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Gold(I)-Catalyzed Cyclization of β-Allenylhydrazones: An Efficient Synthesis of Multisubstituted *N*-Aminopyrroles

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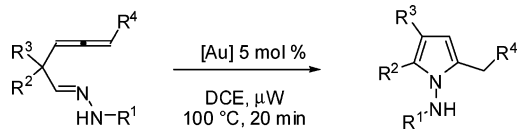
ABSTRACT



The gold(I)-catalyzed cycloisomerization of β-allenylhydrazones provides an efficient access to multisubstituted *N*-aminopyrroles, which are obtained in good to excellent yields. This new intramolecular cyclization method can be applied either to alkyl- or aryl-substituted allenes. The reaction proceeds under mild conditions with short reaction times through a selective intramolecular 1,2-alkyl or -aryl migration extending the general scope of the reaction.

Platinum- and gold-catalyzed cycloisomerization of polyunsaturated compounds has attracted considerable attention due to the significant increase in molecular complexity achieved in a single synthetic step.[1] In the past few years, our group and others have reported several examples of enyne and allenyne cycloisomerizations to form (poly)cyclic compounds.

Recently, we envisaged developing straightforward procedures employing functionalized allenes for the synthesis of heterocyclic compounds.[2] In particular, we focused our attention on highly substituted pyrroles.

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(1) For selected reviews, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3181. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (c) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (d) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. For recent contributions of our group, see: (e) Moreau, X.; et al. *Adv. Synth. Catal.* **2008**, *350*, 43. (f) Moreau, X.; Hours, A.; Fensterbank, L.; Goddard, J. P.; Malacria, M.; Thorimbert, S. *J. Organomet. Chem.* **2009**, *694*, 561. (g) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 29930. (h) Marion, N.; et al. *Chem.—Eur. J.* **2009**, *15*, 3243. (i) Harrak, Y.; Simonneau, A.; Malacria, M.; Gandon, V.; Fensterbank, L. *Chem. Commun* **2010**, *46*, 865. For recent contributions of other groups, see: (j) Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3517. (k) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276. (l) Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543.

(2) For very recent work, see: (a) Gockel, B.; Krause, N. *Eur. J. Org. Chem.* **2010**, 311. (b) Ueda, M.; Sato, A.; Ikeda, Y.; Miyoshi, T.; Naito, T.; Miyata, O. *Org. Lett.* **2010**, *12*, 2594. (c) Teng, T.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **2010**, *132*, 9298. (d) Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888.

(3) (a) Artico, M.; Di Santo, R.; Costi, R.; Massa, S.; Retico, A.; Artico, M.; Apuzzo, G.; Simonetti, H. G.; Strippoli, V. *J. Med. Chem.* **1995**, *38*, 4223. (b) Carson, J. R.; Carmosin, R. J.; Pitis, P. M.; Vaught, J. L.; Almond, H. R.; Stables, J. P.; Wolf, H. H.; Swinyard, E. A.; White, H. S. *J. Med. Chem.* **1997**, *40*, 1578. (c) Biava, M.; Porretta, G. C.; Poce, G.; De Logu, A.; Saddi, M.; Meleddu, R.; Manetti, F.; De Rossi, E.; Botta, M. *J. Med. Chem.* **2008**, *51*, 3644. (d) Rudnitskaya, A.; Huynh, K.; Torok, B.; Stieglitz, K. *J. Med. Chem.* **2009**, *52*, 878. For *N*-aminopyrroles, see: (e) Johnson, R. E.; Soria, A. E.; O'Connor, J. R.; Dobson, R. A. *J. Med. Chem.* **1981**, *24*, 1314. (f) Davies, L.; et al. *J. Med. Chem.* **1996**, *39*, 582. (g) Mai, A.; et al. *J. Med. Chem.* **2002**, *45*, 1180.

