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Synthesis of 2,5-Dihydropyridine Derivatives by Gold-Catalyzed Reactions of β-Ketoesters and Propargylamines

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ABSTRACT

The reaction of simple β-ketoesters and propargylamines under gold(III) catalysis leads to the formation of the elusive 2,5-dihydropyridine system. This new reaction provides the synthesis of potentially bioactive compounds in moderate to high yields.

Since the pioneering work of Hantzsch on the synthesis of dihydropyridines at the end of 19th century,[1] a large area of research has been developed on the chemistry and applications of this interesting class of heterocyclic compounds.[2] As shown in Figure 1, there are five possible isomeric dihydropyridines **1**–**5**. However, most of the work regarding the synthesis and uses of these compounds has been focused on 1,2-dihydro- (**1**) and 1,4-dihydropyridines (**2**). The reason why **1** and **2** are more common than **3**–**5** is presumably the involvement of the nitrogen lone pair in the π-electron system of the former. Thus, **1** and **2** have five sp^2-hybridized centers. The 2,3-dihydro- (**3**) and 5,6-dihydro- (**4**) isomers, having four sp^2-hybridized centers, contain two conjugated double bonds. Finally, the 2,5-dihydropyridine **5** also has four sp^2-hybridized centers but its double bonds are not conjugated and this probably makes this concrete isomer of the dihydropyridynes a very unusual system. In fact, there are very few examples in the literature regarding the synthesis of 2,5-dihydropyridine derivatives.[3]

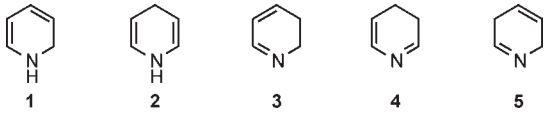

Figure 1. Isomeric forms of dihydropyridines.

At this point the extraordinary incidence of dihydropyridines (mainly 1,4-dihydropyridines) in medicinal chemistry including antitumor activity should also be mentioned;[4] they have been used as antidiabetic agents,[5] in the treatment of vascular disorders,[6] as HIV protease inhibitors,[7] and various others.[8] However, the lack of general methods

(1) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.
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(3) (a) Meyers, A. I.; Betrus, B. J.; Ralhan, N. K.; Rao, K. B. *J. Heterocycl. Chem.* **1964**, *1*, 13. (b) Francis, R. F.; Howell, H. M.; Fetzer, D. T. *J. Org. Chem.* **1981**, *46*, 2213. (c) Marsais, F.; Granger, P.; Quéguiner, G. *J. Org. Chem.* **1981**, *46*, 4494. (d) Junge, H.; Oehme, G. *Tetrahedron* **1998**, *54*, 11027. (e) Rudler, H.; Martín-Vaca, B.; Nicolas, M.; Audouin, M.; Vaissermann, J. *Organometallics* **1998**, *17*, 361. (f) Depature, M.; Siri, D.; Grimaldi, J.; Hatem, J.; Faure, R. *Tetrahedron Lett.* **1999**, *40*, 4547. (g) Depature, M.; Diewok, J.; Grimaldi, J.; Hatem, J. *Eur. J. Org. Chem.* **2000**, 275.
(4) Abbas, H.-A. S.; El Sayed, W. A.; Fathy, N. M. *Eur. J. Med. Chem.* **2010**, *45*, 973.
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(6) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.
(7) Hilgeroth, A. *Mini-Rev. Med. Chem.* **2002**, *2*, 235.
(8) (a) Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. *Am. J. Kidney Dis* **1993**, *21*, 53. (b) Marco-Contelles, J.; Leon, R.; de los Rios, C.; Guglietta, A.; Terencio, J.; López, M. G.; Villarroya, M. *J. Med. Chem.* **2006**, *49*, 7607. (c) Letelier, M. E.; Entrala, P.; López-Alcorcón, C.; González-Lira, V.; Molina-Berríos, A.; Cortés-Troncoso, J.; Jara-Sandoval, J.; Santander, P.; Núñez-Vergara, L. *Toxicol. In Vitro* **2007**, *21*, 1610.

