ORGANIC LETTERS

2012
Vol. 14, No. 20
5184–5187

Palladium-Catalyzed Regioselective [3 + 2] Annulation of Internal Alkynes and Iodo-pyranoquinolines with Concomitant Ring Opening

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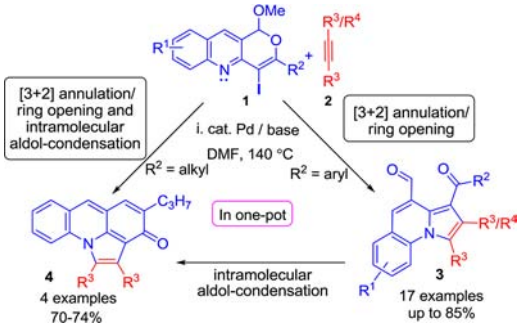
Received August 17, 2012

ABSTRACT



A regioselective tandem synthesis of highly functionalized pyrrolo[1,2-*a*]quinolines has been developed through a novel strategy by palladium-catalyzed [3 + 2] annulation of iodo-pyranoquinolines and internal alkynes with subsequent ring opening. Pyranoquinoline with *n*-alkyl substitution at the 3-position leads to the formation of pyrrolo-acridones *via* [3 + 2] annulations/ring opening and successive intramolecular cross-aldol condensation.

Nitrogen-containing heterocycles are an important class of compounds due to their presence in numerous natural products and potent biological activity.[1] Among various *N*-heterocycles, reduced and oxidized forms of pyrrolo-[1,2-*a*]quinolines occur widely among natural products[2a,b] and exhibit a wide array of biological activities.[2c] Despite various synthetic protocols available for the synthesis of pyrrolo[1,2-*a*]quinoline,[3] a need for novel and versatile methods for their efficient synthesis attracts the interest of synthetic chemists.

The annulation reactions catalyzed by transition metals are among the most demanding synthetic processes for constructing a wide variety of heterocyclic/carbocyclic frameworks.[4,5] Among various annulations, the [3 + 2] annulation represents a breakthrough in the field of

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(1) (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (b) Bailly, C. *Anti-Cancer Agents* **2004**, *4*, 363. (c) Yao, B.; Prinsep, M. R.; Nicholson, B. K.; Gordon, D. P. *J. Nat. Prod.* **2003**, *66*, 1074.

(2) (a) Pearson, W. H.; Fang, W. *J. Org. Chem.* **2000**, *65*, 7158. (b) Santarem, M.; Vanucci-Bacqué, C.; Lhommet, G. *J. Org. Chem.* **2008**, *73*, 6466. (c) Hazra, A.; Mondal, S.; Maity, A.; Naskar, S.; Saha, P.; Paira, R.; Sahu, K. B.; Paira, P.; Ghosh, S.; Sinha, C.; Samanta, A.; Banerjee, S.; Mondal, N. B. *Eur. J. Med. Chem.* **2011**, 2132.

(3) (a) Muthusaravanan, S.; Perumal, S.; Yogeeswari, P.; Sriram, D. *Tetrahedron Lett.* **2010**, *51*, 6439. (b) Li, X.; Li, C.; Zhang, W.; Lu, X.; Han, S.; Hong, R. *Org. Lett.* **2010**, *12*, 1696. (c) Gericke, K. M.; Chai, D. I.; Lautens, M. *Tetrahedron* **2008**, *64*, 6002. (d) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433.

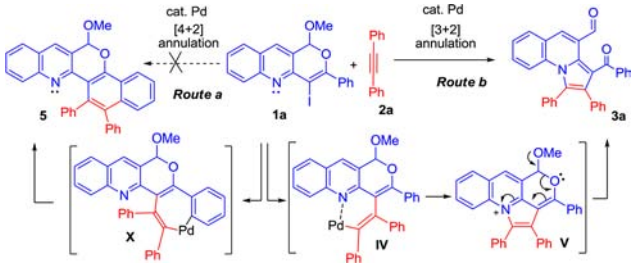
(4) (a) Katritzky, A. R.; Li, J.; Xie, L. *Tetrahedron* **1999**, *55*, 8263. (b) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892. (c) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press Inc.: London, 1987; Vol. 30, p 251. (d) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503. (e) Larock, R. C. *Top. Organomet. Chem.* **2005**, *14*, 147. (f) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (g) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

(5) (a) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075. (b) Straub, B. F. *Chem. Commun.* **2004**, 1726. (c) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (d) Kabalka, G. W.; Ju, Y.; Wu, Z. *J. Org. Chem.* **2003**, *68*, 7915.

