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Regioselective Synthesis of Substituted Pyrroles: Efficient Palladium-Catalyzed Cyclization of Internal Alkynes and 2-Amino-3-iodoacrylate Derivatives

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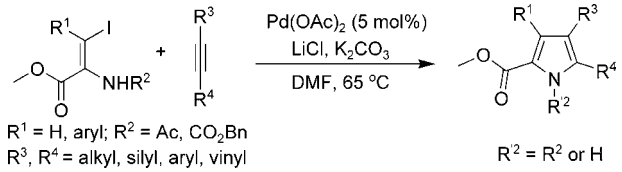
ABSTRACT



The first efficient and regioselective palladium-catalyzed cyclization of internal alkynes and 2-amino-3-iodoacrylates to give moderate to excellent yields of highly functionalized pyrroles has been developed. This approach is applicable to a range of alkynes and affords the deacylated pyrrole under reaction conditions for most substrates.

Pyrroles are prevalent and important heterocycles in natural products,[1] modern pharmaceuticals,[2] and material science.[3] Despite a vast range of published classical[4,5] and recent[6] methods on their synthesis, there are very few general approaches that convert commercially available or readily accessible materials in one step to highly substituted pyrroles. In contrast, the literature is replete with methods for the synthesis of indoles from simple building blocks.[5] In an effort to develop a synthesis of pyrroles relevant to our drug discovery efforts we examined the potential of adapting the "Larock Indole Synthesis[7]" type approach to the synthesis of pyrroles.

Dozens of pyrrole synthesis methods involve alkynes as starting materials;[8] however, despite the depth of prior work on pyrrole synthesis we were surprised to find that, to the best of our knowledge, intermolecular metal-catalyzed cyclizations of alkynes with stabilized iodo enamines have

† Discovery Medicinal Chemistry.
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(1) For a review see: Jones, R. A., Ed. *Pyrroles*; Wiley: New York, 1992; , Part II, Vol. 48.

(2) (a) Thompson, R. B. *FASEB J.* **2001**, *15*, 1671. (b) Muchowski, J. M. *Adv. Med. Chem.* **1992**, *1*, 109. (c) Cozzi, P.; Mongelli, N. *Curr. Pharm. Des.* **1998**, *4*, 181. (d) Fuerstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305.

(3) For a review see: Higgins, S. *Chem. Soc. Rev.* **1997**, *26*, 247.

(4) Widely utilized methods include: (a) "Paal-Knorr pyrrole synthesis": Knorr, L. *Ber.* **1884**, *17*, 1635. Paal, C. *Ber.* **1885**, *18*, 367. (b) "Knorr, pyrrole synthesis": Fischer, H. *Org. Synth. Collect.* **1943**, *2*, 202.

(5) For a review of practical syntheses of both indoles and pyrroles see: Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849.

(6) For recent representative examples, see: (a) Winkler, J. D.; Ragains, J. R. *Org. Lett.* **2006**, *8*, 4437. (b) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468. (c) Shimizu, M.; Takahashi, A.; Kawai, S. *Org. Lett.* **2006**, *8*, 3585.

(7) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

(8) For recent representative examples see: (a) Ishikawa, T.; Aikawa, T.; Watanabe, S.; Saito, S. *Org. Lett.* **2006**, *8*, 3881. (b) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (c) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (d) Harrison, T. J.; Kozak, J. A.; Corbella-Pane, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525. (e) Ohri, R. V.; Radosevich, A. T.; Hrovat, K. J.; Musich, C.; Huang, D.; Holman, T. R.; Toste, F. D. *Org. Lett.* **2005**, *7*, 2501. (f) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (g) Tejedor, D.; Gonzalez-Cruz, D.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; Rodriguez, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 8390. (h) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957. (i) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074.

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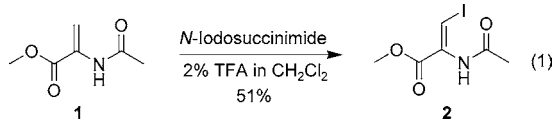
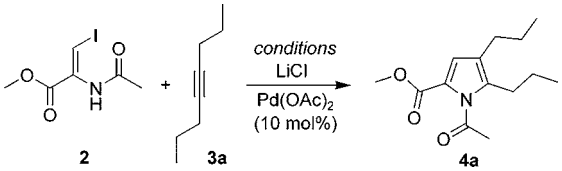
not been reported. Herein we report the first palladium-catalyzed cyclization of alkynes and 2-amino-3-iodoacrylates to form pyrroles.

Commercial acylated dehydroamino ester **1** was converted to the *Z* vinyl iodide **2** in 51% yield utilizing *N*-iodosuccinimide in TFA/DCM based on an adaptation of the method reported by Turner for a branched dehydroamino ester (eq 1).[9] Only the *Z* isomer of product was detected and isolated.



