Facile approaches toward the synthesis of 6H-isoindolo[2,1-α]indol-6-ones via palladium-catalyzed carbonylation with carbon monoxide

Qingshuai Han, Shurong Fu, Xiaofeng Zhang, Shen Lin, Qiufeng Huang

PII: S0040-4039(16)30976-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.07.108
Reference: TETL 47970

To appear in: *Tetrahedron Letters*

Received Date: 15 June 2016
Revised Date: 27 July 2016
Accepted Date: 30 July 2016

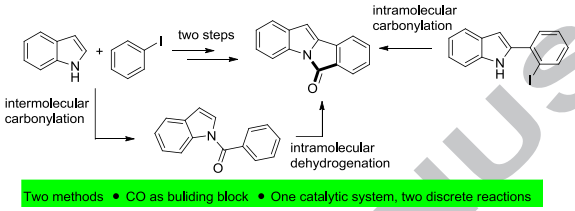
Please cite this article as: Han, Q., Fu, S., Zhang, X., Lin, S., Huang, Q., Facile approaches toward the synthesis of 6H-isoindolo[2,1-α]indol-6-ones via palladium-catalyzed carbonylation with carbon monoxide, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.07.108

Graphical Abstract

Facile approaches toward the synthesis of 6H-isoindolo[2,1-α]indol-6-ones via palladium-catalyzed carbonylation with carbon monoxide

Leave this area blank for abstract info.

Qingshuai Han, Shurong Fu, Xiaofeng Zhang, Shen Lin, Qiufeng Huang*



Tetrahedron Letters
journal homepage: www.elsevier.com

Facile approaches toward the synthesis of 6H-isoindolo[2,1-α]indol-6-ones via palladium-catalyzed carbonylation with carbon monoxide

Qingshuai Han, Shurong Fu, Xiaofeng Zhang, Shen Lin, Qiufeng Huang*

College of Chemistry & Chemical Engineering, Fujian Normal University, Fuzhou, 350007, P. R. China and Fujian Key Laboratory of Polymer Materials, Fuzhou, 350007, P. R. China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
6H-isoindolo[2,1-α]indol-6-one
Palladium-catalyzed
carbonylation
carbon monoxide

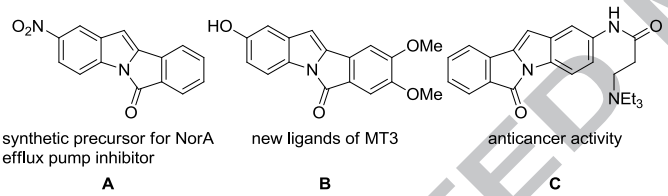
ABSTRACT

Two facile methods for the preparation of 6H-isoindolo[2,1-α]indol-6-ones were developed. In the first protocol, 6H-isoindolo[2,1-α]indol-6-ones were prepared from 2-(2-iodophenyl)-1*H*-indoles via palladium-catalyzed intramolecular aminocarbonylation. The second involves intermolecular carbonylation of indoles with iodobenzenes followed by intramolecular cross-dehydrogenative-coupling.

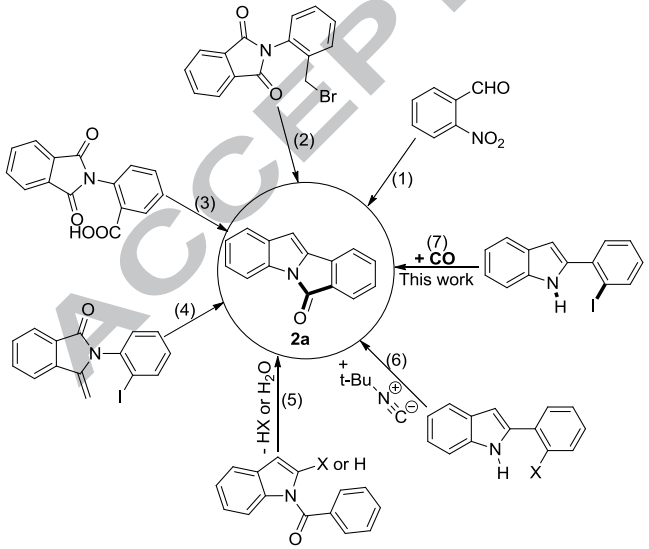
* Corresponding author. Tel.: +86-13599081672; fax: +86-591-228-67399; e-mail: qiufenghuang@fjnu.edu.cn