10.1021/ol3022935
Published on Web 09/28/2012

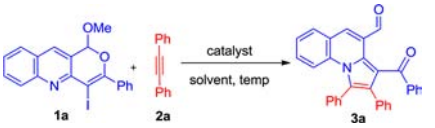
organic synthesis.[6] In 1998, Larock et al. reported an elegant approach for the synthesis of indoles by [3 + 2] annulations[7] and other polycyclic compounds through CH activation.[8] Recently, Cramer and Tran reported the synthesis of substituted indenes by [3 + 2] annulations of aromatic ketimines with internal alkynes using a Rh(I)-catalyst along with chiral ligands.[9] As a part of our ongoing efforts in the synthesis of heterocycles using alkyne chemistry,[10] for the first time herein we report the Pd-catalyzed intermolecular [3 + 2] annulation of internal alkynes and iodo-pyranoquinolines with subsequent ring opening for the synthesis of pyrrolo[1,2-*a*]quinolines **3** (Scheme 1). The developed chemistry was successfully extended for the synthesis of pharmaceutically important pyrrolo acridinones[11] **4** from easily accessible iodo-pyrano quinolines[12] (R^2 = *n*-alkyl) *via* [3 + 2] annulations/ring opening and successive intramolecular cross-aldol condensation.

Scheme 1. Design of Polyheterocycles via [4 + 2]/[3 + 2] Alkyne Annulation



Based on the previous studies by Larock[13] and our group,[14] we hypothesized and envisioned the formation of polyheterocycle **5** by [4 + 2] annulation via palladacycle **X** (Scheme 1, route **a**). We also anticipated the possible formation of product **3a** by [3 + 2] alkyne annulation (using pyridyl nitrogen) and successive pyran ring opening via generation of vinylpalladium intermediate **IV** and adduct **V** (Scheme 1, route **b**). A preliminary study showed that the reaction failed to afford the polyheterocycle **5** under Pd-catalyzed conditions (Scheme 1, route **a**). However, an interesting product **3** was detected and isolated, which was characterized by spectroscopic analysis and further confirmed by X-ray crystallographic studies of compound **3k**.[15]

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	base	catalyst	mol %	yield[b]
1	DMF	NaOAc	$Pd(OAc)_2$	5	30[c]
2	DMF	NaOAc	$Pd(OAc)_2$	5	80
3	DMF	NaOAc	$Pd(OAc)_2$	3	55
4	DMF	NaOAc	$Pd(OAc)_2$	5	60[d]
5	DMF	NaOAc	$PdCl_2$	5	78
6	DMF	NaOAc	$Pd(PPh_3)_2Cl_2$	5	75
7	DMF	NaOAc	CuI	5	0
8	DMF	NaOAc	$Cu(OTf)_2$	5	0
9	DMF	NaOAc	$Cu(OAc)_2$	5	0
10	DMF	NaOAc	$Pd(OAc)_2$	5	0[e]
11	DMF	KOAc	$Pd(OAc)_2$	5	65
12	DMF	K_2CO_3	$Pd(OAc)_2$	5	20
13	DMF	Na_2CO_3	$Pd(OAc)_2$	5	30
14	DMSO	NaOAc	$Pd(OAc)_2$	5	77
15	DMF	NaOAc	$Pd(OAc)_2$	5	50[f]
16	DMF	NaOAc	$Pd(OAc)_2$	5	78[g]
17	DMF	NaOAc	$Pd(OAc)_2$	5	60[h]

[a] Reactions were performed using 0.25 mmol of **1a**, 1.2 equiv of **2a**, 2.0 equiv of base, 3.0 equiv of LiCl in 2.0 mL of solvent at 140 °C for 36 h unless otherwise noted. [b] Isolated yield. [c] For 24 h. [d] 1.0 equiv of NaOAc and 1.5 equiv of LiCl used. [e] Absence of LiCl. [f] At 120 °C for 40 h. [g] Using microwave irradiation at 120 °C for 20 min. [h] Using microwave irradiation at 120 °C for 15 min.

