ORGANIC LETTERS

2004
Vol. 6, No. 16
2741−2744

Synthesis of Quinolines, 2-Quinolones, Phenanthridines, and 6(5*H*)-Phenanthridinones via Palladium[0]-Mediated Ullmann Cross-Coupling of 1-Bromo-2-nitroarenes with *β*-Halo-enals, -enones, or -esters

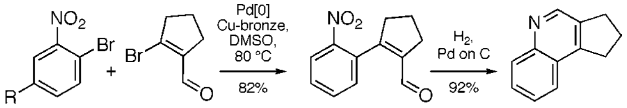
Martin G. Banwell,* David W. Lupton, Xinghua Ma, Jens Renner, and Magne O. Sydnes

Research School of Chemistry, Institute of Advanced Studies,
The Australian National University, Canberra, ACT 0200, Australia

mgb@rsc.anu.edu.au

Received May 24, 2004

ABSTRACT



1 (R=H) **9** **10** **11**

Palladium[0]-mediated Ullmann cross-coupling of 1-bromo-2-nitrobenzene (1 R = H) and its derivatives with a range of *β*-halo-enals, -enones, or -esters readily affords the corresponding *β*-aryl derivatives, which are converted into the corresponding quinolines, 2-quinolones, phenanthridines, or 6(5*H*)-phenanthridinones on reaction with dihydrogen in the presence of Pd on C or with TiCl$_3$ in aqueous acetone.

Quinolines and related heterocyclic systems represent privileged moieties in medicinal chemistry[1] and are ubiquitous substructures associated with biologically active natural products.[2] As a consequence, numerous methods for their preparation have been described.[1,3,4] One of the most effective is the Friedländer quinoline synthesis[4] wherein an aminoarene incorporating an *ortho*-tethered enal or enone moiety engages in an intramolecular Schiff base condensation or related reaction to deliver the target heterocycle. However, the construction of the substrates required in the application of this method can be problematic. Herein, therefore, we describe a simple, economical, and effective two-step procedure (Scheme 1) for the synthesis of quinolines that involves the palladium[0]-mediated Ullmann cross-coupling[5]

---

(1) (a) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, Chapter 5.06, p 245. (b) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett*. **2001**, *3*, 1109.

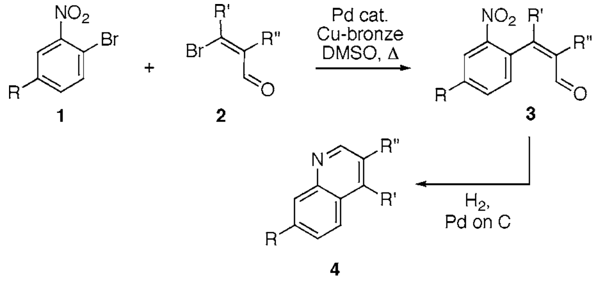
(2) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742.

(3) (a) Jones, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ress, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 2, pp 395−510. For examples of recently developed methods (other than the Friedländer approach) for the synthesis of quinolines, see: (b) Pouységu, L.; Avellan, A.-V.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 3425. (c) Ichikawa, J.; Wada, Y.; Miyazaki, H.; Mori, T.; Kuroki, H. *Org. Lett.* **2003**, *5*, 1455. (d) Mehta, B. K.; Yanagisawa, K.; Shiro, M.; Kotsuki, H. *Org. Lett.* **2003**, *5*, 1605. (e) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765.

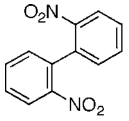
(4) (a) Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37. For recent examples of the Friedländer-type approach to quinolines, see: (b) Hsiao, Y.; Rivera, N. R.; Yasuda, N.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2001**, *3*, 1101. (c) Cho, C. S.; Kim, B. T.; Kim, T.-J. Shim, S. C. *Chem. Commun.* **2001**, 2576. (d) Arcadi, A.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Synlett* **2003**, 203. (e) Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371. (f) McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257. (g) Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467.