Introduction

Development of synthetic methods for 6H-isoindolo[2,1-α]indol-6-ones (**2a**) is an important research work in organic synthesis, as such types of compounds are not only applied as versatile intermediates in diverse organic synthesis (Scheme 1**A**),[1] but also exhibit various important biological activities (Scheme 1**B** and **C**).[2] A number of synthetic methods have been established in recent years.[3-9] For example, a two-step strategy starting from *o*-nitrobenzaldehydes through wittig reaction and tandem reductive cyclization-lactamization was established by Tilve et al (Scheme 2, route 1).[4] The synthesis of **2a** can also be carried out via an intramolecular wittig reaction from *o*-phthalimidobenzyl bromide (Scheme 2, route 2).[5] Griffiths et al. reported a convenient route to **2a** from 2-(N-phthaloyl)benzoic acid via β-ketophosphonates (Scheme 2, route 3).[6] Kim et al. have developed the synthesis of **2a** by intramolecular heck reaction from methylenephthalimidine (Scheme 2, route 4).[7] More recently, transition-metal-catalyzed intramolecular C-H coupling from N-benzoylindole derivatives has become a powerful method for the preparation of **2a** (Scheme 2, route 5).[8] Furthermore, a Pd-catalyzed intramolecular cyclization via tert-butyl isocyanide insertion from 2-(2-bromophenyl)-1*H*-indoles was also issued by Zhu et al (Scheme 2, route 6).[9] However, these methods often suffer from tedious experimental proceduces, harsh reaction conditions, expensive starting materials, and unsatisfactory yields. Since seminal work by Heck and co-workers,[10] carbonylation of aryl halides with carbon monoxide (CO) is an effective approach for introducing a carbonyl group



Scheme 1. Examples of important 6H-isoindolo[2,1-a]indol-6-ones



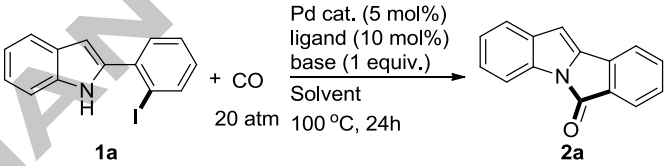
Scheme 2. Strategies toward the synthesis of 6H-isoindolo[2,1-a]indol-6-ones

into organic molecules.[11] In view of recent advances in carbonylation, we envisage that **2a** could be readily constructed starting from 2-(2-iodophenyl)-1*H*-indoles (**1a**) via intramolecular carbonylation by using CO as a C1 building block.

Results and discussion

The intramolecular carbonylation of 2-(2-iodophenyl)-1*H*-indole (**1a**) was initially chosen as a model reaction to establish the optimum reaction conditions as summarized in Table 1. Among the palladium catalysts examined, $Pd(OAc)_2$ was superior to $PdCl_2$ and $Pd(PPh_3)Cl_2$ (Table 1, entries 1-3). The addition of PPh_3 led to a much greater increase of the yield, affording **2a** in 75% yield (Table 1, entry 4). Notably, bases played a crucial role in the reaction. The employment of DBU brought about a much decrease of product **2a** (40%; Table 1, entry 5); and the best result was obtained by addition of K_2CO_3 (86%; Table 1, entry 5). In order to further enhance the formation of **2a**, various solvents, such as DMSO, EtOH, THF, CH_3CN, xylene and toluene were also tested ((Table 1, entries 7-12) and toluene was found to be the most effective solvent, thus giving **2a** in 95% yield (Table 1, entry 12). A change of the carbon monoxide pressure to 10 atm (85%; Table 1, entry 14) or 30 atm (88%; Table 1, entry 13) decreased the yield slightly. However, only 6% yield of **2a** was formed under atmospheric pressure of CO (Table 1, entry 15). If taken together, these results indicated the following as the