To test our hypothesis, we began an investigation from the reaction of 4-iodo-1-methoxy-3-phenyl-1*H*-pyrano-[4,3-*b*] quinoline (**1a**) and diphenylacetylene (**2a**) using NaOAc and LiCl with different Pd(II) catalysts in DMF at 140 °C. When 5 mol % of $Pd(OAc)_2$ was used, only a 30% yield of product **3a** was observed after 24 h, while an 80% yield of the product was obtained after 36 h (Table 1, entries 1 and 2). Further lowering of the catalyst loading decreases the yield to 55% (entry 3). No significant effect on the yield was observed by decreasing the amount of base

(6) (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215 and references cited therein. (b) Hanhan, N. V.; Ball-Jones, N. R.; Tran, N. T.; Franz, A. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 989. (c) Wang, Z.-Q.; Lei, Y.; Zhou, M.-B.; Chen, G.-X.; Song, R.-J.; Xie, Y.-X.; Li, J.-H. *Org. Lett.* **2011**, *13*, 14. (d) Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 440. (e) Kim, H.; Lee, K.; Kim, S.; Lee, P. H. *Chem. Commun.* **2010**, *46*, 6341. (f) Yang, M.; Zhang, X.; Lu, X. *Org. Lett.* **2007**, *9*, 5131. (g) Mizumura, M.; Shinokubo, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5378.

(7) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

(8) (a) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770. (b) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536.

(9) Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11098.

(10) (a) Joshi, M.; Tiwari, R. K.; Verma, A. K. *Org. Lett.* **2012**, *14*, 1106. (b) Rustagi, V.; Aggarwal, T.; Verma, A. K. *Green Chem.* **2011**, *13*, 1640. (c) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138.

(11) (a) Ralifo, P.; Sanchez, L.; Gassner, N. C.; Tenney, K.; Lokey, R. S.; Holman, T. R.; Valeriote, F. A.; Crews, P. *J. Nat. Prod.* **2007**, *70*, 95. (b) West, R. R.; Mayne, C. L.; Ireland, C. M.; Brinen, L. S.; Clardy, J. *Tetrahedron Lett.* **1990**, *31*, 3271. (c) Smith, C. J.; Venables, D. A.; Hopmann, C.; Salomon, C. E.; Jompa, J.; Tahir, A.; Faulkner, D. J.; Ireland, C. M. *J. Nat. Prod.* **1997**, *60*, 1048. (d) Thale, Z.; Johnson, T.; Tenney, K.; Wenzel, P. J.; Lobkovsky, E.; Clardy, J.; Media, J.; Pietraszkiewicz, H.; Valeriote, F. A.; Crews, P. *J. Org. Chem.* **2002**, *67*, 9384.

(12) (a) Aggarwal, T.; Imam, M.; Kaushik, N. K.; Chauhan, V. S.; Verma, A. K. *ACS Comb. Sci.* **2011**, *13*, 530. (b) Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691. (c) Verma, A. K.; Aggarwal, T.; Rustagi, V.; Larock, R. C. *Chem. Commun.* **2010**, *46*, 4064.