To probe the viability of the reaction, we explored the cyclization of 4-octyne **3a** and iodide **2** to generate pyrrole **4a** utilizing classic Larock conditions as the starting point (Table 1, entry 1). Product was isolated though the yield (7%) was low and multiple byproducts were formed.

Table 1. Optimization of Cyclization Conditions[a]



entry	alkyne equiv	time (h)	temp (°C)	base (5 equiv)	solvent	yield (%) [conv][c]
1	3	2	100	KOAc	DMF	7
2	3	0.5	100	KOAc	DMF	18
3	3	12	25	KOAc	DMF	12 [40]
4	3	2	65	KOAc	DMF	48 [95]
5	3	2	65	Na_2CO_3	DMF	36 [90]
6	**3**	**2**	**65**	**K_2CO_3**	**DMF**	**81**
7	1	2	65	K_2CO_3	DMF	42 [70]
8	2	2	65	K_2CO_3	DMF	70
9	3	2	65	K_2CO_3	THF	[<10]
10	3	2	65	K_2CO_3	DMSO	14 [45]
11	**3**	**1**	**65**	**K_2CO_3**	**DMF**	**80**
12	3	1	65	K_2CO_3 and H_2O	DMF	0 [100]

[a] All reactions were run with iodide **2** as the limiting reagent on a 0.50 mmol scale under N_2 atmosphere. [b] All bases and solvents used were anhydrous unless otherwise specified. [c] The conversion was determined by LCMS monitoring, using UV at 220 nM. All starting material was consumed if the conversion is not shown.

A careful examination of the reaction progress over time revealed that even when the reaction was stopped and cooled after consumption of starting material only an 18% yield of product was isolated (Table 1, entry 2). At room temperature the reaction produced fewer side products though with low conversion (12%); running the reaction to complete consumption of starting material at 65 °C afforded a significantly higher yield of product (48%) (Table 1, entries 3 and 4). The main side product was consistent with deacylated material by LCMS.

An examination of the importance of the base in this reaction (Table 1, entries 4−6) revealed that potassium carbonate was significantly better than sodium carbonate or potassium acetate and eliminated all side products, except deacylated pyrrole, that were formed in the reaction. We speculate that trace amounts of water over time in the solvent combined with the carbonate base facilitated the deacylation. Attempts to further optimize the conditions by changing the alkyne equivalents or altering the solvent (Table 1, entries 7−10) were unsuccessful. We did observe that the reaction time could be shortened from 2 to 1 h without impacting the yield. It is important to note that the DMF must be as anhydrous as possible; addition of several equivalents of water to the reaction is detrimental (Table 1, entry 12).

Though the improved conditions were acceptable for work with new substrates, we were curious as to what if any effect introduction of a phosphine ligand would have on the reaction. Addition of triphenylphosphine (0.20 equiv) or diphenylphosphinopropane (0.10 equiv) to the palladium acetate significantly decreased the yield while replacement of the palladium acetate with palladium dibenzylideneacetone (0.20 equiv) or $Pd(dppf)Cl_2$ (0.10 equiv) eliminated formation of the desired product.

To investigate the scope of the cyclization reaction, a series of symmetrical alkynes was examined (Table 2). The optimized conditions from Table 1 functioned equivalently when the palladium loading was reduced from 10 to 5 mol % (Method A). The yield of the cyclization of alkyne **3a** to pyrrole **4a** was comparable (78% vs 81%) with the lower catalyst loading (Table 2, entry 1). Reaction of 2-butyne **3b** with iodide **2** gave the expected product **4b** (Table 2, entry 3) albeit in lower yield than with 4-octyne. The volatility of the alkyne and the formation of some deacylation byproduct (detected by LCMS) could account for this change.

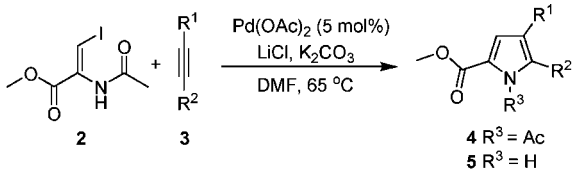
The formation of the minor deacylated side product of the reaction under reaction conditions in these cases was noteworthy. Since the unprotected pyrrole **5a** was the eventual synthetic target, we examined liberation of the *N*-acylpyrrole **4a** under reaction conditions. Addition of 3 drops of water after complete conversion of iodide **2** to acyl product **4a** followed by additional stirring at 65 °C cleanly afforded the pyrrole **5a** in remarkably high 94% yield (Table 2, entry 3). This protocol is Method B.

Surprisingly, when 2-butyne-1,4-diol **3c** was probed as a substrate (Table 2, entry 4), starting material was rapidly consumed and no desired product was formed utilizing either Method A or B.

