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New MCR−Heck−Isomerization Cascade toward Indoles

Laurent El Kaim,* Marion Gizzi, and Laurence Grimaud*

Laboratoire Chimie et Procédés, Ecole Nationale Supérieure de Techniques Avancées, 32 Bd Victor, 75739 Paris Cedex 15, France

laurent.elkaim@ensta.fr; laurence.grimaud@ensta.fr

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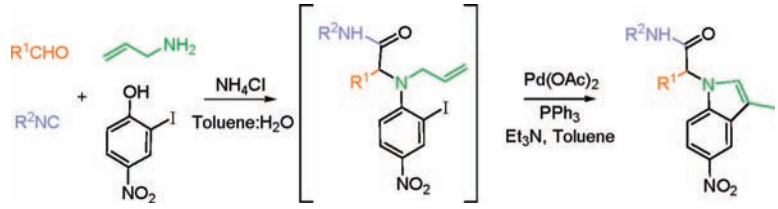
ABSTRACT

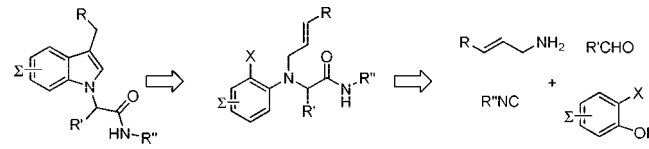


The use of *ortho*-iodonitrophenol in Ugi-Smiles reaction coupled with Heck cyclization gives new access to indole scaffolds. The sequence can be performed in a one-pot reaction if the residual isocyanide is neutralized prior to the addition of the palladium catalyst.

Research on indoles has been and still represents one of the most active fields in heterocyclic chemistry.[1] The constant search for new synthetic routes to this bicyclic core stems from the impressive diversity of the biological activities[2] displayed by indole alkaloids. Among all the synthetic approaches reported in the last decades, palladium catalysis has emerged as a powerful tool for the construction of these scaffolds.[3] More recently, diverse strategies have been adapted to new multicomponent formation of indoles which can be used for high-throughput screenings.[4]

We recently disclosed a new four-component conversion of phenols into highly functionalized aniline derivatives. Inspired by this straightforward formation of *N*-allylanilines, we envisaged a modular route to the indole core based on a Ugi-Smiles−Heck coupling cascade sequence (Scheme 1).

Scheme 1. General Strategy for the Synthesis of Indoles



Furthermore, the easy functionalization of the starting phenols (halogenation, Mannich, Claisen,...) could lead to indoles with high molecular diversity.

Since we had already reported the successful coupling of the commercially available 2-chloro-4-nitrophenol in the Ugi-Smiles reaction, this strategy was initially tested on chlorinated compounds.[5] Various catalyst systems were investi-

(1) Gribble, G. W. *J. Chem. Soc., Perkin Trans 1* **2000**, 1045. Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.

(2) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761. Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278.

(3) For recent reviews, see: Patil, S.; Buolamwini, J. K. *Curr. Org. Synth.* **2006**, *3*, 477–498. Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. For selected recent examples, see: Jia, Y.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826–7834. Zhao, J.; Larock, R. *J. Org. Chem.* **2006**, *71*, 5340–5348.

(4) For a recent review, see: Campo, J.; Garcia-Valverde, M.; Marcaccini, S.; Rojo, M. J.; Torroba, T. *Org. Biomol. Chem.* **2006**, *4*, 757–765. For recent examples, see: Kalinski, C.; Umkehrer, M.; Schmidt, J.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W.; Hoffmann, S. D. *Tetrahedron Lett.* **2006**, *47*, 4683–4686. Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4223–4226. Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295–2298. Barluenga, J.; Jimenez-Aquino, A.; Valdes, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1529–1532. Leogane, O.; Lebel, H. *Angew. Chem., Int. Ed.* **2008** *47*, 350−352, and references cited therein.

(5) For an example of Heck coupling using chlorinated compounds, see: Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11.