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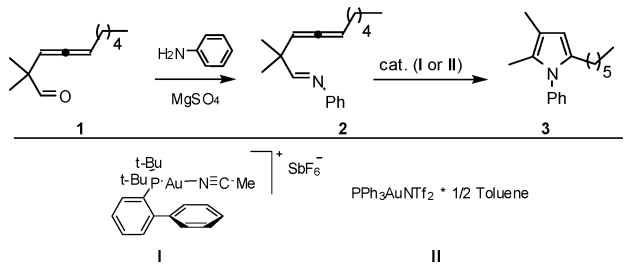
These compounds are ubiquitous constituents in pharmaceuticals[3] or natural products[4] and are also frequently used as subunits in material sciences.[5] Several groups are currently investigating transition-metal-catalyzed synthesis of these heteroaromatic compounds.[6] However, many procedures still present limitations in terms of substituents, which in turn narrow the substrate scope. Thus, the development of versatile methods for the direct access to functionalized pyrroles is highly desirable.

Herein, we report a new gold(I)-catalyzed cycloisomerization of β-allenylimines and β-allenylhydrazones, which allows the formation of 2,3,5-substituted pyrroles through a selective intramolecular [1,2] alkyl or aryl shift extending the scope of the reaction.

To probe the viability of this cycloisomerization process, we first investigated the reactivity of β-allenylimine[7] **2** as model. Treatment of this compound with 5 mol % of AuCl, $AuCl_3$, and catalysts **I** or **II**, respectively (Scheme 1), in

Scheme 1. Cycloisomerization Reactions of β-Allenylimines

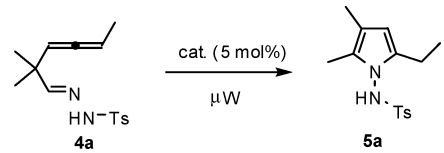


CH_2Cl_2 at room temperature resulted in the recovery of the starting material. A set of different reaction conditions were screened, and catalyst **I** was found to promote the desired cycloisomerization in THF, at 100 °C, under microwave irradiation (30 W) for 20 min. Under these conditions, pyrrole **3** could be isolated as the only product, albeit in a low but encouraging 15% yield.

The anticipated reduced nucleophilicity and stability of β-allenylimines prompted us to examine the gold(I)-catalyzed cycloisomerization of β-allenylhydrazones, readily available from the corresponding β-allenylaldehydes and easily purified by silica gel chromatography.[8]

The proposed cycloisomerization was first investigated using β-allenylhydrazone **4a** under microwave conditions in dichloroethane (DCE) at 100 °C for 20 min with 5 mol % of Echavarren's catalyst (**I**). Gratifyingly, the expected cycloisomerization/1,2-alkyl migration proceeded smoothly to give the corresponding pyrrole **5a** in 57% yield (Table 1, entry 2). Other catalysts known to induce isomerization processes (Au(I), Au(III) Ag(I),[9] Cu(I),[10] Cu(II), and Fe(III)[11]) were screened, but catalysts **I** and **II** turned out to be the most effective (Table 1, entries 2 and 5).

Table 1. Catalysts Screening for Pyrrole Synthesis[a]



entry	catalyst	solvent	product (%)
1	**I**	THF	51
2	**I**	DCE	57
3	$AuCl_3$	DCE	SM
4	AuCl	DCE	SM
5	**II**	DCE	55
6	$AgNO_3$	DCE	SM
7	$AgSbF_6$	DCE	traces
8	AgOTf	DCE	SM
9	CuI	DCE	SM
10	$Cu(OTf)_2$	DCE	SM
11	$FeCl_3$	DCE	SM
12	TfOH	DCE	SM
13	$HN(OTf)_2$	DCE	SM

[a] Conditions: 0.2 mmol of **4a** (c = 57 mM), 5 mol % of catalyst, μW, 100 °C, 20 min.

(4) See, for example: (a) Fürstner, A.; Grabowski, E. J. *ChemBioChem* **2001**, *2*, 706. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (c) Fürstner, A.; Reinecke, K.; Prinz, H.; Waldmann, H. *ChemBioChem* **2004**, *5*, 1575. (d) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213. (e) McArthur, K. A.; Mitchell, S. S.; Tsueng, G.; Rheingold, A.; White, D. J.; Grodberg, J.; Lam, K. S.; Potts, B. C. M. *J. Nat. Prod.* **2008**, *71*, 1732. (f) Mao, S. C.; Liu, Y.; Morgan, J. B.; Jekabson, M. B.; Zhou, Y. D.; Nagle, D. G. *J. Nat. Prod.* **2009**, *72*, 1927.

