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Synthesis of Indoles via Palladium[0]-Mediated Ullmann Cross-Coupling of *o*-Halonitroarenes with α-Halo-enones or -enals

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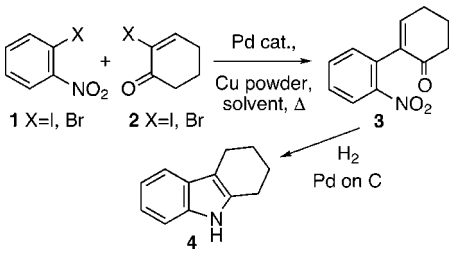
ABSTRACT



Palladium[0]-mediated Ullmann cross-coupling of *o*-halonitrobenzene (1) and various related nitroarenes with a range of α-halo-enones (e.g., 2) or -enals readily affords the expected α-arylenones, e.g., 3, or -enals, which are converted into the corresponding indoles, e.g., 4, on reaction with dihydrogen in the presence of Pd on C.

The indole moiety represents a key substructure associated with many biologically active natural products and medicinal entities.[1] Various methods[1,2] have been developed for the construction of this ring system. The most well-known and venerable is the Fischer indole synthesis[2] wherein an arylhydrazine is condensed with a enolizable ketone to give, after loss of ammonia, the corresponding 2,3-disubstituted heterocycle. While being an enormously important procedure, this approach suffers from a number of drawbacks, not the least being the rather harsh reaction conditions required to effect [3,3]-sigmatropic rearrangement of the initially produced hydrazone and the lack of regiocontrol available when employing ketones that can exist in more than one enolic form. These difficulties have been addressed by Rawal and co-workers[3] through the coupling of *o*-nitrophenylphenyliodonium fluoride (NPIF) with various trimethylsilyl enol ethers followed by $TiCl_3$-induced reductive cyclization of the resulting α-(*o*-nitrophenyl)ketone to give 2,3-disubstituted indoles. The NPIF employed in such conversions is produced over two steps from the corresponding *o*-iodonitroarene, while the TMS-enol ether can be generated through 1,4-reduction/enolate trapping of the relevant enone or enolization of the appropriate ketone under conditions of kinetic or thermodynamic control followed by trapping with chlorotrimethylsilane. In recent and related work, Scott and Söderberg have reported[4] that the products of Stille cross-coupling of *o*-(tri-*n*-butylstannyl)nitrobenzene with various α-iodocycloalkenones engage in a novel metal-catalyzed reductive N-heteroannulation in the presence of 6 atm of CO to give 1,2-dihydro-4(3*H*)-carbazolones. In Shibasaki's recently communicated[5] synthesis of (−)-strychnine, the indole

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(2) (a) Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607.

(3) Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673.

(4) Scott, T. L.; Söderberg, B. C. G. *Tetrahedron Lett.* **2002**, *43*, 1621.

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Table 1. Optimization of Conditions for Coupling Reaction **1** + **2** → **3**

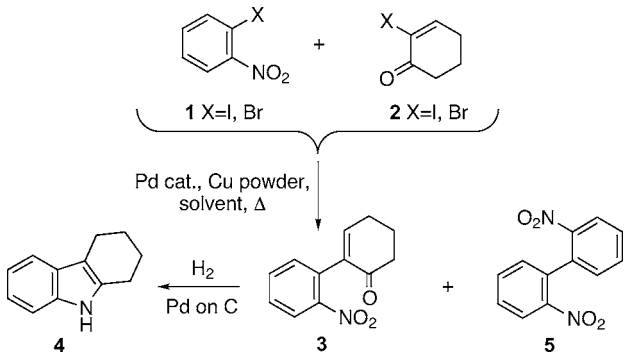
entry	halide **1** (mmol)	halide **2** (mmol)	catalyst[a,b] (equiv of Cu)[c]	solvent	temp (°C)/time (h)	% yield[d] (of **3**)
1	X = I (1.0)	X = I (0.5)	A (10)	DMSO	90/1	80
2	X = I (1.0)	X = I (0.5)	A (10)	DMSO	70/1	74
3	X = I (1.0)	X = I (0.5)	A (10)	DMSO	50/21	83
4	X = I (1.0)	X = I (0.5)	A (10)	DMF	70/5	58
5	X = I (1.0)	X = I (0.5)	A (10)	NMP	70/30	67
6	X = I (1.0)	X = I (0.5)	A (10)	DME	70/30	no rxn
7	X = I (1.0)	X = I (0.5)	B (10)	DMSO	50/1	91
8	X = I (1.0)	X = I (0.5)	C (10)	DMSO	50/3	85
9	X = I (1.0)	X = I (0.5)	D (10)	DMSO	50/4	89
10	X = Br (1.0)	X = Br (0.5)	B (10)	DMSO	70/2	88
11	X = I (5.0)	X = Br (0.5)	B (10)	DMSO	70/6	72
12	X = Br (1.0)	X = I (0.5)	B (10)	DMSO	70/1.5	88
13	X = I (1.0)	X = I (0.5)	B (5)	DMSO	70/1	87[e]

