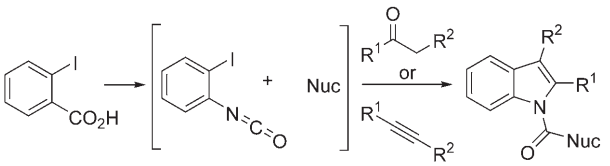
Multicomponent Reactions

DOI: 10.1002/ange.200703671

One-Pot Multicomponent Synthesis of Indoles from 2-Iodobenzoic Acid**

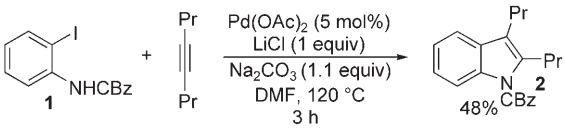
*Olivier Leogane and Hélène Lebel**

Considerable attention has been devoted to the synthesis of indole scaffolds because of their prominence as a motif in a wide variety of bioactive natural products and pharmaceutical compounds.[1] The seminal work of Fischer and Jourdan[2] has been followed by numerous other approaches to prepare this useful framework.[3] Recently, the palladium-catalyzed annulation of 2-iodoanilines or anilides with internal alkynes or carbonyl compounds has emerged as one of the most powerful synthetic methods to access the indole skeleton.[4] However, drawbacks such as the high cost and the low stability of 2-iodoanilines are still associated with this process.[5] To overcome this problem, a one-pot strategy could be envisioned.[6] Not only would such a process eliminate the need for isolation of the potentially unstable 2-iodoanilines, but also it would decrease the amount of chemical waste generated.[7] Furthermore, it has been shown that the overall yields for one-pot procedures are higher than those of step-by-step processes.[8] Synergistic effects between reactions are also likely, and it is possible that a by-product from a reaction could become a reagent in a subsequent reaction. Herein we report a novel multicomponent process that allows the transformation of readily available 2-iodobenzoic acid into indole derivatives by a one-pot Curtius rearrangement/palladium-catalyzed indolization process (Scheme 1). In this strategy the 2-iodoaniline intermediate is not isolated, and moreover one of the by-products of the Curtius rearrangement becomes an essential reagent for the next step of the transformation.



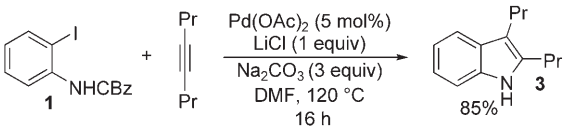
Scheme 1. One-pot multicomponent synthesis of indoles from 2-iodobenzoic acid. Nuc = nucleophile.

There are few reported examples of an intermolecular palladium-catalyzed indolization with alkynes in which a carbamate substrate is used.[9] Initially the annulation reaction of benzyl 2-iodophenylcarbamate (**1**) and 4-octyne was investigated. By using the optimized reaction conditions of palladium acetate, one equivalent of lithium chloride, and sodium carbonate, the carbobenzoxy (CBz) protected indole **2** was isolated in 48% yield after three hours [Eq. (1)].[10] This



(1)

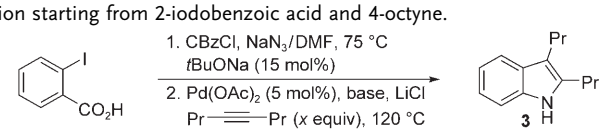
moderate yield was a consequence of cleavage of the CBz-protecting group and indeed, a longer reaction time of 16 hours and an excess of base led to the exclusive formation of the unprotected indole **3** in an excellent yield [Eq. (2)].[11] No indolization reaction occurred in the absence of lithium chloride, however an excess of the salt led to low yields.[10]



(2)

We then investigated the formation of indole **3** using a one-pot Curtius-indolization process starting from 2-iodobenzoic acid (Table 1). This substrate was treated under the standard Curtius reaction conditions recently reported by our research group which allows the direct conversion of aromatic carboxylic acids into carbamates and ureas.[12] The CBz-protected aniline intermediate **1** was not isolated, but directly subjected to the palladium-catalyzed indolization reaction

Table 1: One-pot Curtius rearrangement/palladium-catalyzed indolization starting from 2-iodobenzoic acid and 4-octyne.