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(6) (a) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855. (b) Kim, J. T.; Kel'in, A.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 98. (c) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (d) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (e) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 3855. (f) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066. (g) Rodríguez Rivero, M.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (h) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181. (i) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (j) Peng, L.; Zhang, X.; Ma, J.; Zhong, Z.; Wang, J. *Org. Lett.* **2007**, *9*, 1445. (k) Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2010**, *12*, 312. (l) Du, X.; Xie, X.; Liu, Y. *J. Org, Chem.* **2010**, *75*, 510. (m) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443. (n) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372. (o) Lamandé-Langle, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A; Parrain, J.-P. *Chem. Commun.* **2010**, 5157.

(7) For the synthesis of β-allenylaldehydes and β-allenylimines, see the Supporting Information. In our hands, β-allenylaldehydes have not been reactive under gold catalysis.

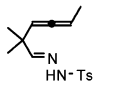
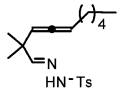
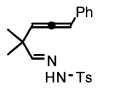
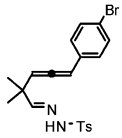
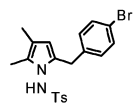
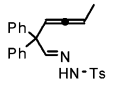
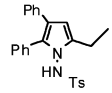
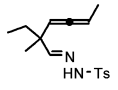
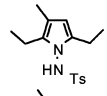
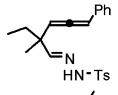
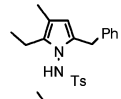
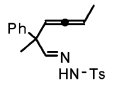
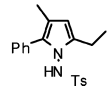
(8) For the synthesis of β-allenylhydrazones, see the Supporting Information. For radical cyclizations of β-allenylhydrazones, see: (a) Marco-Contelles, J.; Blame, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.; Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202. (b) Departure, M.; Grimaldi, J.; Hatem, J. M. *Eur. J. Org. Chem.* **2001**, 941.

(9) (a) Dieter, R. K.; Chen, N.; Gore, V. K. *J. Org. Chem.* **2006**, *71*, 8755. (b) Cordier, P.; Aubert, C.; Malacria, M.; Lacôte, E.; Gandon, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8757. (c) Belmont, P.; Parker, E. *Eur. J. Org. Chem.* **2009**, 6075.

(10) Cu-catalyzed cyclization of iminoallenes to pyrroles has been reported; see: (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Nedolya, N. A.; Brandsma, L.; Tplmachev, S. V. *Chem. Heterocycl. Compd.* **2002**, *38*, 745. (c) Brandsma, L.; Nedolya, N. A.; Tplmachev, S. V. *Chem. Heterocycl. Compd.* **2002**, *38*, 54. (d) Tsuhako, A.; Oikawa, D.; Sakai, K.; Okamoto, S. *Tetrahedron Lett.* **2008**, *49*, 6529.

These promising results incited us to explore the scope of the reaction using various β-allenylhydrazones (Table 2).