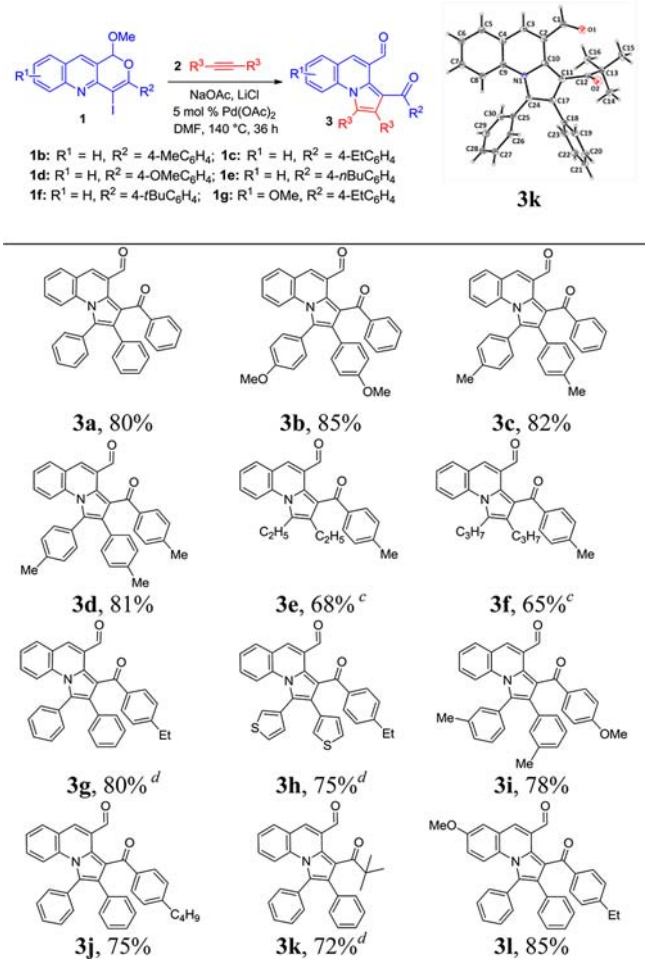
(13) (a) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 223. (b) Yue, D.; Ca, N. D.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3381. (c) Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511.

(14) Verma, A. K.; Shukla, S. P.; Singh, J.; Rustagi, V. *J. Org. Chem.* **2011**, *76*, 5670.

(15) See Supporting Information.

to 1.0 equiv and LiCl to 1.5 equiv (entry 4). Also, 5 mol % of $PdCl_2$ and $Pd(PPh_3)_2Cl_2$ were found to be effective (entries 5 and 6). The Cu(I) salts such as CuI, $Cu(OTf)_2$, and $Cu(OAc)_2$ were found to be ineffective (entries 7–9). No product formation was observed in the absence of LiCl (entry 10). Use of KOAc afforded the product **3a** in lower yield (entry 11). Inferior results were observed when K_2CO_3 and Na_2CO_3 were used as a base (entries 12 and 13). Using DMSO as a solvent, the desired product was obtained in 77% yield (entry 14). Lowering the reaction temperature to 120 °C leads to the incomplete conversion of the substrate (entry 15).

Scheme 2. Substrate Scope of the Palladium-Catalyzed [3 + 2] Alkyne Annulation[a,b]

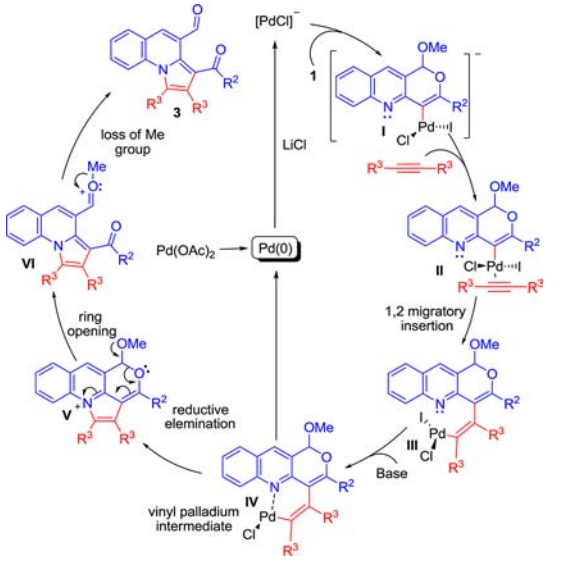


[a] Unless otherwise specified, reactions were performed using 0.25 mmol of **1**, 1.2 equiv of **2**, 5 mol % $Pd(OAc)_2$, 2.0 equiv of NaOAc, 3.0 equiv of LiCl in 2.0 mL of DMF at 140 °C for 36 h. [b] Isolated yield. [c] For 40–44 h. [d] Using microwave irradiation at 120 °C for 20 min.

