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New protocols for the synthesis of 3,4-annulated and 4-substituted quinolines from β-bromo-α,β-unsaturated aldehydes and 1-bromo-2-nitrobenzene or 2-bromoacetanilide

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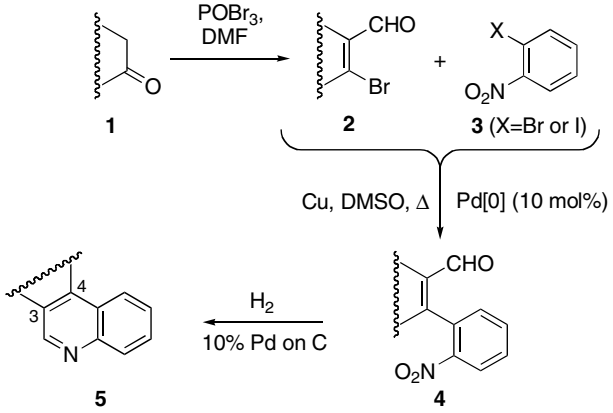
Abstract—The palladium[0]-mediated Ullmann cross-coupling of readily available β-bromo-α,β-unsaturated aldehydes of the general form **2** with 1-bromo-2-nitrobenzene (**3**, X = Br) delivers products, **4**, that undergo reductive cyclization to novel quinolines (**5**) upon exposure to indium in aqueous ammonium chloride or to Raney-nickel in the presence of dihydrogen. Analogous cross-coupling of 2-bromoacetanilide (**6**) with **2** affords products of type **7** that undergo in situ and K_2CO_3-mediated cyclization to give the same types of quinolines (**5**).

1. Introduction

Quinolines and the related 4-quinolones represent important classes of compound that have found manifold applications in medicinal chemistry by virtue of their broad range of pharmacological properties.[1] Accordingly, numerous methods for the assembly of the quinoline ring system have been developed with the most well recognized being the Skraup,[2] Doebner–Miller,[2] Friedlander[3] and Combes[4] protocols, all of which likely involve an initial and intermolecular reaction of an aniline with a carbonyl-containing compound or a precursor thereof. Certain disadvantages apply to these procedures, most notably the need to employ strongly acidic conditions along with sometimes refractory substrates such as *o*-aminobenzaldehydes (as required in the Friedlander synthesis). Recently, we developed a new protocol for the preparation of quinolines (Scheme 1)[5] involving the subjection of certain enolizable (and often cyclic) ketones **1** to a Vilsmeier–Haack haloformylation reaction,[6] then engaging the resulting β-bromo-α,β-unsaturated aldehyde, **2**[7] in a



Scheme 1.

Pd[0]-mediated Ullmann cross-coupling reaction[8] with 1-bromo- or 1-iodo-2-nitrobenzene (**3**) so as to generate the corresponding β-(*o*-nitrophenyl)-α,β-unsaturated aldehyde **4**. Subjection of this last type of compound to reductive cyclization using dihydrogen in the presence of 10% Pd on C or a large excess of $TiCl_3$ then gave the target quinoline **5**. Despite the likely utility of this method for the preparation of quinolines, a disadvantage is the somewhat variable yields observed in the reductive cyclization process when this is carried out under the conditions just described. A further limitation to the