Table 2. Cycloisomerization Reactions of Tosylhydrazones

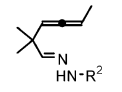
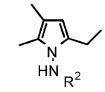
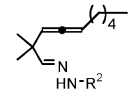
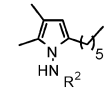
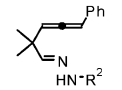
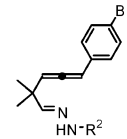
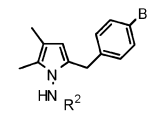
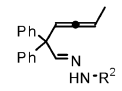
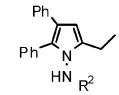
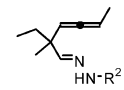
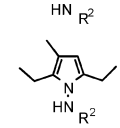
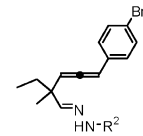
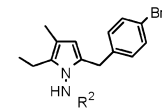
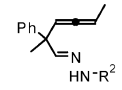
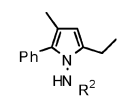
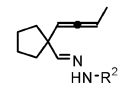
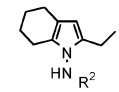
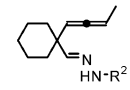
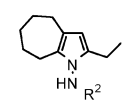
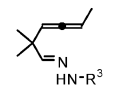
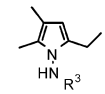
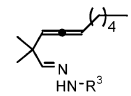
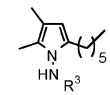
entry		starting material		product	yield
1	**4a**		**5a**		55%[b]
2	**4b**		**5b**		61%[a] 52%[b]
3	**4c**		**5c**		67%[a]
4	**4d**		**5d**		70%[b]
5	**4e**		**5e**		69%[a]
6	**4f**		**5f**		94%[b]
7	**4g**		**5g**		71%[b]
8	**4h**		**5h**		quant%[b]

[a] Conditions: 0.2 mmol of SM (c = 57 mM), 5 mol % of catalyst **I**, μW, DCE, 100 °C, 20 min. [b] Conditions: 0.2 mmol of SM (c = 57 mM), 5 mol % of catalyst **II**, μW, DCE, 100 °C, 20 min.

Under the optimized conditions, isomerization of β-allenylhydrazones **4a**−**h** afforded the desired pyrroles **5a**−**h** in good to excellent yields. A variety of aryl and alkyl groups were tolerated at the allenyl terminus position. Interestingly, selective 1,2 migration of ethyl group over the methyl group occurred both in β-allenylhydrazones **4f** and **4g** to give products **5f** and **5g** in 94% and 71% yields, respectively (Table 2, entries 6 and 7). An analogous selective 1,2 migration of the phenyl group over the methyl group was also observed in the cyclization of β-allenylhydrazone **4h**, which is in accordance with the results of Gevorgyan (Table 2, entry 8).[12]

Substitution influence at the nitrogen atom was then examined with β-allenyl-2,4-dinitrophenylhydrazones **6a**−**j** as shown in Table 3.

Table 3. Cycloisomerization Reactions of 2,4-Dinitrophenylhydrazones and Carboxymethyl Hydrazones

entry		starting material		product	yield
1	**6a**		**7a**		93%[b]
2	**6b**		**7b**		92%[b]
3	**6c**		**7c**		quant[b]
4	**6d**		**7d**		quant[b]
5	**6e**		**7e**		90%[a]
6	**6f**		**7f**		quant[b]
7	**6g**		**7g**		quant[a]
8	**6h**		**7h**		quant[b]
9	**6i**		**7i**		quant[b]
10	**6j**		**7j**		83%[b]
11	**8a**		**9a**		61%[a]
12	**8b**		**9b**		51%[a]
13	**8c**		**9c**		67%[a]

[a] Conditions: 0.2 mmol of SM (c = 57 mM), 5 mol % of catalyst **I**, μW, DCE, 100 °C, 20 min. [b] Conditions: 0.2 mmol of SM (c = 57 mM), 5 mol % of catalyst **II**, μW, DCE, 100 °C, 20 min.

In this case, the cyclization took place to produce **7a**−**j** in excellent yields. Once again, selective 1,2-migration of the ethyl and phenyl groups over the methyl group yielded

(11) For selected reviews, see: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Correa, A.; Garcia Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (c) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem.*−*Eur. J.* **2006**, *12*, 1677.

(12) (a) Dudnik, A. S.; Sromek, A. W.; Rubina, M; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440. (b) Dudnik, A. S.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 7645.

pyrroles **7f**, **7g**, and **7h** in very high yields from the corresponding β-allenylhydrazones **6f**, **6g**, and **6h** (Table 3, entries 6−8). Clear NOE correlations between the proton of the pyrrole ring and the methyl group confirmed the regiochemistry of compounds **7f** and **7h**.[13]

To our delight, cyclization and subsequent ring expansion of cyclopentylallenyl hydrazone **6i** provided fused pyrrole **7i** in quantitative yield (Table 3, entry 9). Cyclohexylallenyl hydrazone **6j** was also employed affording the desired fused bicyclic product **7j** in 83% yield (Table 3, entry 10).