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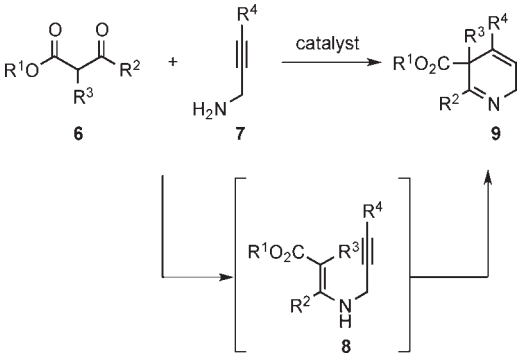
to construct the 2,5-dihydropyridine skeleton has prevented an in depth investigation on the biological activity of this isomer of dihydropyridines.

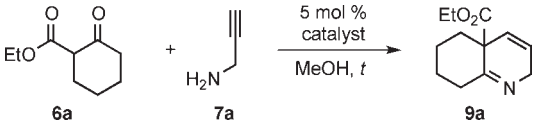
All the above-mentioned reasons led us to evaluate new methods for the synthesis of 2,5-dihydropyridine derivatives. Thus, inspired by the work of S. Cacchi and G. Fabrizi on the synthesis of pyridines and pyrroles,[9] we hypothesized that the condensation of 2-substituted β-ketoesters **6** and propargyl amines **7** would provide *N*-propargylic β-enaminoester intermediates **8**, which in the presence of a catalyst able to activate the alkyne could react by a 6-*endo*-*dig* cyclization process to form the 2,5-dihydropyridine derivatives **9** in an apparently very simple way from readily available starting materials (Scheme 1).[10] The excellent work of S. F. Kirsch and co-workers on metal-catalyzed reactions of propargyl vinyl ethers (related to β-enaminoester intermediates **8**) to get different heterocyclic compounds should be remarked upon at this point.[11]

Scheme 1. Proposed Reaction for the Synthesis of 2,5-Dihydropyridine Derivatives



To check the feasibility of the proposed reaction, the initial proof-of-concept investigations were performed with ketoester **6a** and propargylamine **7a** (Table 1). Considering the high affinity of gold to alkynes and having in mind the specific quality of gold(III) salts of accelerating the condensation between ketones and amines,[12] we focused our attention on this specific kind of catalysts. Thus, by using 5 mol % of dichloro(2-pyridinecarboxilato)gold in methanol as solvent at room temperature for 48 h, we were able to observe the formation of the desired 2,5-dihydropyridine derivative **9a** although in low yield (Table 1, entry 1).

Table 1. Synthesis of 2,5-Dihydropyridine Derivative **9a** under Different Reaction Conditions



entry	catalyst	temperature (T, °C)	yield (%)[a]
1	(pic)$AuCl_2$[b]	rt	10
2	(pic)$AuCl_2$[b]	40	82
3	(pic)$AuCl_2$[b]	75	55
4	$NaAuCl_4$	40	91[c]
5	$(Ph_3P)AuCl/AgOTf$	40	–[d]
6	$PtCl_2$	rt	–[d]
7	$PtCl_4$	rt	–[e]
8	TfOH	40	–[d]

[a] Determined by ^1H NMR analysis of the crude reaction mixture by using *p*-xylene as internal standard. [b] (pic)$AuCl_2$ = dichloro(2-pyridinecarboxilato)gold. [c] Reaction performed in the presence of 4 Å molecular sieves. In the absence of 4 Å molecular sieves the yield was slightly lower (85%). [d] Starting materials were recovered. [e] We only observed the formation of the corresponding condensation product **8**.