From the above studies, the optimal conditions consist of 2.0 equiv of NaOAc and 3.0 equiv of LiCl with 5 mol % of $Pd(OAc)_2$ in DMF for 36–44 h to carry out this transformation in good yields. Interestingly, under microwave irradiation at 120 °C the reaction is complete within 20 min, affording a 78% yield of product **3a** (entry 16), whereas, in 15 min, only a 60% yield was obtained (entry 17).

After optimizing the reaction conditions, we examined the scope of the reaction by utilizing a variety of pyrano-[4,3-*b*]quinolines **1** and internal alkynes **2**. The substrate 4-iodo-pyrano[4,3-*b*]quinolines **1a**–**f** were readily prepared by electrophilic iodocyclization using the reported procedure.[12] Phenyl substituted pyranoquinoline reacted well with symmetrical internal alkynes and afforded the desired product **3a**–**d** in 80–85% yields under the optimized reaction conditions (Scheme 2). Electron-donating substituents at R^2 had no considerable effect on the reaction and afforded the desired product **3d**–**j**, **3l** in good to excellent yields. The aryl substituted symmetrical internal alkynes also afforded the products in good yield, while a comparatively lower yield of product **3h** was obtained with 1,2-di(thiophen-3-yl)ethyne (**2f**). The aliphatic internal alkynes reacted slowly and afforded the desired product **3d**–**e** in 68 and 65% yield, respectively. With 3-*tert*-butyl-iodo-pyrano[4,3-*b*]quinoline **1f**, the product **3k** was obtained in 72% yield. When a methoxy group was substituted at R^1, the reaction proceeded smoothly in 30 h and afforded the product **3l** in 85% yield.

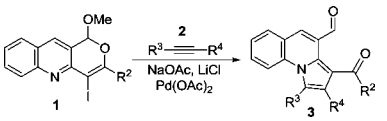
Scheme 3. A Plausible Mechanism



With the above results, a plausible mechanism was proposed on the basis of the reported mechanism[7] (Scheme 3). The reaction proceeds *via* reduction of the $Pd(OAc)_2$ to Pd(0), and then LiCl donates Cl^- to Pd(0) as a ligand and forms $[PdCl]^-$. The oxidative addition of the aryl iodide to Pd(0) (**I**) and coordination of the alkyne to the Pd-atom resulted in palladium alkyne intermediate **II**. The regioselective insertion of alkyne into the aryl palladium bond leads to the formation of intermediate **III**. The attack of the nitrogen lone pair on the vinylpalladium intermediate forms a palladacyclic complex (**IV**)[16] which upon reductive elimination forms the [3 + 2] annulated

adduct (**V**) and regeneration of the Pd(0). The instability of intermediate **V** subsequently leads to the opening of the pyran ring to form intermediate **VI**, which upon loss of Me provided the product **3**.[8a]

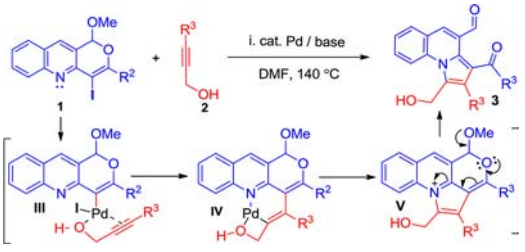
Table 2. Synthesis of Pyrrolo[1,2-*a*]quinolines Using Unsymmetrical Internal Alkynes[a]



entry	substrate	internal alkyne	product	yield%[b]
1	**1a**	**2h**, R^3 = Ph, R^4 = 4-MeOC$_6$H$_4$	**3m**	70(70:30)
2	**1a**	**2i**, R^3 = CH_2OH, R^4 = 4-MeC$_6$H$_4$	**3n**	62
3	**1b**	**2i**	**3o**	65
4	**1c**	**2i**	**3p**	68[c]
5	**1c**	**2j**, R^3 = COOEt, R^4 = Ph	**3q**	60

[a] Unless otherwise specified, reactions were performed using 0.25 mmol of **1**, 1.2 equiv of **2**, 5 mol % $Pd(OAc)_2$, 2.0 equiv of NaOAc, 3.0 equiv of LiCl in 2.0 mL of DMF at 140 °C for 36 h. [b] Isolated yields. [c] At 120 °C for 20 min in microwave.