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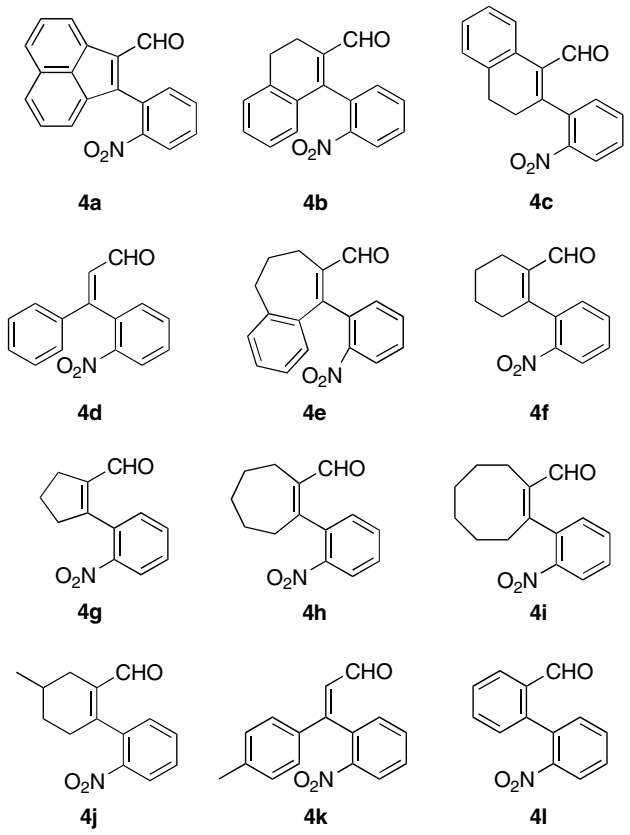
exploitation of the Pd[0]-mediated Ullmann cross-coupling reaction in the preparation of nitrogen heterocycles,[8] including quinolines,[5] is the apparent need to use coupling partners that incorporate strongly electron-withdrawing substituents such as nitro-groups. Herein, therefore, we detail significant modifications to our previously reported protocols that (i) allow for the efficient and conveniently executed reductive cyclization of compounds of the general form **4** by indium metal in ammonium chloride[9] or by exposure to Raney-nickel[10] in the presence of dihydrogen and (ii) permit the one-pot assembly of quinolines by cross-coupling of *N*-acetyl-*o*-bromoacetanilides with β-bromo-α,β-unsaturated aldehydes, then in situ and K_2CO_3-mediated cyclization of the product β-[*o*-(*N*-acetylamino)phenyl]-α,β-unsaturated aldehyde to quinolines. Such protocols are exemplified through the generation of both previously reported and new quinoline derivatives.

2. Results and discussion

The series of β-(*o*-nitrophenyl)-α,β-unsaturated aldehydes, **4a–k**, used for the reductive cyclization studies was generated in good to excellent yields (Table 1) by treating the appropriate β-bromo-α,β-unsaturated aldehyde **2** with 1-bromo-2-nitrobenzene (**3**, X = Br) under the previously described Pd[0]-mediated Ullmann cross-coupling conditions, viz. using DMSO in the presence of Cu powder and ca. 10 mol % of $Pd(PPh_3)_4$ at 80–85 °C for 4–6 h. No products arising from homo-coupling of substrates **2a–k** or **3** (X = Br) were observed. The cross-coupling product **4l** was also prepared by analogous methods from compound **3** (X = Br) and *o*-bromobenzaldehyde. The β-(*o*-nitrophenyl)-α,β-unsaturated aldehydes **4a**, **4c**, **4e**, **4i**, **4j** and **4k** so formed have not been reported previously. However, the spectral data derived from these cross-coupling products were entirely consistent with the assigned structures.[14]

The reductive cyclization of each of the β-(*o*-nitrophenyl)-α,β-unsaturated aldehydes **4a–k** could be effected using either indium metal/NH_4Cl or Raney-nickel (Ra-Ni) in the presence of dihydrogen. In each instance the expected quinoline, **5a–k**, was obtained. Subjection of the related aromatic aldehyde **4l** to the same conditions afforded phenanthridine **5l**. Details of the outcomes of these cyclizations are presented in Table 2 and reveal that the Ra-Ni/H_2 protocol is superior, in terms of the yield of the product quinolines, although the dissolving metal method involving indium is still a rather effective one. With the exception of compounds **5a** and **5e**, each of the product quinolines has been prepared previously and the derived spectral data matched those reported.

The route shown in Scheme 2 has also been used to prepare the same quinoline derivatives, viz. compounds **5a–l**. Thus, the β-bromo-α,β-unsaturated aldehydes **2a–k** as well as *o*-bromobenzaldehyde each engages in an efficient Pd[0]-mediated Ullmann cross-coupling reaction with 2-bromoacetanilide (**6**) under the same conditions employed earlier and so providing products of type **7**.