Entry	LiCl	Base [equiv]	Alkyne [equiv]	Yield [%]
1	yes	K_2CO_3 (5.0)	5.0	29
2	no	Na_2CO_3 (1.5)	1.5	71
3	no	K_2CO_3 (1.5)	1.5	73
4	no	Cs_2CO_3 (1.5)	1.5	40
5	**no**	**Na_2CO_3 (3.0)**	**3.0**	**84**
6	no	K_2CO_3 (3.0)	3.0	73

[*] O. Leogane, Prof. H. Lebel
Département de Chimie
Université de Montréal
PO Box 6128, Station Downtown, Montréal
Québec, H3C 3J7 (Canada)
Fax: (+1) 514-343-2177
E-mail: helene.lebel@umontreal.ca

[**] This research was supported by the NSERC (Canada), AstraZeneca Canada Inc., Boehringer Ingelheim (Canada) Ltd, Merck Frosst Canada Ltd, the CFI (Canada), the Canada Research Chair Program, and the Université de Montréal. O.L. thanks the Conseil général de la Guadeloupe for a graduate scholarship. We thank Prof. Dean Toste for helpful discussions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

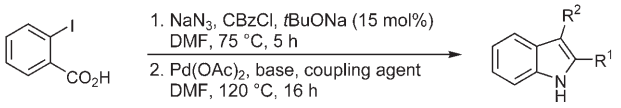
conditions. A disappointing 29% yield of the desired indole **3** was observed when the standard reaction conditions for indolization (including one equivalent of lithium chloride) were used (Table 1, entry 1). It has been shown previously that an excess of a chloride salt is detrimental for palladium-catalyzed heteroannulations.[4f] An equivalent of sodium chloride is generated in situ as a by-product after the Curtius rearrangement, thus remained in the reaction mixture and led to a low yield.

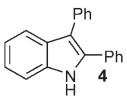
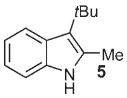
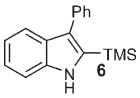
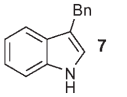
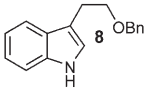
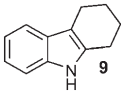
Significantly lower yields (67%) were observed for the indolization reaction in the presence of one equivalent of lithium chloride or one equivalent of sodium chloride, which are considerably less soluble than the in situ generated species.[10] Conversely, when no lithium chloride was added, the reaction with 1.5 equivalents of both potassium carbonate and alkyne resulted in the yield of **3** improving to 73% (Table 1, entry 3). A real synergy was observed between the two reactions (namely the Curtius rearrangement and the indolization processes), as one by-product of the first step became a reagent in the second step. To our knowledge this is one of the few examples of such a synergistic effect in a one-pot strategy. After optimization, three equivalents of sodium carbonate proved to be the best base and gave **3** in 84% yield (compare Table 1, entry 5 to entries 2–4 and 6). This yield is comparable to that obtained for the individual indolization step [see Eq. (2)], which clearly illustrates that one-pot processes lead to higher yields than step-by-step procedures.

The above one-pot process is also compatible with aryl-substituted alkynes (Table 2, entry 1) and affords the corresponding indoles in good yield. Unsymmetrical alkynes gave the corresponding indole **5** and **6** with complete regiocontrol in 56% and 82% yields, respectively (Table 2, entries 2 and 3). Aldehydes and ketones could also be used as coupling partners by using 1,4-diazabicyclo[2.2.2]octane (DABCO) instead of the carbonate base.[4l] Under these modified reaction conditions, 2-iodobenzoic acid was converted into 3-benzylindole (**7**) in 50% yield using hydrocinnamaldehyde (Table 2, entry 4). A benzyl ether was also tolerated, producing indole **8** in 53% yield (Table 2, entry 6), and when cyclohexanone was employed, the tetrahydrocarbazole **9** was recovered in 56% yield.[13]

The preparation of indole *N*-carboxamide derivatives,[1,14] which are important pharmacophores, typically proceeds through the acylation of indoles.[15] No intermolecular heteroannulation has so far been reported with aromatic ureas.[7] Thus, we investigated a novel one-pot urea synthesis by using palladium-catalyzed heteroannulation with internal alkynes, to produce 2,3-disubstituted indole-carboxamide derivatives (Table 3). Treatment of 2-iodobenzoic acid with phenyl chloroformate and sodium azide, followed by addition of an amine led to the formation of the corresponding urea

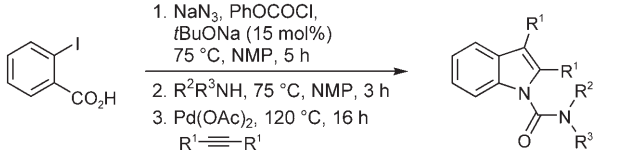
Table 2: Synthesis of indoles from 2-iodobenzoic acid by a one-pot Curtius rearrangement/palladium-catalyzed indolization process.

