



**HAL**  
open science

## Domino allylic amination/Sonogashira/heterocyclisation reactions: palladium-catalysed three-component synthesis of pyrroles

Sandrine Lamandé-Langle, Mohamed Abarbri, Jérôme Thibonnet, Alain Duchêne, Jean-Luc Parrain

► **To cite this version:**

Sandrine Lamandé-Langle, Mohamed Abarbri, Jérôme Thibonnet, Alain Duchêne, Jean-Luc Parrain. Domino allylic amination/Sonogashira/heterocyclisation reactions: palladium-catalysed three-component synthesis of pyrroles. *Chemical Communications*, 2010, 46, pp.5157-5159. 10.1039/c0cc00500b . hal-00679647

**HAL Id: hal-00679647**

**<https://hal.science/hal-00679647>**

Submitted on 16 Mar 2012

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Domino allylic amination/Sonogashira/heterocyclisation reactions: palladium-catalysed three-component synthesis of pyrroles†

Sandrine Lamandé-Langle,<sup>a</sup> Mohamed Abarbri,<sup>b</sup> Jérôme Thibonnet,<sup>b</sup> Alain Duchêne\*<sup>b</sup> and Jean-Luc Parrain\*<sup>c</sup>

Received 20th March 2010, Accepted 13th May 2010

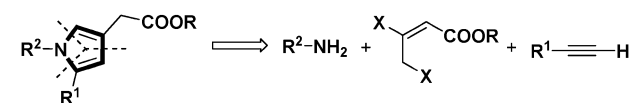
First published as an Advance Article on the web 7th June 2010

DOI: 10.1039/c0cc00500b

**Three-component reactions with 3,4-diiodoalk-2-enoic derivatives, primary amines, and terminal alkynes proceeded to give trisubstituted pyrroles in fair to good yields in the presence of palladium and copper catalysts under mild reaction conditions.**

Pyrroles are key structural motifs in various classes of natural products,<sup>1</sup> synthetic pharmaceuticals and electrically conducting polymers<sup>2</sup> and are also valuable synthetic intermediates.<sup>3</sup> In addition to a number of traditionally employed approaches, several transition-metal-catalyzed methods have recently emerged for the synthesis of pyrroles.<sup>4</sup> However, the construction of multiply substituted pyrrole rings still relies largely on the classical condensation methods such as Paal–Knorr synthesis,<sup>5</sup> although catalytic multicomponent coupling approaches have attracted recent attention as environmentally benign alternatives.<sup>6</sup> Nevertheless, and despite recent advances in domino reactions,<sup>7</sup> very flexible and general approaches with wide functional group tolerance are still lacking.

As a continuation of our interest in the design of new reactions for the synthesis of lactones and lactams through tandem C–C bond formation/heterocyclisation,<sup>8</sup> we hypothesised that dihaloalkenoic derivatives might react with different nucleophiles such as amines and alkynes in a sequential way. The palladium species acts either as a Sonogashira catalyst<sup>9</sup> or as a Lewis acid promoter for the 5-*endo* dig heterocyclisation reaction (Scheme 1). To the best of our knowledge little attention has been paid to the dual reactivity of vinylic and allylic dihaloalkenes<sup>10,11</sup> and no use has been made of this class of reagent in multicomponent reactions. We report here a novel palladium-catalyzed domino reaction for the synthesis of pyrroles. This approach involves



**Scheme 1** Retrosynthetic analysis of trisubstituted pyrroles.

<sup>a</sup> Groupe S.U.C.R.E.S – UMR 7565 Nancy Université – CNRS, BP 70239, F-54506, Nancy Vandoeuvre, France

<sup>b</sup> Laboratoire de Physicochimie des Matériaux et des Biomolécules, Faculté des Sciences de Tours, EA 4244, Parc de Grandmont, 37200 Tours, France. E-mail: alain.duchêne@univ-tours.fr

<sup>c</sup> Institut des Sciences Moléculaire de Marseille (ISM2), Equipe STeReO UMR CNRS-6263 Aix-Marseille Université, Campus Scientifique de St Jérôme, 13397 Marseille cedex 20, France. E-mail: j.l.parrain@univ-cezanne.fr

† Electronic supplementary information (ESI) available: Experimental details; <sup>1</sup>H and <sup>13</sup>C NMR. See DOI: 10.1039/c0cc00500b

allylic amination and Sonogashira cross-coupling, followed by a heterocyclisation/aromatisation sequence using readily available primary amines, alkynes and dihaloalkenoic derivatives and, importantly, allows for the double function of amine (Scheme 1).