We then demonstrated the feasibility of this cycloisomerization process using β-allenylmethylhydrazone carboxylates **8a**−**c**, which would constitute an interesting atom-economical approach to this convenient pyrrole synthesis. Under the optimized conditions, isomerization proceeded smoothly to yield pyrroles **9a**−**c** with good reaction efficiency (Table 3, entries 11−13). Moreover, this type of compounds could possess valuable antitubercular activity.[14]

Finally, structure of pyrrole **7d** was confirmed by X-ray crystallographic analysis, clarifying the general scope of the reaction (Figure 1).[15]

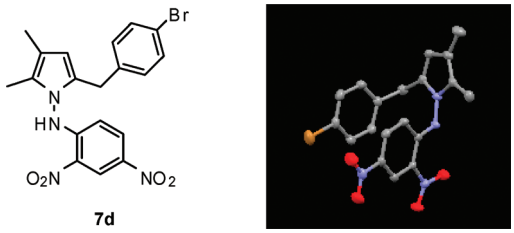
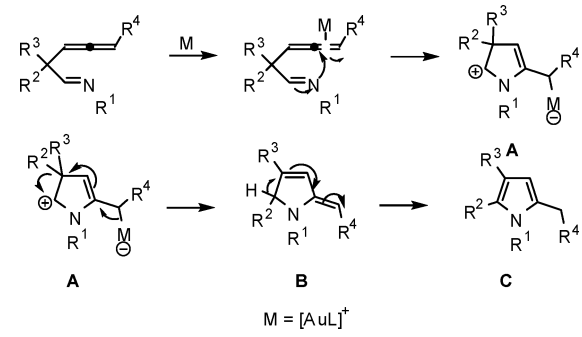


Figure 1. X-ray structure of compound **7d**.

A possible mechanism for these cyloisomerizations is outlined in Scheme 2. An initial π-complexation of the allene moiety to the Au(I) entity triggers the nitrogen nucleophilic attack at the central atom of the allene. This leads to the reactive zwitterion **A**, which evolves to the formation of **B** through a [1,2] alkyl or aryl shift.[16] Final rearomatization of intermediate **B** provides the desired pyrrole **C**.

Scheme 2. Proposed Mechanism



In conclusion, we developed an original and easy to handle gold(I)-catalyzed cycloisomerization of β-allenylhydrazones for the synthesis of functionalized pyrroles. Selective intramolecular 1,2-alkyl or -aryl migrations were observed, extending the general scope of this reaction. This protocol was effective for a broad range of *N*-substituted precursors and tolerated both alkyl and aryl groups at the terminal allenyl atom.

Development of a convenient one-pot reaction for the rapid conversion of readily available β-allenylaldehydes into multisubstituted pyrroles is currently under investigation in our laboratory.

Acknowledgment. This work was supported by MRES, CNRS, IUF, and the ANR Blan 0302 "Allènes". Special thanks to G. Gontard (UPMC) for the X-ray structure determination of **7d** and to M. Amatore (UPMC) for her careful reading of the manuscript.

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

OL101889H

(13) The regiochemistry of **5f**, **5g**, **5h**, and **7g** has been assigned by analogy with compounds **7f** and **7h**.

(14) Hearn, M. J.; Chen, M. F.; Terrot, M. S.; Webster, E. R.; Cynamon, M. H. *J. Heterocycl. Chem.* **2010**, *47*, 707.

(15) CCDC 784441 contains the supplementary crystallographic data for **7d** that can be obtained, free of charge, from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html.

(16) For a review, see: (a) Corne, B.; Kirsch, S. F. *Chem.—Eur. J.* **2008**, *14*, 3514. For tutorial discussion about migratory aptitudes, see: Smith, M. B.; March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; Wiley & Sons: New York, 1992; Chapter 18, p 1051.