By increasing the temperature to 40 °C the yield of the reaction also increased to a promising 82% yield after 48 h of reaction (Table 1, entry 2). Surprisingly, the yield diminished when the temperature was increased to 75 °C probably due to the decomposition of the product under these conditions (Table 1, entry 3). The best result was obtained by using as catalyst the simpler and cheaper gold(III) salt $NaAuCl_4$. With this catalyst we observed the formation of the 2,5-dihydropyridine derivative **9a** in 91% yield when the reaction was performed at 40 °C for 48 h (Table 1, entry 4). The cationic gold(I) complex in situ formed by mixing $(Ph_3P)AuCl$ and AgOTf did not promote the reaction (Table 1, entry 5). We also checked the possibility of using platinum(II) and platinum(IV) catalysts but we did not observed the formation of the desired product (Table 1, entries 6,7). Finally, to check if a simple Brønsted acid could promote the process, we performed an experiment by using triflic acid (TfOH) as catalyst, but we did not observe any conversion and we recovered the starting materials (Table 1, entry 8). Among the different solvents used, methanol gave the best results.

Under the optimized conditions, 5 mol % of $NaAuCl_4$ as catalyst in methanol as solvent in the presence of 4 Å molecular sieves at 40 °C, we examined the scope of this new synthesis of 2,5-dihydropyridine derivatives (Scheme 2). As shown, different substitution on both, the ketoester and the propargylamine is allowed and the corresponding 2,5-dihydropyridine derivatives are isolated, in general, in moderate to good yields. The reaction seems to work better with propargylamines unsubstituted at the triple bond (R^4 = H) or with an aromatic ring at this position. However, when R^4 is an aliphatic chain we observed the lowest yields (see **9e**). We have not observed isomerization of the obtained 2,5-dihydropyridine derivatives **9** to any of the other possible isomers **1**–**4**. The structure of compounds **9**

(9) (a) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629. See also:(b) Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959.

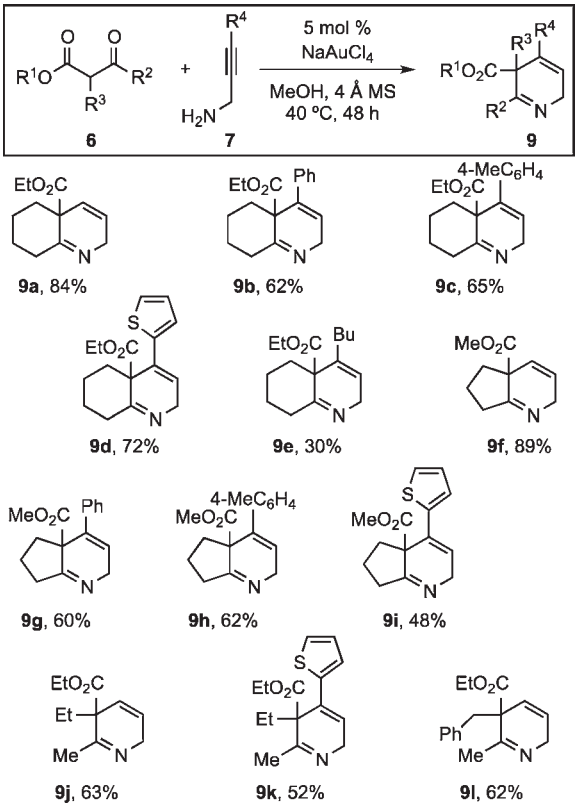
(10) Note that dihydropyridines **9** could be considered as 2,5-dihydropyridine derivatives or alternatively as 3,6-dihydropyridinecarboxylates.

(11) (a) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925. (b) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (c) Menz, H.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 4795. (d) Harschneck, T.; Kirsch, S. F. *J. Org. Chem.* **2011**, *76*, 2145.

(12) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443.

was assigned on the basis of different NMR studies and confirmed by single-crystal X-ray analysis performed on dihydropiridine **9b**.