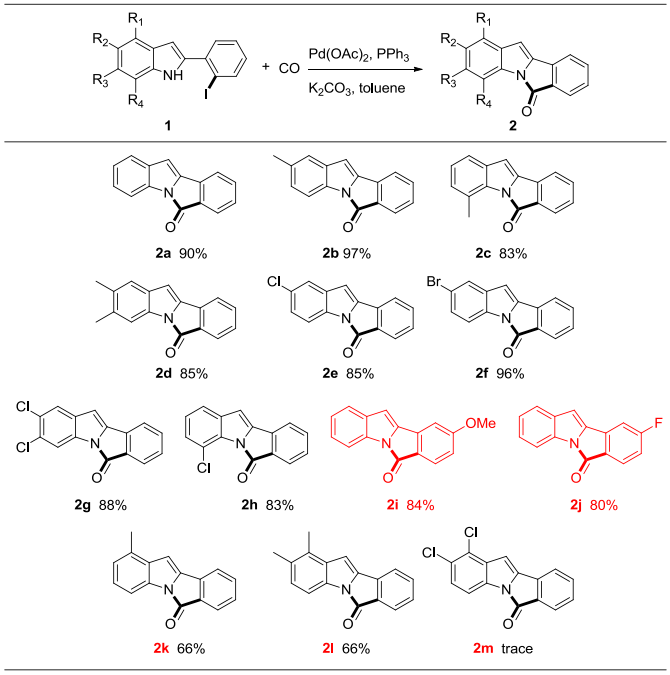
Table 1. Optimization of reaction conditions[a]



Entry	Pd Cat.	Ligand	Base	Solvent	Yield(%)[b]
1	$PdCl_2$		Et_3N	DMF	NR
2	$Pd(PPh_3)_2Cl_2$		Et_3N	DMF	trace
3	$Pd(OAc)_2$		Et_3N	DMF	16
4	$Pd(OAc)_2$	PPh_3	Et_3N	DMF	75
5	$Pd(OAc)_2$	PPh_3	DBU	DMF	40
6	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	86
7	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMSO	73
8	$Pd(OAc)_2$	PPh_3	K_2CO_3	EtOH	78
9	$Pd(OAc)_2$	PPh_3	K_2CO_3	THF	38
10	$Pd(OAc)_2$	PPh_3	K_2CO_3	CH_3CN	76
11	$Pd(OAc)_2$	PPh_3	K_2CO_3	Xylene	87
12	**$Pd(OAc)_2$**	**PPh_3**	**K_2CO_3**	**Toluene**	**95(90)**
13[c]	$Pd(OAc)_2$	PPh_3	K_2CO_3	Toluene	88
14[d]	$Pd(OAc)_2$	PPh_3	K_2CO_3	Toluene	85
15[e]	$Pd(OAc)_2$	PPh_3	K_2CO_3	Toluene	6

[a] Reaction conditions: **1a** (0.2 mmol), Pd cat. (5 mol%), Ligand (10 mol%), base (1 equiv.) solvent (1 mL), CO (20 atm), 100 ^{0}C, 24h; [b] Yield according to GC analysis on the basis of the amount of **1a** used, Number in parenthesis is isolated yield, NR=No reaction; [c] CO (10 atm); [d] CO (30 atm), [e] CO (1 atm).