[a] Catalysts: A = $Pd(PPh_3)_4$; B = $Pd_2(dba)_3$; C = $PdCl_2(dppf)$; D = $Pd(OAc)_2$. [b] Catalyst loadings of 6 mol % were used in these optimization studies. [c] Equiv with respect to **2**. [d] Yield calculations based on quantities of **2** employed. [e] Yield of homocoupling product **5** was 51%.

residue is assembled via Stille cross-coupling of an α-iodocyclohexenone with *o*-(tri-*n*-methylstannyl)nitrobenzene and then reductive cyclization of the coupling product with zinc in methanolic aqueous ammonium chloride. In an especially important development, Buchwald and co-workers have demonstrated[6] that methyl and certain other enolizable ketones can couple with *o*-chloro- or *o*-bromonitrobenzenes in the presence of $Pd_2(dba)_3$ and phenolic additives to give α-(*o*-nitroaryl)ketones that undergo reductive cyclization to the corresponding indoles on exposure to $TiCl_3/NH_4OAc$. It is against this background that we now report a complementary and operationally simple two-step indole synthesis that employs readily available starting materials and reagents, avoids the need for using stannanes or hypervalent iodine-containing species, and still addresses the deficiencies associated with, inter alia, the Fischer indole synthesis (vide supra).

The essential aspects of our approach are shown in Scheme 1 with the pivotal step involving a palladium[0]-mediated

Scheme 1



Ullmann cross-coupling reaction[7,8] of an *o*-iodo- or *o*-bromonitrobenzene, e.g., **1**, with an α-halo-α,β-unsaturated ketone, e.g., **2**, or aldehyde. Reduction of the ensuing coupling product, e.g., **3**, with dihydrogen in the presence of Pd on C then affords the target indole, e.g., **4**. The requisite α-halo-enones or -enals are readily obtained by halogenation of the corresponding enone or enal according to the simple and highly effective procedures reported by Johnson[9a] and Smith.[9b]

Preliminary studies were focused on optimization of the coupling reaction **1** + **2** → **3**[10] and involved efforts to identify the most effective solvent, catalyst, temperature, stoichiometry, etc. The results of such studies are summarized in Table 1 and reveal that DMSO is the best solvent and that reaction temperatures of 50−70 °C are required. A range of palladium catalysts can be employed, including $Pd(OAc)_2$, which is presumably reduced to an active Pd[0] species by the copper powder. Not surprisingly, efficient and rapid reactions are observed with the iodinated versions of coupling partners **1** and **2**, although their brominated counterparts can also be employed, either together (see entry 10) or individually (see entries 11 and 12). In contrast, neither *o*-chloronitrobenzene (**1**, X = Cl) nor *o*-nitrophenyl triflate (**1**, X = OTf) could be induced to couple with **2** (X = I) under any of the conditions defined in Table 1. In the optimization experiments, ca. 5−10 equiv (with respect to **2**) of copper powder were employed and the chromatographically separable byproduct **5**,[8] arising from homocoupling of **1**, was always observed. This unwanted process could be suppressed, although generally not completely eliminated, by reducing the amount of iodoarene employed and/or by slow addition of compound **1** to the reaction mixture. Bearing such

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(6) Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168.
(7) Shimizu, N.; Kitamura, T.; Watanabe, K.; Yamaguchi, T.; Shigyo, H.; Ohta, T. *Tetrahedron Lett.* **1993**, *34*, 3421.
(8) Banwell, M. G.; Smith, J. A. *Org. Biomol. Chem.* **2003**, *1*, 296.
(9) (a) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917. (b) Smith, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855 (see also: Ramanarayanan, G. V.; Shukla, V. G.; Akamanchi, K. G. *Synlett* **2002**, 2059).
(10) Compound **3** has previously been obtained via mutlistep reaction sequences: (i) ref 4. (ii) Solé, D.; Bosch, J.; Bonjoch, J. *Tetrahedron* **1996**, *52*, 4013.

outcomes in mind, the optimal conditions, in terms of a favorable time/yield ratio, for effecting this Ullmann-type coupling were considered to involve those shown in entry 13 and employing 5 equiv of copper at 70 °C for 1 h. The predominance of the cross-coupling product in these reactions is consistent with the mechanistic proposals advanced by Shimizu et al.[7]

