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Intramolecular cyclization of *N*-propargylic β-enaminones catalyzed by silver

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ABSTRACT

The efficient synthesis of 1,2-dihydropyridine from the intramolecular cyclization reaction of *N*-propargylic β-enaminones [$R^2C(O)CH{=}C(R^1)(N(R)CH_2C{\equiv}CH)$, where R = Pr, Bn, Ph, 4-Me-C_6H_4, R^1 = Me, Et, Pr, R^2 = CF_3, CO_2Et] using $AgNO_3$ as a catalyst (12 h at 25 °C) is reported. The products were obtained at good yields (70–90%). In particular, when the reaction of *N*-propargylic β-enaminone with R = Me was performed over a 24 h period, the intramolecular cyclization resulted in the formation of a pyrrole with 80% yield.

The reactivity associated with the conjugated systems O=C–C=C–N (OR) makes β-enaminones[1,2] and β-alkoxyvinyl ketones[3,4] valuable reagents with many applications in organic synthesis. A variety of intra-[5] and intermolecular[6] reactions have been performed taking advantage of their electronic properties. In particular, *N*-propargylic β-enaminones can be a potential precursor to intramolecular cyclocondensation when activated by transition metal catalysis.[7] From the literature,[8–13] it is known that various metals such as silver, gold, and platinum form a positive ion which has a high affinity for C≡C triple bonds. The ion forms a triple bond that is electrophilic enough to be attacked by various nucleophilic carbon species such as the α-carbon of enamines,[7] resulting in the formation of a heterocycle.[11]

There are important works in the literature where the reactivity of *N*-propargylic β-enaminones in the presence of metal catalyst is investigated.[7,12,13] In some cases, 1,2-dihydropyridines are formed[7,12] and in other situations, pyrroles are isolated.[7,13] The formation of pyrroles or 1,2-dihydropyridines appears to be related to substituent at the frame of *N*-propargylic β-enaminones and to reaction conditions, including catalyst. Cacchi et al.[7] for example, obtained a pyrrole when using Cs_2CO_3 at room temperature, whereas a pyridine was formed when using CuBr and heating the mixture.

It is important to note that in all of these works the *N*-propargylic β-enaminones studied were not substituted with trifluoromethyl groups.

Over the years, our research group has developed strategies for the synthesis of heterocycles, especially trifluoromethylated ones, since the presence of halogen in organic molecules gives the molecules interesting properties.[14] Our methodology uses the trifluoromethyl β-alkoxyvinyl ketones[4] and β-enaminones[15] (CCC Block) as 1,3-dieletrophile in cyclizations [3 + 2] or [3 + 3], [3 + 4] type in order to form halogenated heterocycles. We recently published the synthesis of novel *N*-propargylic β-enaminones in one step from the reaction of β-alkoxyvinyltrifluoromethyl[carboxyethyl ketones and propargyl amines.[16] Thus, considering the importance of developing new methods for the synthesis of heterocycles, we present herein a reactivity study of *N*-propargylic β-enaminones trifluoromethylated in intramolecular cyclizations for the synthesis of 1,2-dihydropyridines using silver nitrate as the catalyst.

We began our study by investigating the reaction of trifluoromethylated *N*-propargylic β-enaminones (**1a**) and silver nitrate as the catalyst (10 mol %), in the presence of chloroform. The mixture was stirred for 12 h at 25 °C in a nitrogen atmosphere and in the absence of light.

The product isolated was a 1,2-dihydropyridine **3a** at 80% yield (Scheme 1). To support this result, *N*-propargylic β-enaminones **1b** were also tested. The product obtained was also 1,2-dihydropyridine **3b**, but at 70% yield (Scheme 3). Other reaction conditions (variations in time 6–24 h and temperature 25–60 °C) were tested; however, they were unsuccessful for the synthesis

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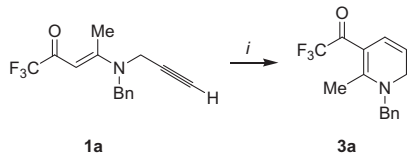
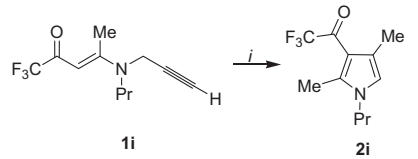


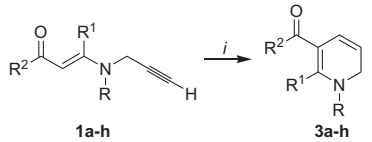
1a 3a

Scheme 1. Reagents and conditions: $AgNO_3$ (10 mol %), $CHCl_3$, 25 °C, 12 h.