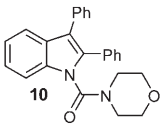
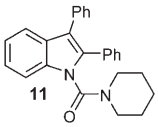
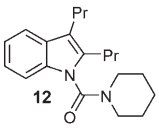
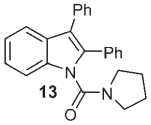
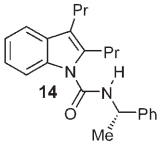
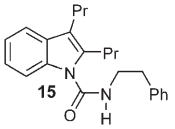


Entry	Coupling agent Base	Product	Yield [%][a]
1	Ph—≡—Ph, Na_2CO_3	 **4**	77
2	Me—≡—*t*Bu, Na_2CO_3	 **5**	56
3	Ph—≡—TMS, Na_2CO_3	 **6**	82
4	Ph, CHO, DABCO	 **7**	50
5	BnO, CHO, DABCO	 **8**	53
6	O, DABCO	 **9**	56

[a] Yields of isolated products. TMS = trimethylsilyl, Bn = benzyl.

Table 3: Synthesis of indole *N*-carboxamides from 2-iodobenzoic acid by a one-pot Curtius rearrangement/palladium-catalyzed indolization process.



Entry	Product	Yield [%][a]
1	 **10**	64
2	 **11**	68
3	 **12**	54
4	 **13**	62
5	 **14**	59
6	 **15**	39

[a] Yields of isolated products. NMP = *N*-methyl-2-pyrrolidinone.

intermediate. Without isolation, the intermediate was directly engaged in palladium-catalyzed indolization with diphenylpropyne or 4-octyne to give indole-carboxamides. The cyclic amines morpholine, piperidine, and pyrrolidine produced indoles **10**–**13** in 54–68% yield (Table 3, entries 1–4), whereas a substituted acyclic amine produced indole **14** in 59% yield (Table 3, entry 5). A moderate yield of indole **15** was obtained with phenylethylamine (Table 3, entry 6).

In conclusion, we have developed a novel one-pot Curtius rearrangement/palladium-catalyzed indolization process that allows the direct synthesis of 2,3-disubstituted and 3-substituted indoles starting from readily available 2-iodobenzoic acid. A synergistic effect between the two reactions of the process was observed, with a by-product of the first reaction serving as a reagent in the second synthetic step. In addition, the use of a one-pot procedure leads to higher yields while generating less by-products and chemical residues. This multicomponent process was also used to synthesize the first indole *N*-carboxamide derivatives through a heteroannulation procedure.

Experimental Section

Typical procedure: Benzyl chloroformate (150 μL, 1.10 mmol) was added to a solution of sodium azide (0.110 g, 1.70 mmol), sodium *tert*-butoxide (14.4 g, 0.15 mmol), and 2-iodobenzoic acid (0.248 g, 1.0 mmol) in *N*,*N*-dimethylformamide (DMF, 5.0 mL) at 25 °C. The resulting mixture was then stirred at 75 °C for 5 h and then cooled to room temperature. $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), the base (Na_2CO_3 for alkynes or DABCO for carbonyl compounds (3 mmol)), and the alkyne (3 mmol) or the carbonyl compound (3 mmol for ketones and 0.90 mmol for aldehydes) were then added and the mixture was heated at 120 °C for 16 h. The reaction mixture was then cooled to room temperature and then filtered through celite, which was washed with EtOAc (100 mL). The resulting organic layer was washed with saturated NH_4Cl (2 × 40 mL) and brine (40 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

Received: August 10, 2007
Published online: November 23, 2007

Keywords: heteroannulation · indole · one-pot process · palladium · rearrangement

[1] For recent reviews on indole-containing natural products, see a) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2004**, *21*, 278–311; b) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73–103.

[2] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241–2245; b) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559–563; c) B. Robinson, *Chem. Rev.* **1969**, *69*, 227–250.

[3] G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911.

[4] Reviews: a) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2309; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920; selected examples with alkyne compounds: c) S. Kamijo, Y. Sasaki, C. Kanazawa, T. Schusseler, Y. Yamamoto, *Angew. Chem.* **2005**, *117*, 7896; *Angew. Chem. Int. Ed.* **2005**, *44*, 7718; d) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690; e) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652–7662; selected examples with carbonyl compounds: f) H. Iida, Y. Yuasa, C. Kibayashi, *J. Org. Chem.* **1980**, *45*, 2938–2942; g) T. Sakamoto, T. Nagano, Y. Kondo, H. Yamanaka, *Synthesis* **1990**, 215–218; h) K. Koerber-Plé, G. Massiot, *Synlett* **1994**, 759–760; i) C. Y. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1997**, *62*, 2676–2677; j) K. Yamazaki, Y. Nakamura, Y. Kondo, *J. Org. Chem.* **2003**, *68*, 6011–6019; k) T. Watanabe, S. Arai, A. Nishida, *Synlett* **2004**, 907–909; l) M. Nazaré, C. Schneider, A. Lindenschmidt, D. W. Will, *Angew. Chem.* **2004**, *116*, 4626–4629; *Angew. Chem. Int. Ed.* **2004**, *43*, 4526–4528; m) Y. Jia, J. Zhu, *J. Org. Chem.* **2006**, *71*, 7826–7834.