Conversion of coupling product **3** into the annulated indole **4** was best effected by reduction of the former compound with dihydrogen (at 1 atm) in the presence of 10% Pd on C. The spectral data derived from the carbazole **4**[11] so obtained proved to be identical, in all respects, with those of an authentic sample. Conversion **3** → **4** proceeded in essentially quantitative yield, as judged by ^{1}H NMR analysis of the crude reaction mixture, but attempts to rigorously purify this slightly air- and light-sensitive product by flash chromatography resulted in some decomposition. As a consequence, only a ca. 60% yield of analytically pure **4** was finally obtained. Nevertheless, this reductive cyclisation procedure proved to be perfectly adequate in carrying forward related coupling products to the target indoles (vide infra).

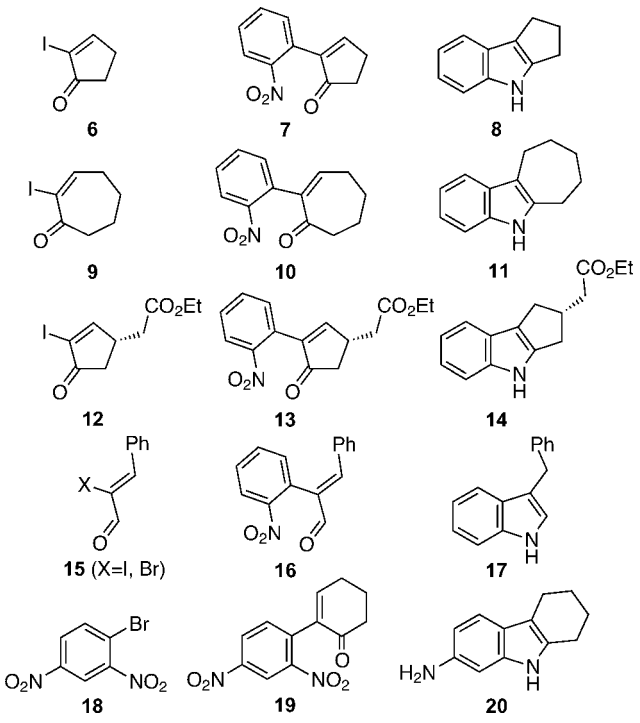
The reaction conditions established above for the first step of the two-step conversion shown in Scheme 1 were applied to a range of other coupling partners, with the products then being reduced to the corresponding indoles. The relevant structures are shown below and outcomes of these reaction sequences presented in Table 2. Thus, the lower homologue

Table 2. Indole Synthesis via an Ullmann Coupling/Reductive Cyclization Sequence

entry	nitro-arene	enone/enal	cross-coupling product[a]	% yield	% yield of 2,2′-dinitro-biphenyl	indole	% yield
1	**1** (X = I)	**6**	**7**	75	46[c]	**8**	90
2	**1** (X = I)	**9**	**10**	66	55[c]	**11**	72
3	**1** (X = I))	**12**	**13**	68	48[c]	**14**	90
4	**1** (X = I)	**15** (X = I)	**16**	67	54[c]	**17**	88
5	**1** (X = Br)	**15** (X = Br)	**16**	50	52	**17**	88
6	**18**	**2** (X = I)	**19**	82	46[d]	**20**	80
7	**21**	**2** (X = I)	**22**	80	56[e]	**23**	97
8	**24**	**2** (X = I)	**25**	71	56[f]	**4**	90
9			**26**[b]	77		**28**	77[g]
10	**1** (X = I)	**29**	**30**	64	45[c]	**31**	92
11	**1** (X = Br)	**29** (X = Br)	**30**	64	47[c]	**31**	92
12	**1** (X = I)	**32**	**33**	75	53[c]	**34**	88

[a] Reaction conditions defined in entry 13, Table 1, were employed for the Ullmann couplings listed here. [b] Product obtained via Suzuki−Miyaura cross-coupling of compound **25** with 1,3-benzodioxol-5-ylboronic acid. [c] Yield of compound **5**. [d] Yield of 2,2′,4,4′-tetranitrobiphenyl (see Supporting Information for spectral data). [e] Yield of 2,2′-dimethoxy-4,4′-dinitrobiphenyl.[7] [f] Yield of 4,4′-dibromo-2,2′-dinitrobiphenyl (see: Yamoto, T.; Hideshima, C.; Suehiro, K.; Tashiro, M.; Surya Prakash, G. K.; Olah, G. A. *J. Org. Chem.* **1991**, *56*, 6248). [g] Yield after an extended reaction time (see text and Supporting Information).