Table 2. Synthesis of 6H-isoindolo[2,1-α]indol-6-ones via palladium-catalyzed intramolecular carbonylation[a]



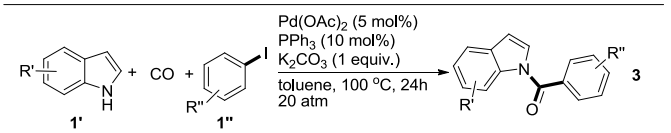
[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (1 equiv.), toluene(1 mL), CO (20 atm), 100 ^{0}C, 24h; Isolated yields

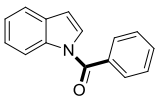
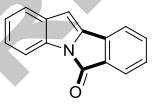
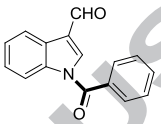
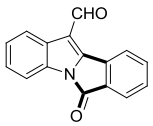
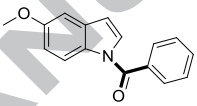
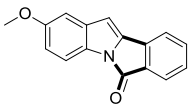
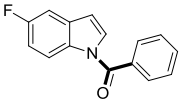
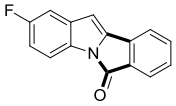
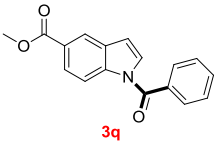
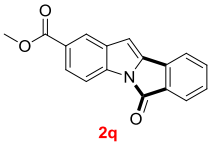
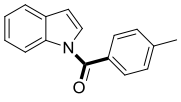
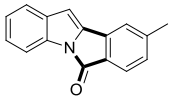
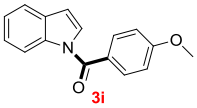
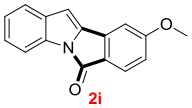
optimal reaction conditions: $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (1 equiv.) in toluene under CO (20 atm) at 100 ^{o}C.

A number of substituted 6H-isoindolo[2,1-α]indol-6-ones could be synthesized by the present catalytic procedure. The carbonylation of 2-(2-iodophenyl)-5-methyl-1*H*-indole, 2-(2-iodophenyl)-7-methyl-1*H*-indole and 2-(2-iodophenyl)-5,6-dimethyl-1*H*-indole gave desired product in 97%, 83% and 85% yield, respectively (Table 2, **2b**-**d**). However, upon employing 2-(2-iodophenyl)-4-methyl-1*H*-indole and 2-(2-iodophenyl)-4,5-dimethyl-1*H*-indole, lower yields of carbonylation products were obtained (**2k** and **2l**). The same is true for chloro-substituted 2-(2-iodophenyl)-1*H*-indole. The substrates with chloro group at the 5-, 6-, or 7-position of the indole ring underwent carbonylation successfully, affording 6H-isoindolo[2,1-α]indol-6-ones **2e**, **2g** and **2h** in 83-88% yield. However, upon employing 2-(2-iodophenyl)-4,5-dichloro-1*H*-indole, only trace amount of product **2m** was detected. These results suggest that a substituent at the 4-position in the indole ring has deleterious effect in delivering 6H-isoindolo[2,1-α]indol-6-one. It is found that the electronic properties of the substituents on the indole ring or (iodo)phenyl ring have no effect on the observed reactivity. 2-(2-iodophenyl)-1*H*-indoles with electron-donating or electron-withdrawing groups, such as alkyl, methoxy, chloro, bromo, and fluoro were good substrates and afforded the desire products in excellent yields (80-97% yield, **2b**-**j**). It is worthy of noting that this catalytic system can tolerate halogen. Halogen-substituted 6H-isoindolo[2,1-α]indol-6-ones could provide opportunities for further functionalization.

During the course of our current investigations, we also found that this catalytic system could be extended to the intermolecular carbonylation. Under the optimized reaction conditions as indicated in entry 12 of Table 1, the intermolecular carbonylation between indoles and iodobenzenes proceeded smoothly to give the corresponding *N*-benzoylindoles in moderate to good yields(48-93%, **3a**, **3i** and **3n**-**r**). After intermolecular carbonylation, intramolecular dehydrogenation of *N*-benzoylindoles (under a slight modification of the procedure