[5] It is possible to use the cheaper 2-chloro or 2-bromo derivatives with a palladium catalyst containing an electron-rich ferrocenylphosphine ligand, see M. Shen, G. S. Li, B. Z. Lu, A. Hossain, F. Roschangar, V. Farina, C. H. Senanayake, *Org. Lett.* **2004**, *6*, 4129–4132.

[6] a) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1–21; b) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; c) H. C. Guo, J. A. Ma, *Angew. Chem.* **2006**, *118*, 362–375; *Angew. Chem. Int. Ed.* **2006**, *45*, 354–366; d) A. Domling, *Chem. Rev.* **2006**, *106*, 17–89; e) V. Dragutan, I. Dragutan, *J. Organomet. Chem.* **2006**, *691*, 5129–5147; f) B. Schmidt, *Pure Appl. Chem.* **2006**, *78*, 469–476; g) A. de Meijere, P. Von Zezschwitz, S. Brase, *Acc. Chem. Res.* **2005**, *38*, 413–422; h) J. C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; i) S. J. Broadwater, S. L. Roth, K. E. Price, M. Kobaslija, D. T. McQuade, *Org. Biomol. Chem.* **2005**, *3*, 2899–2906; j) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628–1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; k) L. F. Tietze, N. Rackelmann, *Pure Appl. Chem.* **2004**, *76*, 1967–1983; l) A. Ajamian, J. L. Gleason, *Angew. Chem.* **2004**, *116*, 3842–3848; *Angew. Chem. Int. Ed.* **2004**, *43*, 3754–3760; m) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365–2379; n) G. Prestat, G. Poli, *Chemtracts* **2004**, *17*, 97–103; o) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302–312.

[7] A. Bruggink, R. Schoevaart, T. Kieboom, *Org. Process Res. Dev.* **2003**, *7*, 622–640.

[8] H. Lebel, V. Paquet, *J. Am. Chem. Soc.* **2004**, *126*, 11152–11153.

[9] a) N. Gathergood, P. J. Scammells, *Org. Lett.* **2003**, *5*, 921; b) J. Ma, W. Yin, H. Zhou, J. M. Cook, *Org. Lett.* **2007**, *9*, 3491. Intramolecular heteroannulations of carbamate and urea derivatives have been previously reported, see c) J. X. Liu, M. Shen, Y. D. Zhang, G. S. Li, A. Khodabocus, S. Rodriguez, B. Qu, V. Farina, C. H. Senanayake, B. Z. Lu, *Org. Lett.* **2006**, *8*, 3573–3575.

[10] See the Supporting information for the optimization details.

[11] Similar cleavage has been previously observed with trifluoroacetate protected indole in another palladium-indolization process, see a) A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1992**, *33*, 3915–3918; b) G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.* **2002**, 2671–2681; c) B. Z. Lu, W. Y. Zhao, H. X. Wei, M. Dufour, V. Farina, C. H. Senanayake, *Org. Lett.* **2006**, *8*, 3271–3274.

[12] a) H. Lebel, O. Leogane, *Org. Lett.* **2006**, *8*, 5717–5720; b) H. Lebel, O. Leogane, *Org. Lett.* **2005**, *7*, 4107–4110; c) H. Lebel, O. Leogane, K. Huard, S. Lectard, *Pure Appl. Chem.* **2006**, *78*, 363–375.

[13] It should be noted that in this case the use of a chloride salt is not required.

[14] Selected examples: a) J. Bermudez, S. Dabbs, K. A. Joiner, F. D. King, *J. Med. Chem.* **1990**, *33*, 1929–1932; b) T. W. von Geldern, J. A. Kester, R. Bal, J. R. Wu-Wong, W. Chiou, D. B. Dixon, T. J. Opgenorth, *J. Med. Chem.* **1996**, *39*, 968–981.

[15] Selected examples: a) D. L. Boger, M. Patel, *J. Org. Chem.* **1987**, *52*, 3934–3936; b) J. E. Macor, A. Cuff, L. Cornelius, *Tetrahedron Lett.* **1999**, *40*, 2733–2736; c) J. B. Bremner, W. Sengpracha, *Tetrahedron* **2005**, *61*, 5489–5498.