1i 2i

Scheme 2. Reagents and conditions: $AgNO_3$ (10 mol %), $CHCl_3$, 25 °C, 24 h, 80%.

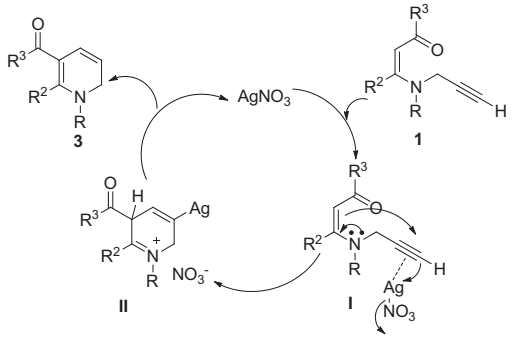


1a-h 3a-h

R	R^1	R^2	Product	Yield (%)
Bn	Me	CF_3	**3a**	80
Ph	Me	CF_3	**3b**	70
Pr	Et	CF_3	**3c**	90
Pr	Pr	CF_3	**3d**	87
Bn	Et	CF_3	**3e**	89
Ph	Me	CO_2Et	**3f**	80
4-Me-C_6H_4	Me	CF_3	**3g**	85
4-Me-C_6H_4	Pr	CF_3	**3h**	75

Scheme 3. Reagents and conditions: $AgNO_3$ (10 mol %), $CHCl_3$, 12 h, 25 °C.

of 1,2-dihydropyridine. To evaluate the scope and limitations of this reaction, we performed the reaction in accordance with the previous optimization for other *N*-propargylic β-enaminones. Fortunately, we derived a method for other *N*-propargylic β-enaminones and obtained a series of 1,2-dihydropyridines at good to excellent yields (Scheme 3).[19] Reactions were also performed in the absence of light in a nitrogen atmosphere. Although it is reported in the literature that some dihydropyridines are very sensitive to the presence of oxygen,[18] 1,2-dihydropyridine obtained in this work showed a relative stability (5 days) in the presence of oxygen. The stability of 1,2-dihydropyridines was retained even during purification in a chromatography column, probably due to use of nitrogen atmosphere. The collected products were either light yellow solid or light brown oil. When left in solution for this time, 1,2-dihydropyridines undergo degradation.



Scheme 4.

When the *N*-propargylic β-enaminone **1h** was reacted, unexpectedly, polysubstituted pyrrole was obtained at 50% yield. In an attempt to increase the product yield, the mixture was stirred for 24 h and the pyrrole was obtained at an excellent yield (80%) (Scheme 2).[17] Other reaction conditions (variations in time 6–24 h and temperature 60 °C) were tested; however, they were unsuccessful for the synthesis of pyrrole. The formation of pyrrole indicates an attack of the α-carbon in the internal carbon triple bond, as described by Cacchi et al.[7] occurred. An aza-Claisen rearrangement[13] could occur, but from the product it can be seen that a 5-exo-dig mechanism is operating. If aza-Claisen rearrangement had occurred, the methyl group would be attached at 2-position of pyrrole and not at 3. The conditions to the formation of this product have been investigating in our laboratories and the results will be published hereafter.

The identification of 1,2-dihydropyridines synthesized in this work was done using ^1H and ^{13}C NMR, and mass spectroscopy. The NMR and ^1H spectra of the 1,2-dihydropyridines synthesized showed the presence of a characteristic signal of 1,2-dihydropiridines. From the data obtained by mass spectrometry for the compounds **3a–i** it was observed that all the compound showed a molecular ion and a stable fragment ion (base peak) corresponding to the loss of a proton for all compounds, except for **3c–d**. In these compounds, loss of proton corresponded to a peak intensity of 5% relative to the base peak.