Table 3. Synthesis of 6H-isoindolo[2,1-α]indol-6-ones via palladium-catalyzed intermolecular carbonylation and subsequent cross-dehydrogenative-coupling[a,b]



entry	product **3**	yield (%)	product **2**	yield (%)
1	 **3a**	88	 **2a**	77
2	 **3n**	92	 **2n**	73
3	 **3o**	90	 **2o**	50
4	 **3p**	88	 **2p**	52
5	 **3q**	93	 **2q**	60
6	 **3r**	48	 **2r**	77
7	 **3i**	51	 **2i**	79

[a] Reaction conditions for intermolecular carbonylation: **1'** (0.2 mmol), **1"** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (1 equiv.), toluene(1 mL), CO (20 atm), 100 ^{0}C, 24h; Isolated yields.
[b] Reaction conditions for intramolecular dehydrogenation: **3** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (10 mol%), AgOAc (1 equiv), PivOH (0.2 mL), 120 ^{0}C, 24 h; Isolated yields.

reported by Fagnou et al.[8e]) conveniently generated the 6H-isoindolo[2,1-α]indol-6-ones (**2a** **2i** and **2n**-**r**) in 50-79% yield. Remarkably, the synthesis of aldehyde or ester substituted 6H-isoindolo[2,1-α]indol-6-ones (compound **2n** and **2q**) can also be accomplished.

Conclusion

In summary, the palladium-catalyzed intramolecular C-I aminocarbonylation of 2-(2-iodophenyl)-1*H*-indoles to form 6H-isoindolo[2,1-α]indol-6-ones was developed. $Pd(OAc)_2$ as catalyst, PPh_3 as ligand and K_2CO_3 as base gave the best results under 20 atm pressure of CO. This catalytic system and optimal reaction conditions could be extended to the intermolecular carbonylation of indoles with iodobenzenes affording N-

benzoylindoles, and subsequent palladium-catalyzed dehydrogenation of N-benzoylindoles also provided the 6H-isoindolo[2,1-α]indol-6-ones in good yields. These methods offer far greater generality than previous methods for the synthesis of 6H-isoindolo[2,1-α]indol-6-ones.

Acknowledgments

Financial support from NSFC (Grant No. 21103022 and 61520106015), Foundation of Fujian Educational Committee (Grant No. JK2014010) is gratefully acknowledged.

Supplementary Material

Supplementary material (experimental details, characterization data, and copies of NMR spectra) associated with this article can be found in the online version at http://dx.doi.org/