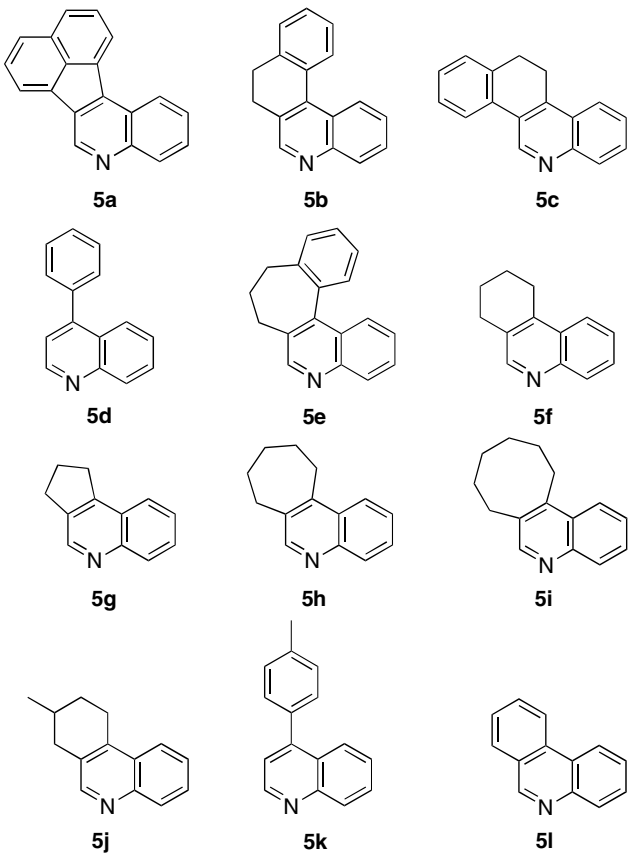
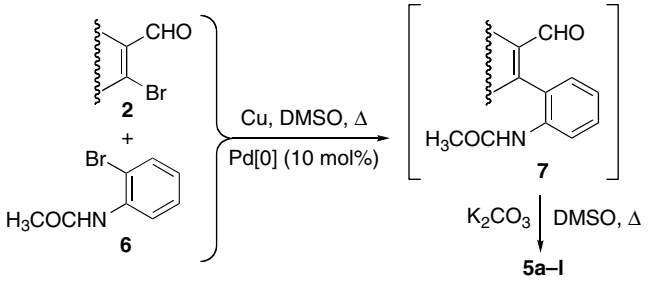


Table 1. Yields of products **4a–l** derived from the Pd[0]-mediated Ullmann cross-coupling of various β-bromo-α,β-unsaturated aldehydes (**2**) with 1-bromo-2-nitrobenzene (**3**, X = Br)

Entry	Substrate	Reaction time (h)	Product	Yield (%)
1	2-Bromoacenaphthylene-1-carbaldehyde (**2a**)	4	**4a**	80
2	1-Bromo-3,4-dihydro-2-naphthalenecarbaldehyde (**2b**)[5]	4.5	**4b**[5]	78
3	2-Bromo-3,4-dihydro-1-naphthalenecarbaldehyde (**2c**)[11]	4.5	**4c**	72
4	*Z*-3-Bromo-3-phenylpropenal (**2d**)[5]	5	**4d**[5]	80
5	9-Bromo-6,7-dihydro-5*H*-benzocycloheptene-8-carbaldehyde (**2e**)[12]	5	**4e**	75
6	2-Bromo-1-cyclohexene-1-carbaldehyde (**2f**)[5]	4.5	**4f**[5]	85
7	2-Bromo-1-cyclopentene-1-carbaldehyde (**2g**)[5]	4.5	**4g**[5]	85
8	2-Bromo-1-cycloheptene-1-carbaldehyde (**2h**)[5]	4.5	**4h**[5]	85
9	2-Bromo-1-cyclooctene-1-carbaldehyde (**2i**)[6a]	4.5	**4i**	78
10	2-Bromo-5-methyl-1-cyclohexene-1-carbaldehyde (**2j**)[13]	5	**4j**	82
11	3-Bromo-3-*p*-tolylpropenal (**2k**)	5	**4k**[14]	82
12	*o*-Bromobenzaldehyde	4	**4l**[15]	85

Table 2. Yields of quinolines **5a–l** derived from the reductive cyclization of β-(*o*-nitrophenyl)-α,β-unsaturated aldehydes **4** with In/NH_4Cl and Ra-Ni/H_2