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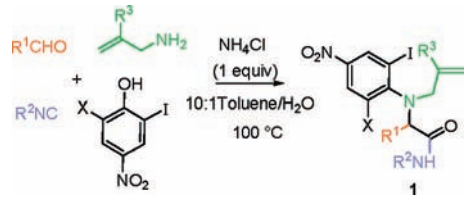
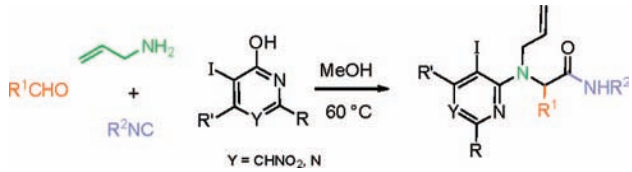
Table 1. Ugi-Smiles Coupling with 2-Iodophenols



entry	R^1	R^2	R^3	X	product (yield %)
1	*i*-Bu	Bn	H	H	**1a** (95)
2	Et	Bn	H	H	**1b** (65)
3	*i*-Bu	Cy	H	H	**1c** (32)
4	*i*-Bu	*p*-ClBn	H	Cl	**1d** (73)
5	*i*-Bu	*p*-ClBn	Me	H	**1e** (49)

Table 2. Ugi-Smiles Coupling with Iodinated Heterocyclic Phenols



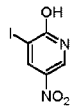
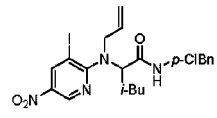
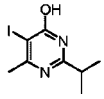
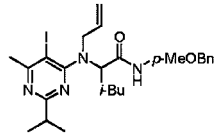
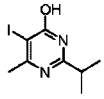
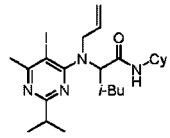
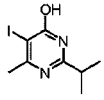
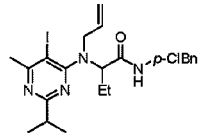
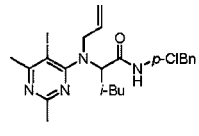
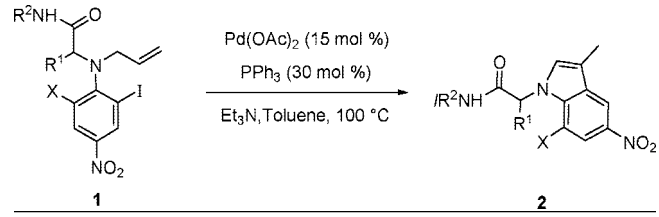
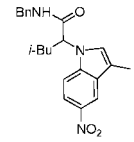
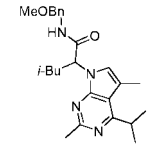
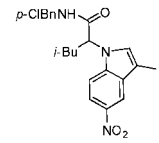
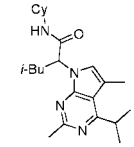
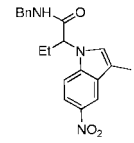
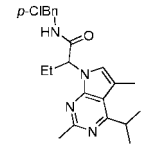
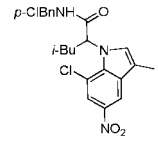
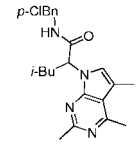
entry	phenol	product (yield %)
1		 **1f** (54)
2		 **1g** (70)
3		 **1h** (47)
4		 **1i** (63)
5		 **1j** (85)

Table 3. Tandem Heck Coupling−Isomerization[a]



entry	indole	entry	indole
1	 **2a** (70%)	5	 **2g** (80%)
2	 **2a'** (70%)	6	 **2h** (69%)
3	 **2b** (64%)	7	 **2i** (89%)
4	 **2d** (74%)	8	 **2j** (83%)

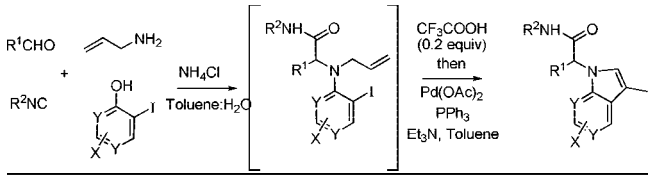
[a] Yields given from Ugi-Smiles adducts.

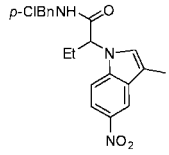
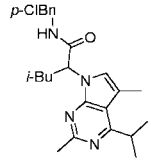
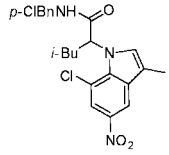
gated: different sources of Pd, namely $Pd_2(dba)_3$ and $Pd(OAc)_2$, and several phosphines (tri-*tert*-butylphosphine, dppf, tricyclohexylphosphine, and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) were used with Cs_2CO_3 in THF or in 1,4-dioxane; however, none of these conditions gave the desired cyclized product (Scheme 2).