Scheme 4. Regioselectivity via Formation of Chelated Complex

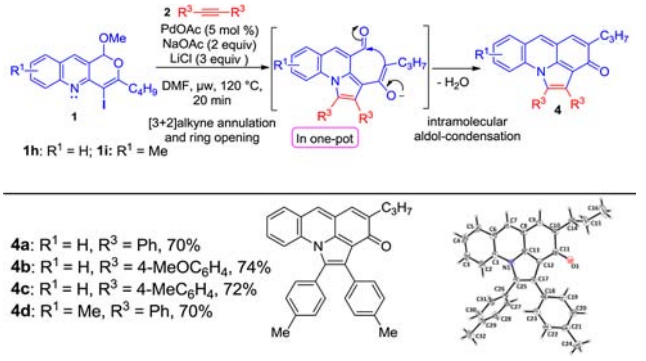


To examine the generality of this developed chemistry, unsymmetrical internal alkynes were allowed to react with the pyrano[4,3-*b*]quinoline under the optimized reaction conditions (Table 2). With 1-methoxy-4-(phenylethynyl)-benzene (**2h**), the product was obtained in 75% yield as a mixture of regioisomers (70:30) (entry 1).

Interestingly, alcohol substituted internal alkyne 3-*p*-tolylprop-2-yn-1-ol (**2i**) afforded the single isomers **3m**−**p** in 62−68% yields (entries 2−4). The effect of the adjacent hydroxyl group on the regioselectivity of the alkyne was due to coordination of the hydroxyl group to the Pd.[14] This is due to the formation of a chelated complex with Pd during the insertion step (**III**), leaving only one position available for the formation of the C−C bond (**IV**), and thus we obtained a single isomer (Scheme 4). Annulation with internal alkyne **2j** having an electron-withdrawing ester group also afforded the single isomer **3q** in 60% yield (entry 5). The reason might be the substantial difference in electron density at the two ends of the C−C triple bond.[8a]

In an effort to synthesize the fused heterocycle, we had employed aliphatic substituted pyranoquinoline which contained α-*H*. With this objective, 3-butyl-4-iodo-1-methoxy-1*H*-pyrano[4,3-*b*]quinoline (**1h**) and **1i** were treated with different internal alkynes **2a**−**c** under microwave conditions. Surprisingly, the corresponding products **4a**−**d** were obtained in good yields by [3 + 2] annulations/ring opening followed by intramolecular cross-aldol condensation (Scheme 5). The structure of pyrrolo-acridones was confirmed by ^{1}H, ^{13}C NMR and finally by X-ray crystallographic studies of compound **4c**.

Scheme 5. Synthesis of Pyrroloacridones via Alkyne Annulations Followed by Intramolecular Cross-Aldol Condensation



In summary, we have demonstrated a Pd-catalyzed tandem synthesis of pyrrolo[1,2-*a*]quinolines by [3 + 2] annulation of iodo-pyranoquinolines with successive ring opening under mild reaction conditions. This chemistry was successfully extended to the synthesis of diverse pharmaceutically important pyrrolo-acridinone via [3 + 2] annulations/ring opening and successive intramolecular cross-aldol condensation. It is noteworthy that unsymmetrical internal alkynes containing a propargyl alcoholic group and ester group selectively afforded a single isomer. Further investigation of the scope and synthetic applications of the present strategy are currently underway and will be reported in due course.

Acknowledgment. The Research work was supported by the Department of Science and Technology (SR/S1/OC-66/2010). We are thankful to the University of Delhi and USIC for instrumental facilities. T.A., R.R.J., S.K., S.K.R.K., and S.K. are thankful to CSIR for a fellowship.

Supporting Information Available. Experimental procedures and characterization of all new compounds (^{1}H NMR, ^{13}C NMR, HRMS) and CIFs for compounds **3n** (CCDC no. 886428) and **4c** (CCDC no. 886429). This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Chernyak, D.; Skontos, C.; Gevorgyan, V. *Org. Lett.* **2010**, *12*, 3242.

The authors declare no competing financial interest.