By analogy with other cyclizations activated by transition metal from acetylenic compounds,[7,20] we propose that the mechanism for the formation of 1,2-dihydropyridine from **1** involves the coordination of the triple bond with silver to give **I**, followed by cyclization of a type 6-endo-dig via intramolecular nucleophilic attack of the carbonyl group's α carbon on the activated triple bond. Substitution of the C–H bond for the C–Ag bond of the resultant vinyl–Ag intermediate **I** yields **II,** with concomitant regeneration of $AgNO_3$, as shown in Scheme 4.

In summary, in this Letter we showed that when a triple bond is activated by silver nitrate, the terminal carbon of the triple is more reactive than internal and it undergoes nucleophilic attack by the carbonyl group's α carbon, resulting in 1,2-dihydropyridine. Thus, we developed an efficient, highly regioselective, and inexpensive method for the synthesis of novel 1,2-dihydropyridine trifluoromethylated from the intramolecular cyclization of *N*-propargylic β-enaminones using silver nitrate as the catalyst.

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Supplementary data

Supplementary data (general procedures and characterization data (^1H NMR, ^{13}CNMR, MS and melting points) of compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.086.

References and notes

1. Elassar, A. Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463.
2. (a) Stanovnik, B.; Steve, J. *Chem. Rev.* **2004**, *104*, 2433; (b) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.
3. Colla, A.; Clar, G.; Martins, M. A. P.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, 483.
4. Martins, M. A. P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Flores, A. F. C.; Bonacorso, H. G.; Zanatta, N. *Curr. Org. Chem.* **2004**, *1*, 391.
5. (a) Tietcheu, C.; Garcia, C.; Gardette, D.; Dugat, D.; Gramain, J.-C. *J. Heterocycl. Chem.* **2002**, *39*, 965; (b) White, J. D.; Ihle, D. C. *Org. Lett.* **2006**, *8*, 1081; (c) Bellur, E.; Langer, P. *Tetrahedron Lett.* **2006**, *47*, 2151; (d) Cruz, M. C.; Jiménez, F.; Delgado, F.; Tamariz, J. *Synlett* **2006**, 749; (e) Ursic, U.; Bevk, D.; Pirc, S.; Pezdirc, L.; Stanovnik, B.; Svete, J. *Synthesis* **2006**, 2376; (f) Davis, F. A.; Xu, H.; Zhang, J. *J. Org. Chem.* **2007**, *72*, 2046; (g) Yan, S.; Wu, H.; Wu, N.; Jiang, Y. *Synlett* **2007**, 2699.
6. (a) Vohra, R. K.; Bruneau, C.; Renaud, J.-L. *Adv. Synth. Catal.* **2006**, *348*, 2571; (b) Hu, H.-Y.; Liu, Y.; Ye, M.; Xu, J.-H. *Synlett* **2006**, 1913; (c) Nishiwaki, N.; Nishimoto, T.; Tamura, M.; Ariga, M. *Synlett* **2006**, 1437; (d) Pešková, M.; Šimùnek, P.; Bertolasi, V.; Macháček, V.; Lyčka, A. *Organometallics* **2006**, *25*, 2025; (e) Tu, S.; Jiang, B.; Jia, R.-H.; Zhang, J.-Y.; Zhang, Y.; Chang-Sheng Yao, C.-S.; Shi, F. *Org. Biomol. Chem.* **2006**, *4*, 3664; (f) Huang, J.; Liang, Y.; Pan, W.; Yang, Y.; Dong, D. *Org. Lett.* **2007**, *9*, 5345; (g) Tu, S.; Li, C.; Li, G.; Cao, L.; Shao, Q.; Zhou, D.; Jiang, B.; Zhou, J.; Xia, M. *J. Comb. Chem.* **2007**, *9*, 1144; (h) Cheng, X.-M.; Liu, X.-M. *J. Comb. Chem.* **2007**, *9*, 906; (i) Cunha, S.; Damasceno, F.; Ferrari, J. *Tetrahedron Lett.* **2007**, *48*, 5795; (j) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. *J. Org. Chem.* **2007**, *72*, 8593.
7. Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629.
8. Dalla, V.; Pale, P. *New J. Chem.* **1999**, 803.
9. Jong, T. T.; Leu, S.-J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 423.
10. Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567.
11. Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, I. K.; Han, W.-S.; Kang, S. O. *J. Org. Chem.* **2006**, *71*, 9366.
12. Kim, H.; Chulbom, L. *J. Am. Chem. Soc.* **2006**, *128*, 6336.
13. Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372.
14. Martins, M. A. P.; Sinhorin, A.; Zimmermann, N. E. K.; Zanatta, N.; Bonacorso, H. G.; Bastos, G. P. *Synthesis* **2001**, 1959.
15. (a) Martins, M. A. P.; Scapin, E.; Frizzo, C. P.; Rosa, F. A.; Bonacorso, H. G.; Zanatta, N. *J. Braz. Chem. Soc.* **2009**, *20*, 205; (b) Moreira, D. N.; Longhi, K.; Frizzo, C. P.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *Catal. Commun.* **2010**, *11*, 476.
16. Martins, M. A. P.; Rossatto, M.; Prola, L. D. T.; Pizzuti, L.; Moreira, D. N.; Campos, P. T.; Frizzo, C. P.; Zanatta, N.; Bonacorso, H. G. *Ultrason. Sonochem.* **2012**, *19*, 227.
17. *Synthesis of 3-trifluoracethyl-2,4-dimethyl-1-propyl-pyrrole (**2i**)*: Silver nitrate (10 mol %) was added in a round-bottomed flask in the absence of light under a N_2 atm. Then were added the *N*-propargylic β-enaminone **1i** (5 mmol) and chloroform (20 mL) solution. The mixture was kept under magnetic stirring at 25 °C for 24 h. After completion of the reaction time the mixture was filtered and the solvent of filtrate was removed in a rotary evaporator. The product **2a** was purified by column chromatography with deactivated silica using ethyl acetate/hexane (1:30) as the eluent. Analytical data for **2i** $C_{11}H_{14}NOF_3$ Mol. W.: 233.23 (80%); oil; ^{1}H NMR (200 MHz, $CDCl_3$) 0.94 (t, 3H, H9), 1.75 (sext, 2H, H8), 2.19 (s, 3H, H10), 2.46 (s, 3H, H6), 3.75 (t, 2H, H7), 6.34 (s, 1H, H5); ^{13}C NMR (200 MHz, $CDCl_3$) 10.9 (10), 12.1 (6), 23.7 (C8), 118.3 (q, $^1J_{C-F}$ = 293, CF_3), 121.1 (q, ^4J = 4, Ar), 140.7 (q, ^4J = 4, Ar), 176.2 (q, ^2J = 30, C=O); MS (CI): *m*/*z* = 233 (M+, 85), 164 (100), 122 (40).
18. Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223.
19. *Synthesis of 1,2-dihydropyridines (**3a**–**h**)*: Silver nitrate (10 mol %) was added in a round-bottomed flask in the absence of light under a N_2 atm. Then, propargylic enaminones **1a**–**h** (5 mmol) and chloroform (20 mL) were added. The mixture was kept under magnetic stirring at 25 °C for 12 h. After completion of the reaction time the mixture was filtered and the solvent of filtrate was removed in a rotary evaporator. The products **3b**–**i** were purified by column chromatography under a nitrogen atmosphere with basic alumina using ethyl acetate/hexane (1:20) as the eluent. *Representative analytical data for **3a** $C_{15}H_{14}F_3NO$ Mol. W.*: 281.28 (80%); oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.60 (s, 3H, H7), 4.09–4,10 (m, 2H, H6), 4.61 (s, 2H, H10), 5.06 (dt, 1H, ^4J = 4, ^3J = 10, H5), 6.47 (d, 1H, ^3J = 10, H4), 7.21 (d, 2H, *J* = 7, H-Ar), 7.32–7.24 (m, 3H, H-Ar); ^{13}C NMR (200 MHz, $CDCl_3$) δ 18.0 (C7), 51.2 (C10), 55.2 (C6), 102.0 (C3), 107.5 (C5), 117.5 (q, $^1J_{C-F}$ = 293, CF_3), 123.4 (q, ^{4}J = 4, C4), 126.3, 128.2, 129.2, 134.0 (C–Ar), 166.1 (C2), 173.7 (q, ^2J = 31, C=O); MS (CI): *m*/*z* = 281 (M+, 15), 280 (5), 212 (5), 190 (5), 91 (100).
20. (a) Messina, F.; Botta, M.; Corelli, F.; Villani, C. *Tetrahedron: Asymmetry* **2000**, *11*, 1681; (b) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525; (c) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277; (d) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843; (e) Hiroya, K.; Itoha, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958.