-methoxybuta-1,3-dien-1-yl acetate **2** in 53% yield.



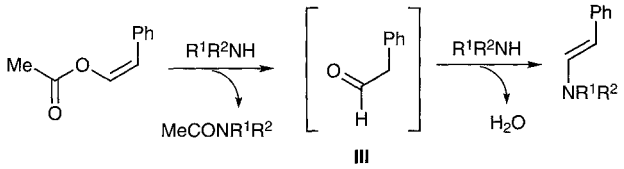
These alk-1-en-1-yl acetates react at room temperature with secondary amines to give (*E*)-enamines and acetamides. In a typical example, 10 mmol of β-styryl acetate **1** and 21 mmol of secondary amine were stirred at room temperature for 30 min in 10 ml of ethyl acetate. An exothermic reaction took place and after elimination of the solvent and the excess of amine, the amide and the enamine were successively recovered by distillation under reduced pressure. The enamines **3-6** obtained by reaction of pyrrolidine, piperidine, morpholine and methyl allyl amine with **1** were obtained in 83-90% isolated yields.[20]



The formation of these enamines likely proceeds *via* acylation of the amine by the enol ester to give the amide and the intermediate aldehyde **III** which reacts with the amine to selectively afford the (*E*)-enamine upon dehydration (Scheme 2). The transformation of phenylacetylene into (*E*)-β-styrylpyrrolidine **3** is possible when the two steps are successively performed in the same pot, without isolation of the intermediate (*Z*)-styryl acetate **1**. Thus, phenylacetylene and acetic acid with 1 mol% of ruthenium catalyst were heated at 45 °C for 4 h in hexane and then 2 equivalents of pyrrolidine were added and stirred at 25 °C for 1 h. The enamine **3** was isolated in 80% yield based on the alkyne.

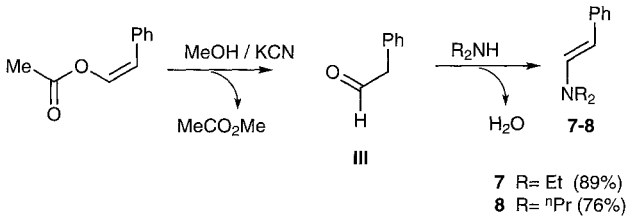
With less reactive secondary amines, such as diethylamine or di-n-propylamine, the initial formation of the aldehyde **III** *via* acylation of methanol catalyzed by KCN was required and the subsequent addition of one equivalent of amine led to the (*E*)-enamine. Thus, when 10 mmol of β-styryl acetate **1** was treated in 10 ml of methanol in the

Downloaded by: University of Illinois. Copyrighted material.



Scheme 2

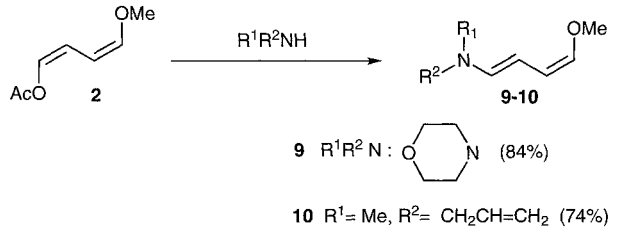
presence of 10 mol% of KCN at room temperature for 10 min, and then 10 mmol of the dialkylamine were added, the enamines **7** and **8** were formed within 4 h and isolated in 89 and 76% yield, respectively. It is noteworthy that even in the presence of KCN as catalyst, but without previous formation of the aldehyde in methanol, the reaction with diethylamine in AcOEt was very slow as the complete conversion of the enol ester **1** required 4 days at room temperature and the enamine **7** was isolated in 78% yield.



Scheme 3

It is noteworthy that enamides have been obtained from vinyl acetate and amides as nucleophiles, but the reaction required the use of Na_2PdCl_4 as catalyst.[21]

This reaction was extended to the functional 4-methoxybuta-1,3-dien-1-yl acetate **2** for the preparation of aminodienes. Under typical conditions, 2 equivalents of morpholine or allyl methyl amine reacted with **2** at room temperature in ethyl acetate to give the (*E,Z*)-1-amino-1,3-dienes **9** and **10** in 84 and 74% yield, respectively.[20] This reaction constitutes a complementary reaction to the Markovnikov amination of alkynes catalyzed by Hg(II) derivatives.[16]



The regio- and stereoselective addition of acetic acid to terminal alkynes makes possible the two-step synthesis of (*E*)-enamines and 1-amino-1,3-dienes from terminal alkynes and enynes, and secondary amines *via* alk-1-en-1-yl acetates. This reaction confirms the potential of alk-1-en-1-yl esters as reactive protected aldehydes. It provides a new synthesis of (*E*)-enamines and (*E*)-dienamines *via* a formal stereoselective *anti*-Markovnikov addition of amines to terminal triple bonds.