These results prompted us to reinvestigate this strategy with iodinated phenols. The multicomponent coupling turned out to be quite inefficient under classical conditions (MeOH or toluene at 60 °C). Use of a 10:1 mixture of toluene/water as solvent (containing 1 equiv of NH_4Cl) improved the yields of the four-component coupling (4-CC) reactions significantly.[6] Under these optimized conditions, the scope of the Ugi-Smiles couplings of iodinated phenols was found to be fairly wide, as shown in Table 1. Various isocyanides and

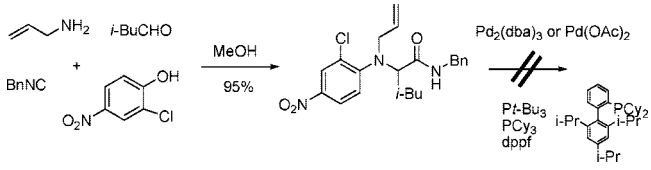
(6) Oble, J.; El Kaïm, L.; Gizzi, M.; Grimaud, L. *Heterocycles* **2007**, *73*, 503–517.

Table 4. One-Pot Procedure



entry	indole	entry	indole
1	 **2b'** (51%)	3	 **2k** (75%)
2	 **2d** (74%)		

Scheme 2. Attempted Indole Synthesis from Chlorophenols



carbonyl derivatives were coupled with allylamine and iodophenols in moderate to excellent yields.

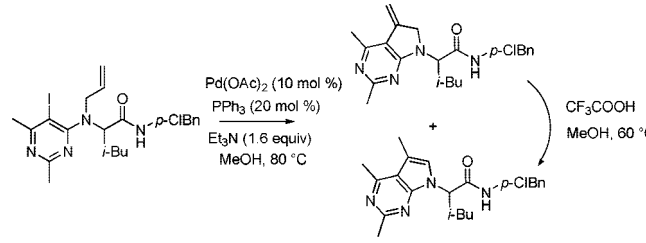
To extend the scope of this reaction, we prepared various 4-CC adducts from iodinated heterocyclic phenol derivatives such as hydroxy pyridines and pyrimidines. The latter were subjected to the Ugi-Smiles coupling under standard conditions (toluene at 80 °C or methanol at 60 °C) to afford the desired products in good yields after a few hours for the pyridines and after 3 days for the pyrimidines (Table 2).

The indole formation was first tested on purified allyl arylamine **1d** under two sets of conditions: with 5 mol % of $Pd(OAc)_2$ and triethylamine in DMF or with 15 mol % of $Pd(OAc)_2$ and triethylamine and triphenylphosphine in toluene. Under both conditions, the tandem Heck coupling−isomerization of the resulting double bond led to the desired indole **2d** in 74% yield (Table 3).

This Heck cyclization−isomerization cascade was then explored using toluene as solvent for further extension to one-pot processes. The reaction gave the expected indoles after one day in satisfying yields (Table 3).

Under the previous conditions, the pyrimidine derivatives cyclized sluggishly, and methanol was finally selected for this transformation (Table 4). In this case, mixtures (from 1:1 to 3:1) of the desired indolopyrimidines and the corresponding *exo*-methylene products were obtained. The latter were stirred overnight in methanol at 60 °C with one equivalent of trifluoroacetic acid to complete the isomerization process, and the indolopyrimidines were obtained as the sole products (Scheme 3).

Scheme 3. Heck Cyclization with Iodopyrimidines



These results called for the extension of this strategy to a one-pot Ugi-Smiles−Heck coupling−isomerization procedure. First trials of such a cascade were disappointing since a significant amount (0.6−0.8 equiv) of Pd(0) was required to drive the reaction to completion. We surmised that an interaction of the residual isocyanide with palladium could alter the catalytic cycle. After completion of the Ugi-Smiles coupling, addition of 0.2−0.3 equiv of trifluoroacetic acid at room temperature allows the hydrolysis of the remaining isocyanide. The following Heck coupling was carried out on the crude mixture using the same amount of palladium as in the two-pot procedure. The desired indoles were obtained in good yields using this new one-pot, three-step procedure (Table 4).

In summary, we have developed a new strategy for the construction of the indole framework. This Ugi-Smiles/Heck coupling/isomerization cascade can be done in a one-pot procedure by destroying the residual isocyanide before the Pd coupling. We are now exploring the formation of polycyclic alkaloids to exploit the diversity offered by such a process.

Acknowledgment. M.G. thanks the Délégation Générale pour l'Armement for a fellowship. Financial support was provided by the ENSTA.

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

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