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Access to 2,5-Diamidopyrroles and 2,5-Diamidofurans by Au(I)-Catalyzed Double Hydroamination or Hydration of 1,3-Diynes

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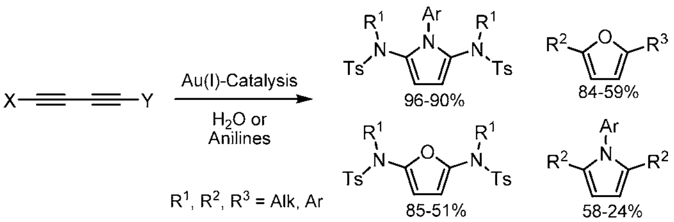
ABSTRACT



A Au(I)-catalyzed hydroamination or hydration of 1,3-diynes to access 2,5-diamidopyrroles and 2,5-diamidofurans has been developed. This method can also be expanded to 2,5-disubstituted furans and 1,2,5-trisubstituted pyrroles including the formation of deuterated heterocycles and ^{18}O-labeled furans.

Due to the high importance of pyrroles and furans in biologically active molecules, a number of synthetic approaches have been devised and published as alternatives to the classical methods represented by the Knorr, Paal−Knorr, and Hantzsch protocols.[1−3] A significant number of these strategies rely on the application of alkynes with carefully chosen functionalities nearby. Such a setup would allow for an intramolecular cyclization to the desired heterocycles, often relying on the use of gold catalysis.[4,5] Recently, terminal alkynes have been exploited for the synthesis of symmetrical 2,5-disubstituted furans by a Ru(II)-catalyzed head-to-head dimerization followed by an intramolecular cyclization.[6] In addition, a Rh(I)-catalyzed head-to-tail dimerization of terminal propargyl amides followed by a Au(III)-catalyzed cyclization have successfully been shown for accessing 1,2,4-trisubstituted pyrroles.[7]

Another approach to symmetrical and nonsymmetrical furans and pyrroles would involve the addition of water or an amine to 1,3-diynes. Access to a variety of diyne starting

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(2) Recent reviews on pyrrole and furan synthesis: (a) Russel, J. S.; Pelkey, E. T.; Yoon-Miller, S. J. P. *Prog. Heterocycl. Chem.* **2009**, *21*, 145. (b) Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2009**, *21*, 179.

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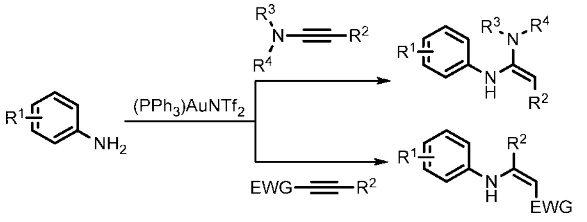
materials can be obtained under mild conditions by the well-established Glaser coupling.[8] The corresponding nonsymmetrical diynes can be obtained by the Negishi, the Codiat−Chodkiewicz, or the Yu−Jiao protocols.[9] Only a few examples of direct pyrrole synthesis from 1,3-diynes exist in the literature.[10,11] In these cases, high temperatures and often stoichiometric Cu salts are required, and rarely are exceptional yields reported. Furthermore, to the best of our knowledge, only one example of a furan synthesis from a 1,3-diyne has been reported using water as the nucleophile. However, the use of HgO makes this a less appealing strategy.[12]

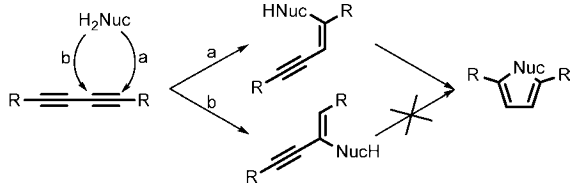
In this communication, we report a Au(I)-catalyzed hydration or hydroamination of 1,3-diynes to access 2,5-diamidofurans and 2,5-diamidopyrroles, as well as 2,5-disubstituted furans and 1,2,5-trisubstituted pyrroles.[13−15] This protocol not only includes full atom economy but also provides straightforward access to isotopically labeled furan and pyrrole analogues.