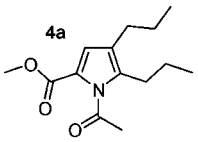
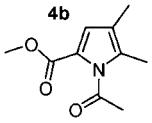
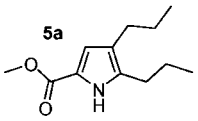
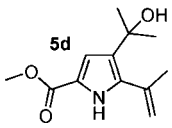
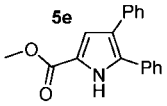
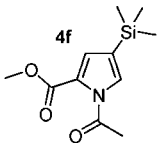
To investigate whether this result was related to the hydroxy groups or was substrate specific, 2,5-dimethyl-3-hexyne-2,5-diol **3d** was subjected to the reaction conditions (Table 2, entry 5). This substrate afforded differentiated 2-vinylpyrrole **5d**, presumably by a selective 1,4-acyl migration/elimination sequence after cyclization was complete. Diphenylacetylene **3e** cyclized to give an adduct that spontaneously deacylated under reaction conditions to afford pyrrole **5e** in 77% yield (Table 2, entry 6). The bis-

(9) Roff, G. J.; Lloyd, R. C.; Turner, N. J. *J. Am. Chem. Soc.* **2004**, *126*, 4098.

Table 2. Pd-Catalyzed Cyclizations with Symmetric Alkynes To Form Substituted Pyrroles



2 **3** **4** R^3 = Ac **5** R^3 = H

entry	M[a]	alkyne	R^1 / R^2	product	yield (%)
1	A	**3a**	*n*-Pr	**4a** 	78
2[b]	A	**3b**	Me	**4b** 	58
3	B	**3a**	*n*-Pr	**5a** 	94
4	A / B	**3c**	CH_2OH	*No product formed*	--
5	A	**3d**	CMe_2OH	**5d** 	62
6	A	**3e**	Ph	**5e** 	77
7	A	**3f**	$SiMe_3$	**4f** 	60

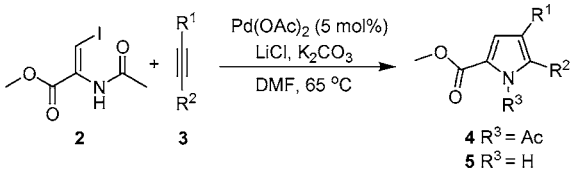
[a] Method A: 0.500 mmol scale, 3 equiv of alkyne, 5 equiv of potassium carbonate, 3 h, rigorously anhydrous. Method B: As per Method A with 5 equiv of water added after consumption of starting material. [b] The reaction was run in a sealed tube to minimize loss of 2-butyne.

(trimethylsilyl)acetylene **3f** afforded monosilyl acyl protected pyrrole **4f** as a single regioisomer of product (Table 2, entry 7).[10]

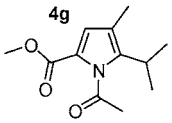
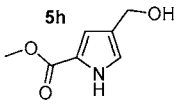
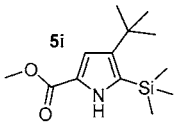
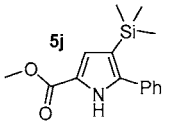
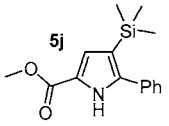
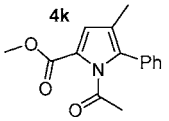
This methodology was then applied to unsymmetric alkynes (Table 3). To prove the regiochemistry of cyclizations to form pyrroles **4g**, **5i**, **5j**, and **4k** (Table 3) the ratio of regioisomers was determined by analytical HPLC and the assignment of regioisomers was determined by NMR experiments (see Figure 1 and the Supporting Information). In the first example a high yield (82%) of a 60:40 mixture of

(10) The two pyrrole proton signals were both singlets, consistent with a 2,4-substitution pattern (see the Supporting Information for spectra).

Table 3. Regioselective Pd-Catalyzed Cyclizations with Unsymmetric Alkynes To Form Substituted Pyrroles



2 **3** **4** R^3 = Ac **5** R^3 = H

entry	M[a]	alkyne	R^1 / R^2	product	yield (%)	ratio[b]
1	A	**3g**	Me / *i*-Pr	**4g** 	82	1.5:1
2	B	**3h**	CH_2OH/ $SiMe_3$	**5h** 	40	>25:1
3	B	**3i**	*t*-Bu / $SiMe_3$	**5i** 	53	9:1
4	A	**3j**	$SiMe_3$ / Ph	**5j** 	64, 15[c]	>25:1
5	B	**3j**	$SiMe_3$ / Ph	**5j** 	81	>25:1
6	A	**3k**	Me / Ph	**4k** 	68	5:1