To investigate the synthesis of pyrrole by this tandem sequence, as depicted in Scheme 1, diiodo butenoic acid **2** bearing two different carbon–iodine bonds as dielectrophile was prepared from buta-2,3-dienoic acid **1** by addition of iodine in ether. The two regioisomers obtained were easily separated by crystallisation, affording 55% yield of pure 3,4-diiodobut-2-enoic acid (*E*)-**2**. The related nitrile and ester dibromides have already been reported, but relatively little use has been made of this class of reagents.<sup>12</sup>

Our initial investigations using (*E*)-**2**, phenylacetylene and *n*-butylamine and palladium complex at 60 °C gave a complex mixture in which a small amount of pyrrole **5** and lactones **3** and **4** were isolated. The effects of different parameters on the model reaction were therefore studied in order to try to separate this process to elementary steps involved (Table 1).

At this time, it was important to find conditions that first allowed the allylic amination reaction that could be in competition with the lactonisation reaction. To probe the

**Table 1** Screening of reaction conditions for the three-component allylic amination/cross-coupling/cyclisation reaction

Entry	[Pd]		Add.	T/°C	t/h	Bu-NH <sub>2</sub>			
	5 mol %	10 mol %				[eq.]	<b>3</b> [%]	<b>4</b> [%]	<b>5</b> [%]
1 <sup>a</sup>	none	—	—	50	5	1	66	—	—
2 <sup>b</sup>	none	—	—	50	5	2	38	—	—
3 <sup>a</sup>	none	—	—	25	24	0	<5	—	—
4 <sup>a</sup>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	—	—	60	24	0	69	—	—
5	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	CuI	—	25	24	0	<5	—	—
6	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	CuI	—	60	24	2	30	31	—
7	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	CuI	—	25	24	2	—	4	35
8	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	CuI	—	25	24	5	—	12	59
9	Pd(PPh <sub>3</sub> ) <sub>4</sub>	CuI	—	25	24	5	—	9	45
10 <sup>c</sup>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	CuI	—	25	24	5	—	5	20

<sup>a</sup> Reaction was conducted without phenylacetylene. <sup>b</sup> Numerous insoluble by-products were formed. <sup>c</sup> One equivalent of phenylacetylene was used.

viability of the anticipated domino reaction, numerous conditions were screened in DMF, a commonly used solvent in the Sonogashira reaction. Optimisation studies revealed that the lactonisation reaction occurred rapidly in the presence of a primary amine at temperatures up to 55 °C, even in the presence of one equivalent of amine [Table 1, entries 1 and 2]. Interestingly, the lactonisation process could be suppressed at room temperature. Similarly, adding a palladium  $\pi$  complex, and without amine or alkyne, the lactonisation reaction occurred at temperatures up to 50 °C [Table 1, entries 4 and 5]. In the presence of an alkyne (phenylacetylene) and at 60 °C, fair yields of the Sonogashira product **4** were obtained along with iodolactone **3**. Surprisingly, in the presence of 2 equivalents of amine at room temperature, we obtained fair yields of pyrrole **5** and compound **4** was detected in small amounts [Table 1, entry 7]. Increasing the number of amine equivalents (5 equivalents) dramatically increased the yield from 35% to 59% [Table 1, entries 7 and 8].

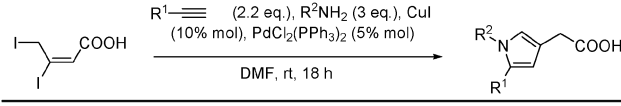
Changing the catalyst from  $\text{PdCl}_2(\text{PPh}_3)_2$  to  $\text{P}(\text{PPh}_3)_4$  had little effect. Bis amination products, vinylaziridines,<sup>13</sup> enediynes and 3-aminomethylenynoic acid<sup>14</sup> were not detected in these reactions. The scope and limitations of this palladium-catalysed, three-component coupling process were next examined using various alkynes and primary amines. The results are summarised in Table 2. All the alkyne precursors gave good yields of the corresponding coupling products. The transformation described here allowed the synthesis of di- and trisubstituted pyrroles. A number of functional groups on alkyne were tolerated, including esters, ethers, acetals and sulfide groups [Table 2].