We have previously shown how the polarization of alkynes influences the reactivity and regioselectivity of a Au(I)-catalyzed hydroamination (Scheme 1).[16] On the basis of these observations, we expected dimerized terminal ynamides (**1**) to be ideal substrates for pyrrole synthesis (Scheme 2, path a) as they would minimize the detrimental and irreversible monoaddition providing the undesired regioselectivity (path b).[17] These substrates would lead to the nontrivial 2,5-diamidopyrroles and 2,5-diamidofurans. Furthermore, these products represent electron-rich pyrroles, which are usually difficult to synthesize. Previous approaches to amidopyrroles have exploited the direct amidation of pyrroles; however, the yields are generally moderate.[18]

Scheme 1. Regioselectivity Based on Alkyne Polarization



Scheme 2. Regioselectivity of the First Addition Step



The double hydroamination of the dimerized ynamides was indeed very effective and highly regioselective using $(Ph_3P)AuNTf_2$[19] as the catalyst, hence securing excellent yields of the desired 2,5-diamidopyrroles (Table 1). A variety of anilines were successfully applied. The position of the substituent did not seem to change the reaction time, except for the anilines with electron-withdrawing groups in the *para*-position, which required longer reaction time for completion (entries 3 and 4). Furthermore, utilization of an N-deuterated aniline afforded a 3,4-dideuteropyrrole (entry 8). Both aliphatic and aromatic substituents on the ynamides were tolerated. Applying water instead of anilines successfully afforded the corresponding 2,5-diamidofurans (Table 2). Although a temperature increase is required, excellent regioselectivity is still observed. The yields are slightly lower due to a competing hydrolysis of the intermediate, which

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(4) Recent gold-catalyzed pyrrole and furan synthesis from alkynes: (a) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372. (b) Davies, P. W.; Martin, N. *Org. Lett.* **2009**, *11*, 2293. (c) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624. (d) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002. (e) Chen, D.-D.; Hou, X.-L.; Dai, L.-X. *Tetrahedron Lett.* **2009**, *50*, 6944. (f) Shu, X.-Z.; Liu, X.-Y.; Xiao, H.-Q.; Ji, K.-G.; Guo, L.-N.; Liang, Y.-M. *Adv. Synth. Catal.* **2008**, *350*, 243. (g) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181. (h) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (i) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (j) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409.

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(10) One example in: (a) Levallo, V.; Frey, G. D.; Donnadieu, B.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5224. (b) Matsumoto, S.; Kobayashi, T.; Ogura, K. *Heterocycles* **2005**, *66*, 319. One example in: (c) Ackermann, L.; Born, R. *Tetrahedron Lett.* **2004**, *45*, 9541. (d) Schulte, K. A.; Reisch, J.; Walker, H. *Chem. Ber.* **1965**, *98*, 98.

(11) Au(I)-catalyzed pyrrole synthesis from 1,5-diynes: Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2009**, *131*, 12100.

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(13) Selected gold-catalyzed hydration of alkynes: (a) Marion, N.; Ramón, R. S.; Nolan, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 448. (b) Leyva, A.; Corma, A. J. *J. Org. Chem.* **2009**, *74*, 2067. (c) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563.

(14) Selected gold-catalyzed hydroaminations of alkynes: (a) Bertrand, G.; Donnadieu, B.; Kinjo, R.; Frey, G. D.; Zeng, X. *J. Am. Chem. Soc.* **2009**, *131*, 8690. (b) Zeng, X.; Frey, G. D.; Kousar, S.; Bertrand, G. *Chem.—Eur. J.* **2009**, *15*, 3056. (c) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645. (d) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349.

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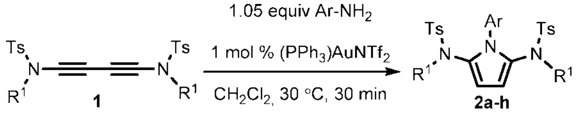
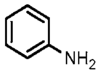
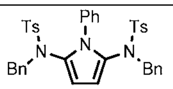
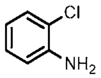
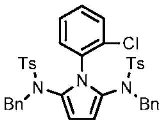
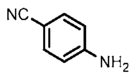
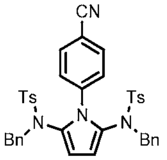
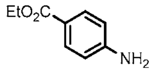
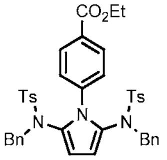
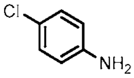
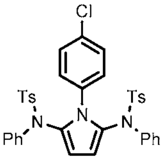
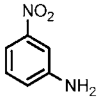
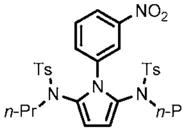
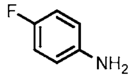
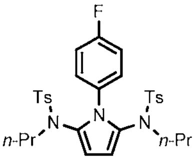
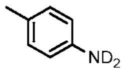
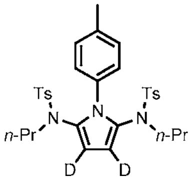
(19) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.