10.1021/ol0490375 CCC: $27.50

Scheme 1



of 1-bromo-2-nitroarenes **1** with β-halo-enals **2** and reductive cyclization, in the Friedländer mode, of the resulting β-nitroaryl-enal **3** to give the corresponding quinoline **4**. This approach mirrors that used in our recently disclosed synthesis of indoles[6] and obviates the need to employ stannanes, boronates, or other metalated species as cross-coupling partners. Further, since numerous 1-halo-2-nitroarenes are commercially available and because compounds of the general type **2** can be readily prepared by Vilsmeier haloformylation[7,8] of the appropriate ketone, a wide range of β-nitroaryl-enals **3**, and thence quinolines, are available by the methods described here. The reaction conditions employed for the pivotal cross-coupling reaction (viz., 5 equiv of Cu, 3 mol % Pd[0], DMSO, 80 °C, 2 h) represent a minor modification of those described earlier[6] and, with maintenance of a 1:1 stoichiometry as well as, in certain cases, slow addition of the bromonitrobenzene, then only very modest amounts (<5%) of homo-coupling products such as **5** are generally observed. The effectiveness of these modifications, which cannot be exploited in our indole synthesis, may arise, in part at least, because of the capacity of β-haloenals and -enones to participate in nucleophilic addition-elimination reactions.



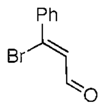
5

Table 1. Quinoline Synthesis via a Pd[0]-Mediated Ullmann Cross-Coupling/Reductive Cyclization Sequence[a]

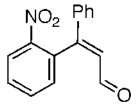
entry	bromo-nitroarene	β-bromo-enal or -enone	cross-coupling product	% yield	quinoline	% yield
1	**1** (R = H)	**6**	**7**	68	**8**	51
2	**1** (R = H)	**9**	**10**	82	**11**	92
3	**1** (R = H)	**12**	**13**	82	**14**	82
4	**1** (R = H)	**15**	**16**	75	**17**	84
5	**1** (R = OMe)	**12**	**18**	88	**19**	68
6	**1** (R = H)	**20**	**21**	71	**22**	46
7	**1** (R = H)	**23**	**24**	73	**25**	61
8	**1** (R = OMe)	**23**	**26**	75	**27**	51
9	**1** (R = H)	**28**	**29**	93	**30**	87
10	**1** (R = OMe)	**28**	**31**	89	**32**	91
11	**1** (R = H)	**33**	**34**	57	**35**	68
12	**1** (R = H)	**36**	**37**[b]	53	**38**	92
13	**1** (R = H)	**39**	**40**	63	**41**	66

[a] Full experimental procedures are given in Supporting Information. [b] This product was accompanied by that arising from homo-coupling of bromoketone **36** (34%).

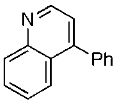
The outcomes of the application of the strategy defined in Scheme 1 to the preparation of a representative series of quinolines are presented in Table 1. Thus, cross-coupling of 1-bromo-2-nitrobenzene **1** (R = H) with (*Z*)-β-bromocinnamaldehyde **6**[8] (entry 1) afforded the *o*-nitroarylated product **7**, which, in turn, underwent reductive cyclization, on exposure to dihydrogen (1 atm) in methanol and in the presence of 10% palladium on carbon or, preferably in this case, to $TiCl_3$ in aqueous acetone, thereby affording 4-phenylquinoline (**8**).[9] The cyclic analogues of **6** (**9**,[8] **12**,[8] and **15**[8]; entries 2−4) engaged in cross-coupling with compound **1** (R = H) to give the corresponding aryl-substituted enals **10**, **13**, and **16**, respectively, each of which then participated in reductive cyclization, under the previously mentioned conditions, to give the [*c*]annulated quinolines **11**,[10] **14**,[11] and **17**,[12] respectively. A related reaction sequence starting from **1** (R = OMe) leads (entry 5), via nitroarene **18**, to quinoline **19**.[13] Hitherto, annulated quinolines of this type have been rather difficult to obtain. The [*b*]annulated quinolines can be obtained by similar means.Thus, each of the compounds **20**[14] and **23**[14] was converted (entries 6 and 7), via the corresponding nitroarenes, **21**[15] and **24**, into quinolines **22**[16] and **25**,[16] respectively. Analogous chemistry using **1** (R = OMe) leads (entry 8), via **26**, to the methoxy derivative, **27**,[17] of quinoline **22**.