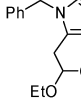

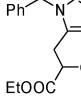








Nevertheless, the use of ethyl propiolate as alkyne failed to provide the expected pyrrole. The scope of the process was found to be less broad with respect to the *N* fragment only and allowed good yields of pyrroles for a variety of  $\alpha$ -unsubstituted alkylamines. For example,  $\alpha$ -methylbenzylamine did not provide the expected heterocycle when coupled with phenylacetylene. Aryl, alkyl, allyl and benzyl amines all performed well, although the basicity on the nitrogen atom was found to be essential. Attempts with tosylamine or benzylcarbamate use in place of a primary amine failed. The silyl and germyl ethynes were found to be good substitutes for acetylene and fair yields of 1,3-disubstituted pyrroles were obtained. These results could be explained by the acidic work-up which cleaved the carbon–metal bond. In order to examine the influence of the carboxylic function, we prepared the corresponding ethyl and *t*-butyl ester from (*E*)-**2** which gave similar results in terms of yield in the same experimental conditions; for example, *t*-butyl ester of (*E*)-**2**, benzylamine (3 equivalents) and phenylacetylene (2 equivalents) afforded a slightly increased yield of ethyl ester (69%). As another interesting point related to using ester, the formation of 3-alkynyl lactones **4** did not occur.

The use of ester in place of acid in the diiodo starting material is particularly appealing for acid-sensitive structures as noted in the reaction of an enyne derived from  $\alpha$ -ionone (**6**). Using the three components sequence, good yields of the sensitive pyrrole retinoid structure **7** could be obtained, giving the protocol a general character (Scheme 2).<sup>15</sup>

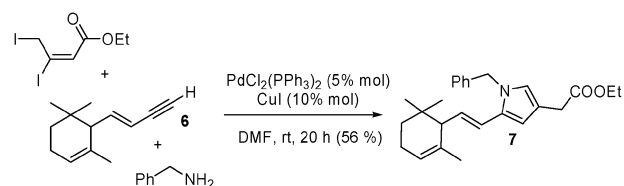
A plausible mechanism accounting for the domino process depicted in Scheme 3 may be: initial C–N allylic amination

**Table 2** Three-component synthesis of pyrroles



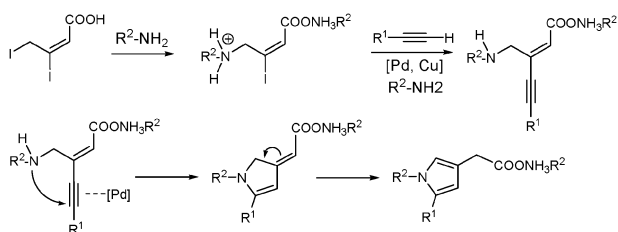
Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield [%]	No.
1	Ph	<i>n</i> -Bu		59	<b>5a</b>
2	Ph	Bn		54	<b>5b</b>
3 <sup>a</sup>				61	
4	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	Bn		53	<b>5c</b>
5	–CH <sub>2</sub> OMe	Bn		44	<b>5d</b>
6	–CH <sub>2</sub> –CH(OEt) <sub>2</sub>	Bn		43	<b>5e</b>
7		Bn		48	<b>5f</b>
8	–CH <sub>2</sub> –S–Bn	Bn		45	<b>5g</b>
9	SiMe <sub>3</sub>	Bn		30	<b>5h</b>
10	GeEt <sub>3</sub>	Bn		28	
11	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	<i>n</i> -Bu		53	<b>5i</b>
12	Ph	allyl		41	<b>5j</b>
13	SiMe <sub>3</sub>	allyl		10	<b>5k</b>
14	Ph	Ph		44	<b>5l</b>
15	COOEt	Bn		0	—

<sup>a</sup> Attempt starting from tributyltin carboxylate of (*E*)-**2**



**Scheme 2** Three-component synthesis of a pyrrole retinoid.

leading to the ammonium salt, followed by a Sonogashira cross coupling reaction<sup>16</sup> and subsequent intramolecular hydroamidation, providing dihydroexoalkylidene pyrrole