References and notes

1. (a) Samosorn, S.; Bremner, J. B.; Ball, A.; Lewis, K. *Bioorg. Med. Chem.* **2006**, *14*, 857-865; (b) Komoda, T.; Shinoda, Y.; Nakatsuka, S. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 659-662; (c) Laha, J. K.; Dayal, N.; Jethava, K. P.; Prajapati, D. V. *Org. Lett.* **2015**, *17*, 1296-1299; (d) Crawford, L. A.; Cle mence, N. C.; McNab, H.; Tyas, R. G. *Org. Biomol. Chem.* **2008**, *6*, 2334-2339; (e) Scopton, A.; Kelly, T. R. *J. Org. Chem.* **2005**, *70*, 10004-10012.
2. (a) Boussard, M.-F.; Truche, S.; Rousseau-Rojas, A.; Briss, S.; Descamps, S.; Droual, M.; Wierzbicki, M.; Ferry, G.; Audinot, V.; Delagrange, P.; Boutin, J. A. *Eur. J. Med. Chem*. **2006**, *41*, 306-320; (b) Pegan, S. D.; Sturdy, M. ; Ferry, G.; Delagrange, P.; Boutin, J. A.; Mesecar, A. D. *Protein Sci.* **2011**, *20*, 1182-1195; (c) Alarma-Estrany, P.; Crooke, A.; Mediero, A.; Peláez, T.; Pintor, J. *J. Pineal. Res*. **2008**, *45*, 468-475; (d) Jean, G.; Stephane, L.; Alain, P.; Pierre, R.; Bruno, P.; Laure, P.; Paola B, A.; Claude, M. *Oncol. Res.* **2003**, *13*, 537-549.
3. (a)Marion, F.; Coulomb, J.; Servais, A.; Courillon, C.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2006**, *62*, 3856-3871; (b) Hayashi, K.; Choshi, T.; Chikaraishi, K.; Oda, A.; Yoshinaga, R.; Hatae, N.; Ishikura, M.; Hibino, S. *Tetrahedron* **2012**, *68*, 4274-4279; (c) Dev, K.; Maurya, R. *RSC Adv*. **2015**, *5*, 13102-13106; (d) Nallapati, S. B.; Adepu, R.; Ashfag, M. S.; Sreenivas, B. Y.; Mukkanti, K.; Pal, M. *RSC Adv.* **2015**, *5*, 88686-88691; (e) Huang, Q.; Campo, M. A.; Yao, T.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 8251-8257; (f) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett*. **2003**, *5*, 5095-5097; (g) García, A.; Rodríguez, D.; Castedo, L.; Saá, C.; Domínguez, D. *Tetrahedron Lett.* **2001**, *42*, 1903-1905; (h) Francisco J, R.; Monica, T.; Juan C, E.; Luis, C.; Ramon J, E. *Synlett* **2003**, 1603-1606.
4. Kadam, H. K.; Tilve, S. G. *Eur. J. Org. Chem*. **2013**, 4280-4284.
5. Guillaumel, J.; Léonce, S.; Pierré, A.; Renard, P.; Pfeiffer, B.; Arimondo, P. B.; Monneret, C. *Eur. J. Med. Chem*. **2006**, *41*, 379-386.
6. Duncanson, P.; Cheong, Y.-K.; Motevalli, M.; Griffiths, D. V. *Org. Biomol. Chem.* **2012**, *10*, 4266-4279.
7. Kim, G.; Kim, J. H.; Kim, W.; Kim, Y. A. *Tetrahedron Lett.* **2003**, *44*, 8207-8209
8. (a) He, H.-F.; Dong, S.; Chen, Y.; Yang, Y.; Le, Y.; Bao, W. *Tetrahedron* **2012**, *68*, 112-3116; (b) Laha, J. K.; Dayal, N.; Singh, S.; Bhimpuria, R. *Eur. J. Org. Chem.* **2014**, 5469-5475; (c) Signori, A. M.; Latocheski, E.; Albuquerque, B. L.; Faggion Jr, D.; Bisol, T. B.; Meier, L.; Domingos, J. B. *New J. Chem.* **2015**, *39*, 1574-1578; (d) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett*. **2007**, *9*, 3137-3139; (e) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022-5028; (f) Kandukuri, S. R.; Oestreich, M. *J. Org. Chem.* **2012**, *77*, 8750-8755.
9. Tang, T.; Jiang, X.; Wang, J.-M.; Sun, Y.-X.; Zhu, Y.-M. *Tetrahedron* **2014**, *70*, 2999-3004.
10. (a) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc*. **1974**, *96*, 7761-7764; (b) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem*. **1974**, 39, 3318-3326; (c) Schoenberg, A.; Heck, R. F. *J. Org. Chem*. **1974**, *39*, 3327-3331.
11. (a) Wu, L.; Fang, X.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X.-F. *ACS Catal*. **2014**, *4*, 2977-2989; (b) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res*. **2014**, *47*, 1563-1574; (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev*. **2011**, *40*, 4986-5009; (d) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed*. **2009**, *48*, 4114-4133; (e) Quesnel, J. S.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2013**, *135*, 16841-16844; (f) Fang, W.; Deng, Q.; Xu, M.; Tu, T. *Org. Lett*. **2013**, *15*, 3678-3681.

Highlights

- ✓ Two facile method for the preparation of 6H-isoindolo[2,1-α]indol-6-ones
- ✓ Carbon monoxide as C1 building block
- ✓ One catalytic system, two discrete reactions