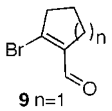
6



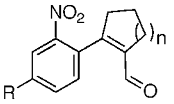
7



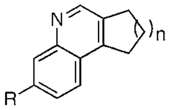
8



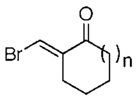
9 n=1
12 n=2
15 n=3



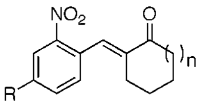
10 n=1, R=H
13 n=2, R=H
16 n=3, R=H
18 n=2, R=OMe



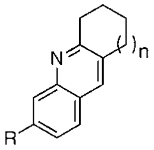
11 n=1, R=H
14 n=2, R=H
17 n=3, R=H
19 n=2, R=OMe



20 n=1
23 n=2



21 n=1, R=H
24 n=2, R=H
26 n=1, R=OMe



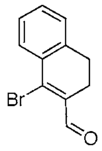
22 n=1, R=H
25 n=2, R=H
27 n=1, R=OMe

The construction of quinolines embedded within more complex frameworks is also possible using the methodologies

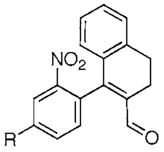
---

(5) (a) Shimizu, N.; Kitamura, T.; Watanabe, K.; Yamaguchi, T.; Shigyo, H.; Ohta, T. *Tetrahedron Lett.* **1993**, *34*, 3421. (b) Banwell, M. G.; Smith, J. A. *Org. Biomol. Chem.* **2003**, *1*, 296. For useful recent reviews on the Ullmann reaction, see: (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (d) Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265.

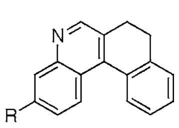
detailed here. For example, the β-bromo-aldehyde **28**[18] (entries 9 and 10, Table 1) cross-couples with **1** (R = H) or **1** (R = OMe) to give compounds **29** and **31**, respectively, which engage in the usual reductive cyclization process, thus affording 7,8-dihydrobenzo[*k*]phenanthridine (**30**)[18] and its 3-methoxy derivative **32**, respectively. In a related vein, the natural product trisphaeridine (**35**)[19] was readily prepared (entry 11), in two steps and via intermediate **34**,[20] by initial cross-coupling of commercially available 6-bromopiperonal (**33**) with **1** (R = H). Alternate and less common modes of ring fusion were achieved by cross-coupling tetralone **36**[21] with **1** (R = H) (entry 12) to give the aryl-substituted tetralone **37**, which participated in a reductive cyclization reaction to give the 5,6-dihydro-4*H*-benz[*kl*]acridine derivative **38**. 2-Formyl-3-iodo-indole **39**[22] engaged in the expected cross-coupling reaction with **1** (R = H) (entry 13) to give product **40**, which underwent smooth reductive cyclization to give 7*H*-indolo[2,3-*c*]quinoline (**41**).[23]



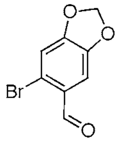
28



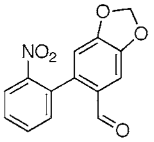
29 R=H
31 R=OMe



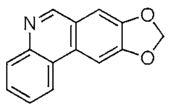
30 R=H
32 R=OMe



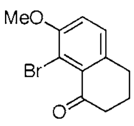
33



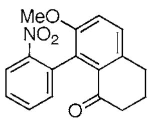
34



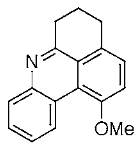
35



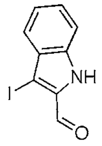
36



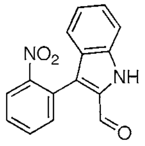
37



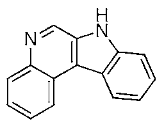
38



39



40



41

The chemistry detailed above can be readily extended to the synthesis of 2-quinolones and phenanthridinones by employing β-bromo-esters as coupling partners (Table 2).