Scheme 3 Proposed mechanism.

which rearranges into pyrrole. The hydroamination step through a 5-endo-dig process is certainly catalyzed by palladium  $\pi$  species, as reported by different groups. Nevertheless, it is difficult in this case to exclude the possibility of a thermodynamically enhanced intramolecular 1,6 Michael addition reaction.<sup>17</sup>

In conclusion, we have developed a novel one-pot allylic amination/palladium-catalysed Sonogashira cross coupling and heterocyclisation process that allows the direct synthesis of 1,2,4-trisubstituted and 1,3-disubstituted pyrroles starting from readily available diiodobutenoic acid. The temperature and the nature of the solvent (DMF) for this domino sequence are crucial parameters. In addition, the use of a one-pot procedure leads to higher yields while generating fewer by-products and chemical residues. This multicomponent process was also used to synthesize a retinoid derivative through this procedure using an enyne.

## Notes and references

- J. T. Gupton, Pyrrole natural products with antitumor properties, *Top. Heterocycl. Chem.*, 2006, **2**, 53–92; H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264–287.
- Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. Scriven, Pergamon Press, Oxford, 1996, vol. 2, p. 207; A. Fürstner, *Synlett*, 1999, 1523; S. Higgins, *Chem. Soc. Rev.*, 1997, **26**, 247; R. D. McCullough and P. C. Ewbank, in *Handbook of Conducting Polymers*, ed. T. A. Skotheim, R. L. Elsenbaumer, and J. R. Reynolds, M. Dekker, New York, 2nd edn, 1998, ch. 9.
- H. M. L. Davies and S. J. Hedley, *Chem. Soc. Rev.*, 2007, **36**, 1109–1119; E. M. Beck, N. P. Grimster, R. Hatley and M. J. Gaunt, *J. Am. Chem. Soc.*, 2006, **128**, 2528–2529.
- K. K. A. D. S. Kathiraratchi, A. I. Siriwardana, I. Nakamura and Y. Yamamoto, *Tetrahedron Lett.*, 2007, **48**, 2267–2270; H. Hamaguchi, S. Kosaka, H. Ohno, N. Fujii and T. Tanaka, *Chem.–Eur. J.*, 2007, **13**, 1692–1708; M. L. Crawley, I. Goljer, D. J. Jenkins, J. F. Mehlmann, L. Nogle, R. Dooley and P. E. Mahaney, *Org. Lett.*, 2006, **8**, 5837–5840; P. E. R. Dhawan and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2004, **126**, 468–469; R. K. Dieter and H. Yu, *Org. Lett.*, 2001, **3**, 3855–3858; A. Arcadi, S. Di Giuseppe, F. Marinelli and E. Rossi, *Adv. Synth. Catal.*, 2001, **343**, 443–446.
- For recent applications of the Paal–Knorr synthesis: Y. Dong, N. Naranjan, S. L. Ablaza, S.-X. Yu, S. Bolvig, D. A. Forsyth and P. W. Le Quesne, *J. Org. Chem.*, 1999, **64**, 2657; C. Haubmann, H. Huebner and P. Gmeiner, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3143–3146; J. Robertson, R. J. D. Hatley and D. J. Watkin, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3389; N. R. Wurtz, J. M. Turner, E. E. Baird and P. B. Dervan, *Org. Lett.*, 2001, **3**, 1201–1203; R. Ballini, G. Bosica, G. Fiorini and G. Giarlo, *Synthesis*, 2001, 2003–2006; R. U. Braun, K. Zeitler and T. J. J. Müller, *Org. Lett.*, 2001, **3**, 3297–3300; J. Arrowsmith, S. A. Jennings, A. S. Clark and M. F. G. Stevens, *J. Med. Chem.*, 2002, **45**, 5458–5470.