of **2** (X = I), viz. compound **6**,[9] coupled with compound **1** (X = I) and the resulting product, **7**,[4] was then converted into the corresponding indole, **8**,[12] using the reductive cyclization procedure defined above. An analogous sequence applied to cycloheptenone **9**[4] produced, via intermediate **10**,[4] the hexahydrocyclohept[*b*]indole **11**[13] in an efficient manner. Cross-coupling of the enantiomerically pure α-iodocyclopentenone **12**[14] with *o*-iodonitrobenzene afforded product **13**, which underwent reductive cyclization to give the indole **14**. Exploitation of the readily available α-halocinnamaldehyde **15** (X = I or Br)[15] in an analogous sequence leading, via **16**, to compound **17**[16] demonstrates that this methodology can be applied to the preparation of non-annulated indoles. The application of more highly substituted *o*-halonitrobenzenes to the synthesis of indoles is highlighted in entries 5−7 of Table 2. Thus, coupling of 2,4-dinitrobromobenzene **18** with iodoenone **2** (X = I) afforded the expected product **19**, which upon reductive cyclization gave the especially air-sensitive 7-amino-substituted tetrahydrocarbazole **20**.[17] A related sequence employing the methoxy-substituted arene **21** affords, via intermediate **22**,[4] the analogous methoxylated system **23**.[18] Interestingly, the dibromonitrobenzene **24** engages in a regioselective cross-coupling reaction with compound **2** (X = I) to give compound **25**, the structure of which follows from its reductive cyclization, with accompanying debromination, to compound **4**.



The bromo-substituent of compound **25** can be exploited in cross-coupling reactions prior to implementing the reductive cyclization process. Thus, Suzuki−Miyaura reaction of this arene with 1,3-benzodioxol-5-ylboronic acid[19] afforded prod-

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(17) Kuehne, M. E. *J. Am. Chem. Soc.* **1962**, *84*, 837.
(18) Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767.
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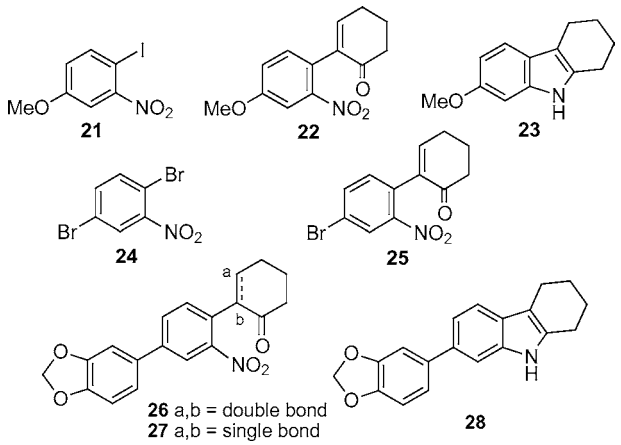
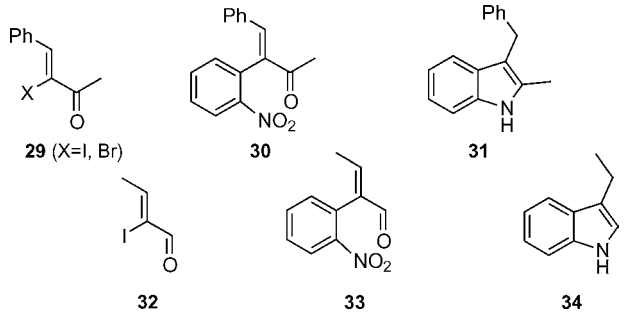
uct **26**, which engaged in the expected reductive cyclization reaction to give indole **28**, although if the usual reaction time (0.75 h) was used then this was accompanied by roughly equal amounts of compound **27**. However, simply running the reaction overnight led to complete and efficient conversion into the indole.



The successful conversion of readily available halo-enone **29** (X = I,[9a] X = Br[20]), via coupling product **30**, into indole **31**[21] highlights the capacity to employ open-chain α-halo-enones in the present cross-coupling/reductive cyclization protocol. The similarly successful conversion of the α-iodocrotonaldehyde **32**, via nitroarene **33**, into 3-ethylindole (**34**)[22] serves to further emphasize the utility of the present work, which provides an exceptionally simple means of gaining access to a wide range of derivatives of the title heterocycle.



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Supporting Information Available: Preparation and characterization of compounds **3**, **4**, **7**, **8**, **10**, **11**, **13**, **14**, **16**, **17**, **19**, **20**, **22**, **23**, **25**−**28**, and **30**−**34** and ^{1}H NMR spectra of compounds **4**, **7**, **8**, **10**, **11**, **13**, **14**, **16**, **19**, **20**, **22**, **23**, **25**−**28**, and **30**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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