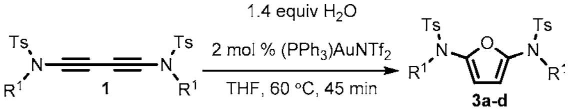
Table 1. Gold-Catalyzed Synthesis of 2,5-Diamidopyrroles

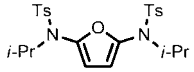
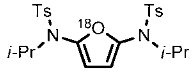
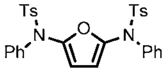
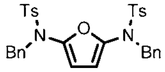


entry	aniline	R^1	product	yield (%)[a]
1		Bn		96 (**2a**)
2		Bn		95 (**2b**)
3[b]		Bn		95 (**2c**)
4[b]		Bn		94 (**2d**)
5		Ph		95 (**2e**)
6		*n*-Pr		93 (**2f**)
7		*n*-Pr		94 (**2g**)
8[c]		*n*-Pr		90 (**2h**)

[a] Isolated yields after column chromatography. [b] Reaction time was 1 h. [c] The product was 90% deuterated, which was also the case for the starting material.

Table 2. Access to 2,5-Diamidofurans via Gold Catalysis



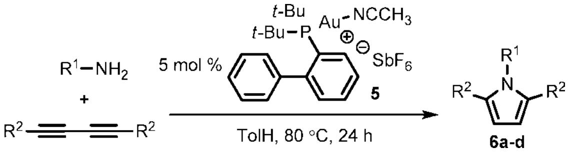
entry	R^1	product	yield (%)[a]
1	*i*-Pr		82 (**3a**)
2	*i*-Pr		80 (**3b**)
3	Ph		85 (**3c**)
4[b]	Bn		51 (**3d**)

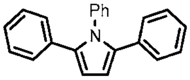
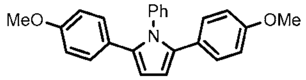
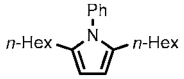
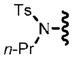
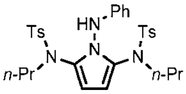
[a] Isolated yield after column chromatography. [b] Reaction time was 1.5 h.

eliminates the free sulfonamide. Again, both aliphatic and aromatic substituents on the ynamide were tolerated. Furthermore, incorporation of ^{18}O proved possible by application of H$_2{}^{18}$O (entry 2).

Encouraged by these results, we set out to expand the scope to include diaryl/alkyl pyrroles; however, this proved more difficult.[20] Only 10% conversion was observed with a 5-fold increase in catalyst loading from the conditions used for the 2,5-diamidopyrrole synthesis. Changing the solvent to DCE or THF and increasing the temperature to 60 °C did not improve the conversion. At this temperature, SPhosAuNTf$_2$, (PhO)$_3$PAuOTf, and IPrAuOTf in either toluene or THF only showed traces of conversion. Only with catalyst **5** in toluene at 80 °C was acceptable conversion obtained (Table 3). However, electronic activation of the diyne significantly improves the reactivity. This is exemplified by entries 1 and 2, where 10.0 equiv of aniline is required to bring the first example to comparable conversion with that of entry 2. Unfortunately, the yield with aliphatic side chains was low (entry 3). Interestingly, the same conditions made

Table 3. Synthesis of 1,2,5-Trisubstituted Pyrroles



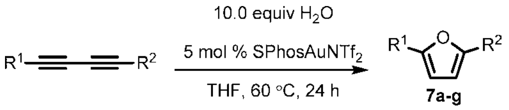
entry	equiv nuc.	R^2	product	yield (%)[a]
1	10.0	Ph		49 (56) (**6a**)
2	1.05	p-MeOC$_6$H$_4$		58 (63) (**6b**)
3	10.0	*n*-Hex		24 (**6c**)
4[b]	5.0			51 (100) (**6d**)

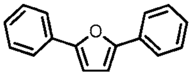
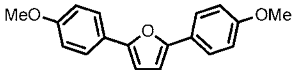
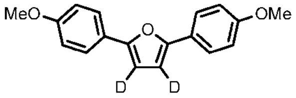
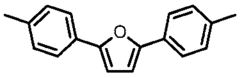
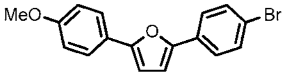
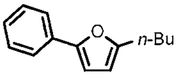
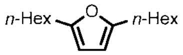
[a] Isolated yields after column chromatography. Conversion of diyne in parentheses. [b] Phenylhydrazine was used instead of aniline.

it possible to synthesize a highly nitrogen-substituted pyrrole in moderate yield (entry 4) starting from phenylhydrazine.