Table 2. 2-Quinolone and Phenanthridinone Synthesis via a Pd[0]-Mediated Ullmann Cross-Coupling/Reductive Cyclization Sequence[a]

entry	bromo-nitroarene	β-bromo-ester	cross-coupling product	% yield	reductive cyclization product	% yield
1	**1** (R = H)	**42**	**43**	39	**44**	78
2	**1** (R = H)	**45**	**46**[b]	nd[c]	**47**	28[d]
3	**1** (R = H)	**48**	**49**	83	**50**	62
4	**1** (R = H)	**51**	**52**	36	**53**	85
5	**1** (R = H)	**54**	**55**	48	**56**	53
6	**1** (R = H)	**57**	**58**[b]	40	**59**	92[e]

[a] Full experimental procedures are given in Supporting Information. [b] This product was accompanied by that arising from homo-coupling of the precursor β-bromo-ester. [c] nd = not determined. [d] Yield over two steps. [e] Yield based on recovered starting material.

Thus, the ester, **42**,[24] derived from aldehyde **12**, can be cross-coupled, under the palladium[0]-catalyzed Ullmann conditions, with 1-bromo-2-nitrobenzene (**1**, R = H) to give the nitro-ester **43** (entry 1), which engages in reductive cyclization on exposure to dihydrogen in the presence of palladium on carbon, thereby affording the 2-quinolone **44**.[25] Phenanthridinones are similarly accessible. Thus, cross-coupling of **1** (R = H) with commercially available methyl 2-iodobenzoate (**45**) afforded biaryl **46**[26] (entry 2). The latter compound engaged in reductive cyclization under the usual conditions to give the parent system **47**, which proved to be identical with commercially available samples. The amino-, methoxy-, and carbomethoxy-substituted derivatives, **50**,[27] **53**,[28] and **56**, are all equally accessible via the reaction sequences implied in entries 3, 4, and 5, respectively, of Table 2 and involving the commercially available bromobenzoates **48**, **51**, and **54** as starting materials. This chemistry has been readily extended to the rapid preparation of the alkaloid crinasiadine (**59**)[19] (entry 6, Table 2). Thus, cross-coupling of compound **1** with the bromo-ester **57**[29] afforded

---

(6) Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. *Org. Lett.* **2003**, *5*, 2497.

(7) Lilienkampf, A.; Johansson, M. P.; Wahala, K. *Org. Lett.* **2003**, *5*, 3387 and references therein.

(8) (a) Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3059. (b) Robertson, I. R.; Sharp, J. T. *Tetrahedron* **1984**, *40*, 3095.

(9) Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117.

(10) Eisch, J. J.; Gopal, H.; Kuo, C. T. *J. Org. Chem.* **1978**, *43*, 2190.

(11) Curran, D. P.; Kuo, S. C. *J. Org. Chem.* **1984**, *49*, 2063.

(12) Case, F. H. *J. Org. Chem.* **1956**, *21*, 1069.

(13) Nicolaou, K. C.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 8908 and references therein.

(14) These compounds were prepared using modifications of the methods reported in the following papers: (a) Bovonsombat, P.; McNelis, E. *Tetrahedron* **1993**, *49*, 1525. (b) Piers, E.; Grierson, J. R.; Lau, K. C.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210. Full details of these preparations will be reported in due course.

(15) Vieweg, H.; Wagner, G. *Pharmazie* **1979**, *34*, 785.

(16) Katritzky, A. R.; Arend, M. *J. Org. Chem.* **1998**, *63*, 9989.