[a] Method A or B: See Table 2. [b] The ratio of regioisomers was determined by analytical HPLC at 220 nM and ^{1}H NMR. [c] The product isolated in 15% yield was **4j**, the acyl group is still on the pyrrole.

regioisomers of pyrrole **4g** was obtained with no evidence of deacylation product. This low regioselectivity was consistent with the ca. 2:1 ratio that Larock observed for this alkyne with 2-iodoaniline in indole synthesis.[7]

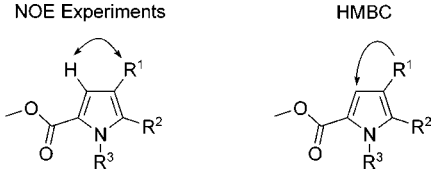


Figure 1. NMR studies on **4g**, **5i**, **5j**, and **4k**.

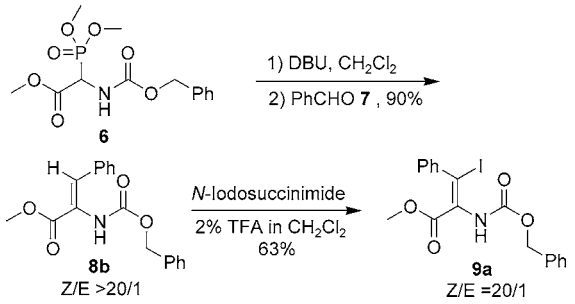
When a significantly differentiated trimethylsilyl-propargyl alcohol **3h** was reacted, a single pyrrole regioisomer formed accompanied by desilylation and deacylation under reaction conditions (Table 3, entry 2);[11] however, the yield of product **5h** was only moderate (40%) in this instance. When 1-trimethylsilyl-3,3-dimethylbutyne **3i** was employed as a substrate, pyrrole **5i** was afforded as a 9:1 mixture of regioisomers. The yield of product **5i** was higher (53%) than in the previous example and curiously, desilylation did not occur under reaction conditions (Table 3, entry 3).

When 1-phenyl-2-trimethylsilylacetylene **3j** was used, a surprising complete reversal of expected regiochemistry occurred. Under these conditions (Method A), a moderate yield (64%) of deacylated pyrrole **5j** and a 15% yield of the acyl protected product **4j**, both as a single regioisomers, were isolated. To achieve complete conversion to a single deacylated product, Method B was employed (Table 3, entry 5). This produced **5j** as a single product in 81% yield. Further investigation of this reversed regiochemical result with similar silyl-aryl substrates is ongoing.

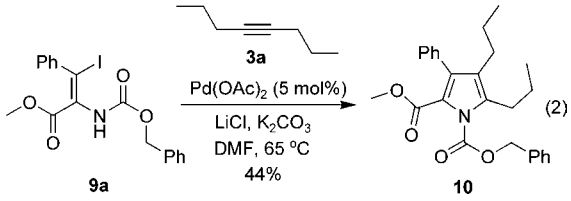
When the difference between two substituents on the alkyne was small, the regioselectivity was moderate; alkyne **3k** afforded pyrrole **4k** in 68% yield as an inseparable 5:1 ratio of regioisomers.

To examine the application of this methodology to elaborate pentasubstituted pyrroles, derivative **9a** was synthesized (Scheme 1). Product **8b** (*E* adduct) was afforded in 94% yield, which was then converted to the *Z*-iodo dehydroalanine **9a** in 63% yield.

Scheme 1. Synthesis of a New Acrylate Derivative



Utilizing the optimized reaction conditions described in Table 2, iodoacrylate **9a** was reacted with 4-octyne **3a** to give pentasubstituted pyrrole **10** in 44% yield (eq 2).[13]



The success of this more substituted example coupled with the previous regioselective results with unsymmetrical alkynes demonstrated the utility of this methodology to synthesize our targeted array of pyrrole compounds. The results of the medicinal chemistry applications will be disclosed in due course.

In conclusion, a novel palladium-catalyzed cyclization of alkynes and 2-amino-3-iodoacrylates has been developed. The reaction is regioselective and efficient, and can be controlled to afford acyl protected or free pyrrole products. This constitutes a new and convenient method to access highly substituted pyrroles.

Acknowledgment. The authors thank the chemical technologies group at Wyeth for analysis of compounds. The corresponding author also thanks Williams College professor J. Hodge Markgraf for inspiring interest in the development of new approaches in heterocyclic synthesis.

Supporting Information Available: Detailed experimentals and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The structure of **5h** was confirmed by synthesis and subsequent reduction of the known methyl 4-formyl-2-pyrrole carboxylate (see the Supporting Information for spectra).

(12) The structure assignment was based on a comparison of proton NMRs to reported data: Sai, H.; Ogiku, T.; Ohmizu, H. *Synthesis* **2003**, *2*, 201.

(13) The main byproduct was protodehalogenated material.