In contrast to the dimerized ynamides, water proved to be a better match as a nucleophile for the diaryl/alkyl diynes. For these hydrations, SPhosAuNTf$_2$ was superior to (Ph$_3$P)AuNTf$_2$ which was also shown by Corma et al.[13b] Applying the conditions shown in Table 4, we obtained a 73% isolated yield of furan **7a** (entry 1). Although a 93% conversion from 1,4-diphenylbuta-1,3-diyne was observed, the low polarization of the alkynes led to a 16% yield of the undesired regioisomer, which was collected as the β-hydroxy-α,β-unsaturated ketone (entry 1).[21] However, when increasing the polarization by introducing *p*-methoxy substituents on the phenyl rings, only traces of the regioisomer were detected. Furthermore, in this case the catalyst loading could be lowered to 2 mol % (entry 2). When the nucleophile was changed to D$_2$O, full incorporation of deuterium on the 3 and 4 position of the furan ring was observed (entry 3). This method also made it possible to synthesize nonsymmetrical furans (entries 5 and 6).

Table 4. Full Incorporation of Water Gives Access to Both Symmetrical and Nonsymmetrical 2,5-Disubstituted Furans

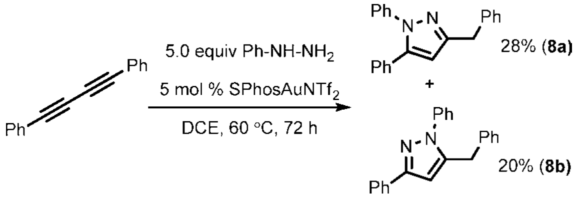


entry	R^1/R^2	product	yield (%)[a]
1	R^1 = Ph R^2 = Ph		73 (**7a**)
2[b]	R^1 = p-MeOC$_6$H$_4$ R^2 = p-MeOC$_6$H$_4$		84 (**7b**)
3	R^1 = p-MeOC$_6$H$_4$ R^2 = p-MeOC$_6$H$_4$		82 (**7c**)
4	R^1 = p-MeC$_6$H$_4$ R^2 = p-McC$_6$H$_4$		80 (**7d**)
5	R^1 = p-MeOC$_6$H$_4$ R^2 = p-BrC$_6$H$_4$		82 (**7e**)
6	R^1 = Ph R^2 = n-Bu		59 (**7f**)
7	R^1 = n-Hex R^2 = n-Hex		68 (**7g**)

[a] Isolated yields after column chromatography. [b] Reaction performed with 2 mol % of catalyst.

Finally, we examined the possibility of exploiting 1,3-diynes to access pyrazoles as well. This was possible using phenylhydrazine as the nucleophile; however, the two regioisomers were obtained in 28% and 20% yield, respectively (Scheme 3).[22] Again, the alkyne polarization is lower than for the dimerized ynamides (**1**), and interestingly, in the case of **8b**, the hydrazine cyclizes in a 5-exo-dig fashion with the alternative nitrogen nucleophile in contrast to that obtained in the case of **6d** (Table 4, entry 4).

Scheme 3. Pyrazole Synthesis from a 1,3-Diyne



In summary, we have discovered a novel route to 2,5-diamidopyrroles and 2,5-diamidofurans. Furthermore, we have shown that the same procedure can be used for the facile synthesis of 2,5-disubstituted furans, 1,2,5-trisubstituted pyrroles, and a pyrazole including examples of nonsymmetrical furans, as well as deuterium and ^{18}O-incorporation. This approach is particularly useful as there is easy access to the starting materials in high-yielding reactions under mild conditions.

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

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[20] (20) The optimization table is included in the Supporting Information.

[21] (21) The first addition creates an enol (Scheme 2), which tautomerizes to the ketone. This affords an electron-poor alkyne, hence directing the second addition to the β-carbon.

[22] (22) Several attempts using hydrazine, Boc-hydrazine, and 1,2-di-Boc-hydrazine followed by deprotection were unsuccessful. In addition, no clean reaction was obtained with the dimerized ynamides.