(17) Kar, G. K.; Karmakar, A. C.; Makur, A.; Ray, J. K. *Heterocycles* **1995**, *41*, 911.

(18) Gilchrist, T. L.; Healy, A. M. M. *Tetrahedron* **1993**, *49*, 2543.

(19) Banwell, M. G.; Cowden, C. J. *Aust. J. Chem.* **1994**, *47*, 2235.

(20) Kallianpur, C. S.; Merchant, J. R. *J. Indian Chem. Soc.* **1961**, *38*, 27.

(21) Bohlmann, F.; Fritz, G. *Chem. Ber.* **1976**, *109*, 3371.

(22) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9318.

(23) Clemo, G. R.; Felton, D. G. I. *J. Chem. Soc.* **1951**, 671; *Chem. Abstr.* **1951**, *45*, 9060c.

(24) Jousseaume, B.; Villeneuve, P. *Tetrahedron* **1989**, *45*, 1145.

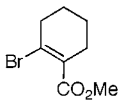
(25) Bailey, A. S.; Seager, J. F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 763.

(26) Muth, C. W.; Elkins, J. R.; DeMatte, M. L.; Chiang, S. T. *J. Org. Chem.* **1967**, *32*, 1106.

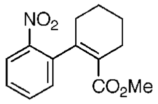
(27) Migachev, G. I.; Grekhova, N. G.; Terent'ev, A. M. *Khimiya Geterotsiklicheskikh Soedinenii* **1981**, 388; *Chem. Abstr.* **1981**, *95*, 42866d.

(28) Swenton, J. S.; Ikeler, T. J.; Smyser, G. L. *J. Org. Chem.* **1973**, *38*, 1157.

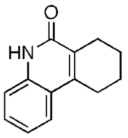
(29) Brown, E.; Robin, J. P.; Dhal, R. *Tetrahedron* **1982**, *38*, 2569.



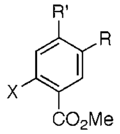
42



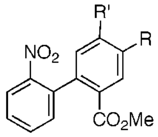
43



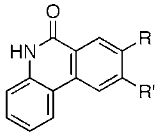
44



45 R=R'=H, X=I
48 R=NO_2, R'=H, X=Br
51 R=OMe, R'=H, X=Br
54 R=H, R'=CO_2Me, X=Br
57 R,R'=OCH_2O, X=Br



46 R=R'=H
49 R=NO_2, R'=H
52 R=OMe, R'=H
55 R=H, R'=CO_2Me
58 R,R'=OCH_2O



47 R=R'=H
50 R=NH_2, R'=H
53 R=OMe, R'=H
56 R=H, R'=CO_2Me
59 R,R'=OCH_2O

biaryl **58** that readily engaged in a reductive cyclization process to give the target natural product, which was identical, in all respects, with an authentic sample.[19]

The foregoing results, when considered in conjunction with our earlier work,[6] should serve to highlight the utility of the Pd[0]-mediated Ullmann cross-coupling reaction in the convergent synthesis of heterocyclic compounds of synthetic and medicinal value.

Acknowledgment. We thank the Alexander von Humboldt Foundation for providing a Feodor Lynen Fellowship to J.R. and the Institute of Advanced Studies for various forms of financial support.

Supporting Information Available: Full experimental details and characterization of compounds **7**, **8**, **10**, **11**, **13**, **14**, **16**−**19**, **21**, **22**, **24**−**27**, **29**−**32**, **34**, **35**, **37**, **38**, **40**, **41**, **43**, **44**, **46**, **47**, **49**, **50**, **52**, **53**, **55**, **56**, **58**, and **59** and ^1H or ^{13}C NMR spectra of compounds **7**, **10**, **13**, **16**, **18**, **21**, **23**, **24**, **26**, **29**, **31**, **37**, **38**, **40**, **41**, **43**, **46**, **49**, **52**, **55**, **56**, and **58**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0490375