- G. Balme, *Angew. Chem., Int. Ed.*, 2004, **43**, 6238–6241; G. Balme, D. Bouyssi and N. Monteiro, *Heterocycles*, 2007, **73**, 87–124; N. T. Patil and Y. Yamamoto, *Archivoc*, 2007, **10**, 121–141.
- D. Tejedor, D. Gonzalez-Cruz, F. Garcia-Tellado, J. J. Marrero-Tellado and M. L. Rodriguez, *J. Am. Chem. Soc.*, 2004, **126**, 8390–8391; B. Alcaide, P. Almendros and M. C. Redondo, *Chem. Commun.*, 2006, 2616–2618; F. Lieby-Muller, T. Constantieux and J. Rodriguez, *J. Am. Chem. Soc.*, 2005, **127**, 17176–17177.
- S. Rousset, M. Abarbri, J. Thibonnet, A. Duchêne and J.-L. Parrain, *Org. Lett.*, 1999, **1**, 701–703; K. Cherry, A. Duchêne, J. Thibonnet, J.-L. Parrain and M. Abarbri, *Synthesis*, 2005, 2349–2356; S. Inack-Ngi, R. Rahmani, L. Commeiras, G. Chourraqui, J. Thibonnet, A. Duchêne, M. Abarbri and J.-L. Parrain, *Adv. Synth. Catal.*, 2009, **351**, 779–788; S. Rousset, M. Abarbri, J. Thibonnet, A. Duchêne and J.-L. Parrain, *Chem. Commun.*, 2000, 1987–1988.
- K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467–4470; K. Sonogashira, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. A. Fleming, Pergamon, Oxford, 1991, vol. 3, pp. 521–549; R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874–922.
- I. Moubarak and R. Vessiere, *Synthesis*, 1980, 52–54.
- A. Padwa and M. Ishida, *Tetrahedron Lett.*, 1991, **32**, 5673–5676; A. Padwa, D. J. Austin, M. Ishida, C. L. Muller, S. S. Murphree and P. E. Yeske, *J. Org. Chem.*, 1992, **57**, 1161–1169.
- P. Kurtz, H. Gold and H. Disselnkotter, *Justus Liebigs Ann. Chem.*, 1959, **624**, 1–25; J. Tendil, J. Vemey and R. Vessiere, *Bull. Soc. Chim. Fr.*, 1972, 4027–4031.
- X. Pan, Q. Cai and D. Ma, *Org. Lett.*, 2004, **6**, 1809–1812.
- For intermolecular palladium-catalyzed cross-coupling of amines with alkenyl bromides, see: J. Barluenga, M. A. Fernandez, F. Aznar and C. Valdes, *Chem. Commun.*, 2002, 2362–2363; J. Barluenga, M. A. Fernandez, F. Aznar and C. Valdes, *Chem.–Eur. J.*, 2004, **10**, 494–507.
- A. F. Barrero, J. F. Sanchez, J. E. Oltra, D. Teva, R. R. Ferrol, J. Elmerabet, R. G. Del Moral, M. A. Lucena and F. O'Valle, *Eur. J. Med. Chem.*, 1994, **29**, 773–780.
- Similar enynes were recently described: D. Steinhuebel, J. M. Baxter, M. Palucki and I. W. Davies, *J. Org. Chem.*, 2005, **70**, 10124–10127.
- For metal catalyzed 5-endo-dig cycloisomerization of 1,5-alkynylamines, see: A. L. Rodriguez, C. Koradin, W. Dohle and P. Knochel, *Angew. Chem., Int. Ed.*, 2000, **39**, 2488–2490; Y. Yin, W. Ma, Z. Chai and G. Zhao, *J. Org. Chem.*, 2007, **72**, 5731–5736; B. C. J. van Esseveldt, F. L. van Delft, J. M. M. Smits, R. de Gelder, H. E. Schoemaker and F. P. J. T. Rutjes, *Adv. Synth. Catal.*, 2004, **346**, 823–834; G. A. Molander and H. Hasegawa, *Heterocycles*, 2004, **64**, 467–474; B. C. J. van Esseveldt, F. L. van Delft, R. de Gelder and F. P. J. T. Rutjes, *Org. Lett.*, 2003, **5**, 1717–1720; L. B. Wolf, K. C. M. F. Tjen, H. T. Brink, R. H. Blaauw, H. Hiemstra, H. E. Schoemaker and F. P. J. T. Rutjes, *Adv. Synth. Catal.*, 2002, **344**, 70–83; D. W. Knight and C. M. Sharland, *Synlett*, 2004, 119–121.