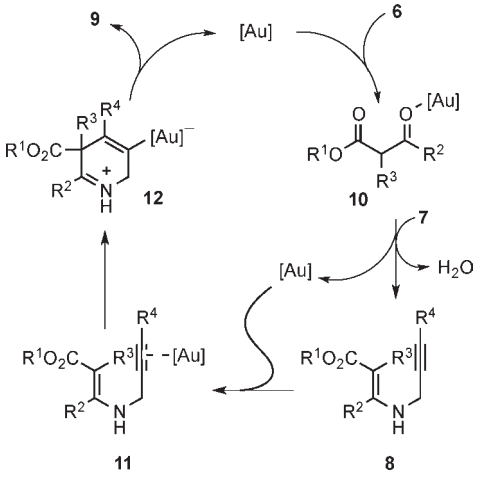
Scheme 2. Gold-Catalyzed Synthesis of 2,5-Dihydropyridine Derivatives **9** from Ketoesters **6** and Propargylamines **7**[a]



[a] Isolated yield based on starting material **6**

A mechanism that explains the formation of the 2,5-dihydropyridine derivatives **9** is shown in Scheme 3. As a first step, we suppose the formation of the *N*-propargylic *β*-enaminoester **8** through a condensation reaction probably promoted by coordination of Lewis acid gold(III) cation to the ketone as shown in **10**. A *π*-complex **11** may be formed between the alkyne moiety and the gold(III) cation. Further 6-*endo-dig* cyclization via the intramolecular nucleophilic attack of the enaminic carbon to activated carbon−carbon triple bond would generate the metalated intermediate **12**. Finally a protodemetalation reaction would form the final 2,5-dihydropyridine derivatives **9** regenerating the gold catalyst. The dual role of gold(III), as a conventional Lewis acid and as a *π*-acid,[13] in this reaction is remarkable.[14] We believe that the lack of reactivity of gold(I) complexes in our reaction (see entry 5 in Table 1) could be due to its poorer Lewis acidity character if compared to gold(III).[15] It should also be noted that other authors have reported the gold(I) catalyzed transformation of *N*-propargylic *β*-enaminoester derivatives into pyrroles through an amino-Claisen/heterocyclization sequence.[16] In our case, the substitution at C2-position of the initial ketoester **6** prevents a similar behavior allowing us to get the desired 2,5-dihydropyridine derivatives instead of pyrroles. It should also be noted that if our reaction is performed with C2-unsubstituted ketoesters (R^3 = H in **6**) we observed the formation of pyridines presumably by aromatization of the dihydropyridine initially formed.[17] This is in complete agreement with the results observed by A. Arcadi and col.[9b]

Scheme 3. Mechanism for the Formation of 2,5-Dihydropyridine Derivatives **9**



In conclusion, we have achieved the synthesis of the elusive 2,5-dihydropyridine skeleton through a new gold(III) catalyzed reaction of *β*-ketoesters and propargylamines. The method is simple and general and the starting materials are easily available. Due to the relevance of dihydropyridines in medicinal chemistry and considering the scarcity of methods for the synthesis of the particular 2,5-dihydro isomers, we believe that our method could find applications in the context of searching for new pharmacological active compounds. In this sense, this new reaction also seems appropriate for the synthesis of small libraries of 2,5-dihydropyridines. In the field of gold-catalysis, an interesting feature of our reaction is the dual role of the gold(III) species as a *σ*- and *π*-acid.

(13) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

(14) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817.

(15) Gold(I) has been proved to be a poor Lewis acid: (a) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem.—Eur. J.* **2000**, *6*, 3491. For a comparative study on the Lewis acidity of gold(I) and gold(III), see ref 14. The higher oxophilicity of gold(III) if compared with gold(I) has been invoked by other authors. See, for example:(b) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500. (c) Duknik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440.

(16) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372.

(17) As an example, under our reaction conditions the reaction of ethyl acetoacetate and propargylamine led to the formation of ethyl 2-methylpyridine-3-carboxylate in 45% yield (unoptimized).

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Supporting Information Available. Experimental procedures and characterization data. Copies of ^{1}H and ^{13}C NMR spectra. Crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.