References and Notes

(1) Warren, S. in *Organic Synthesis : The Disconnection Approach* , J. Wiley & Sons, Chichester, 1994.

(2) Komatsu, M.; Ohgishi, H.; Takamatsu, S.; Ohshiro, Y.; Agawa, T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 213. Nomura, Y.; Kimura, M.; Shibata, T.; Takeuchi, Y.; Tomoda, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3343.

(3) Komatsu, M.; Takamatsu, S.; Vesaka, M.; Yamamoto, S.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1984**, *49*, 2691.

(4) Merla, B.; Arend, M.; Risch, N. *Synlett* **1997**, 177.

(5) Meyer, A. G.; Aumann, R. *Synlett* **1995**, 1011.

(6) Barluenga, J.; Aznar, F.; Barluenga, S. *J. Chem. Soc., Chem. Commun.* **1995**, 1973. Barluenga, J.; Aznar, F.; Ribas, C.; Valdes, C.; Fernandez, M.; Cabal, M.-P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805. Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023. Marc, G.; Nitti, P.; Pitacco, G.; Pizzioli, A.; Valentin, E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 223.

(7) Barluenga, J.; Aznar, F.; Martin, A.; Vazquez, J. T. *J. Am. Chem. Soc.* **1995**, *117*, 9419.

(8) Broekhof, N.L.J.M.; Jonkers, F.L.; van der Gen, A. *Tetrahedron Lett.* **1979**, *26*, 2436.

(9) Ahlbrecht, H.; Raab, W.; Vonderheid, C. *Synthesis*, **1979**, 127.

(10) Hansson, C.; Wickberg, B. *J. Org. Chem.* **1973**, *38*, 3074.

(11) Erker, G.; Pfaff, R. *Organometallics* **1993**, *12*, 1921.

(12) Gaonac'h O.; Maddaluno, J.; Chauvin, J.; Duhamel, L. *J. Org. Chem.* **1991**, *56*, 4045.

(13) Baranger, A.M.; Walsh, P.J.; Bergman, R.G. *J. Am. Chem. Soc.* **1993**, *115*, 2753.

(14) Heider, M.; Henkelmann, J.; Ruehl, T. *Eur. Pat.* 646 571 A1, 1995 ; *Chem. Abstr.* **1995**, *123*, 229254s.

(15) Luo, F.-T.; Wang, R.-T. *Tetrahedron Lett.* **1992**, *33*, 6835.

(16) Barluenga, J.; Aznar, F.; Valdès, C.; Cabal, M.P. *J. Org. Chem.* **1991**, *56*, 6167.

(17) Kabouche, Z.; Bruneau, C.; Dixneuf, P.H. *Tetrahedron Lett.* **1991**, *32*, 5359. Seiller, B.; Heins, D.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 10901.

(18) Doucet, H.; Martin-Vaca, B.; Bruneau, C.; Dixneuf, P.H. *J. Org. Chem.* **1995**, *60*, 7247.

(19) Doucet, H.; Höfer, J.; Derrien, N. Bruneau, C.; Dixneuf, P.H. *Bull. Soc. Chim. Fr.* **1996**, *133*, 939.

(20) Satisfactory spectroscopic data were found for compounds **3-10**.
3[22] : liquid, IR (neat) 2970, 1635 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-6.90 (m, 5 H, Ph), 7.01 (d, 1 H, ^{3}J= 13.8 Hz), 5.12 (d, 1 H, ^{3}J= 13.8 Hz), 3.22 (m, 4 H), 1.91 (m, 4 H) ; MS m/z= 173.119 calcd for $C_{12}H_{15}N$: m/z= 173.120)
9 : liquid, IR (neat) 2934, 1655, 1623 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (d, 1 H, ^{3}J= 13.9 Hz), 5.59 (d, 1 H, ^{3}J= 6.1 Hz), 5.32 (dd, 1 H, ^{3}J= 13.9 and 10.7 Hz), 4.90 (dd, 1 H, ^{3}J= 10.7 and 6.1 Hz), 3.61 (t, 4 H, ^{3}J= 5.0 Hz), 3.52 (s, 3 H), 2.83 (t, 4 H, ^{3}J= 5.0 Hz) ; MS m/z= 169.109 calcd for $C_9H_{15}NO_2$ m/z= 169.110).

(21) Bayer, E.; Geckeler, K. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 533.

(22) Okuma, K.; Komiya, Y.; Ohta, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2402.

Downloaded by: University of Illinois. Copyrighted material.