Entry	Substrate	Product	Yield (%)/Reaction time (h)	
			With In/NH_4Cl	With Ra-Ni/H_2
1	**4a**	**5a**	81/2	90/2
2	**4b**	**5b**[5]	84/2	95/2
3	**4c**	**5c**[16]	80/2	90/2
4	**4d**	**5d**[5]	86/1.5	95/1.5
5	**4e**	**5e**	82/2	90/2
6	**4f**	**5f**[5]	85/1.5	95/1.5
7	**4g**	**5g**[5]	85/1.5	95/1.5
8	**4h**	**5h**[5]	85/1.5	95/1.5
9	**4i**	**5i**[17]	82/2	92/2
10	**4j**	**5j**[18]	82/2	92/1.5
11	**4k**	**5k**[19,20]	82/2	95/1.5
12	**4l**	**5l**[21]	85/2	92/1.5



Scheme 2.

However, these were not isolated but, rather, immediately treated, in situ, with K_2CO_3. In this manner, the expected heterocycles **5a–l** were obtained in preparatively useful yields (Table 3). As such, this sequence provides a complementary route to quinolines.

In summary, we have developed two short, distinct and complementary methods for the synthesis of various 3,4-annulated and 4-substituted quinolines from β-bromo-α,β-unsaturated aldehydes (**2**) and either 1-bromo-2-nitrobenzene (**3**, X = Br) or 2-bromoacetanilide (**6**). New protocols for the reductive cyclization of compounds of the general form **4** have been identified and these should prove broadly applicable to the preparation of quinolines bearing a range of different functional groups.

Table 3. Yields of quinolines **5a–l** derived from sequential cross-coupling of β-bromo-α,β-unsaturated aldehydes **2a–k** or *o*-bromobenzaldehyde with 2-bromoacetanilide (**6**), then in situ and base-promoted cyclization of product **7** with K_2CO_3

Entry	Substrate	Product	Yield (%)
1	**2a**	**5a**	61
2	**2b**	**5b**	65
3	**2c**	**5c**	63
4	**2d**	**5d**	67
5	**2e**	**5e**	60
6	**2f**	**5f**	70
7	**2g**	**5g**	70
8	**2h**	**5h**	70
9	**2i**	**5i**	65
10	**2j**	**5j**	66
11	**2k**	**5k**	69
12	*o*-Bromobenzaldehyde	**5l**	70

3. Typical experimental procedures

3.1. For the palladium[0]-catalyzed Ullmann cross-coupling reaction

A magnetically stirred mixture of the appropriate β-bromo-α,β-unsaturated aldehyde **2** (1.0 mmol), 2-bromonitrobenzene (**3**, X = Br) or 2-bromoacetanilide (**6**) (1.0 mmol), copper powder (8.2 mmol of ~35 micron material) and $Pd(PPh_3)_4$ (10 mol % w.r.t. **2**) in DMSO (3 mL) was degassed for 15 min, then heated at 85 °C under an argon atmosphere for 4–6 h. For coupling processes involving substrate **6**, anhydrous K_2CO_3 (5.5 mmol) was added to the reaction mixture and stirring continued at 80–85 °C for a further 2 h. The cooled reaction mixture was diluted with ethyl acetate (20 mL), then filtered. The filtrate was washed with water (5 × 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The material thus obtained was subjected to column chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the relevant fractions, the corresponding β-(*o*-nitrophenyl)-α,β-unsaturated aldehyde **4** or quinoline **5**.

3.2. For the reductive cyclization of β-(*o*-nitrophenyl)-α,β-unsaturated aldehydes (4)

(i) *Using indium and ammonium chloride in aqueous ethanol:* A magnetically stirred solution of the relevant β-(*o*-nitrophenyl)-α,β-unsaturated aldehyde **4** (0.1 mmol) in ethanol (10 mL) was treated with indium powder (0.3 mmol) then ammonium chloride (0.3 mmol) in water (2 mL) was added and the resulting mixture heated at reflux for 2 h. The cooled reaction mixture was concentrated under reduced pressure and the residue diluted with water (30 mL) and extracted with ethyl acetate (2×30 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The material thus obtained was subjected to preparative thin layer chromatography. Extraction of the appropriate band afforded the corresponding quinoline **5**.

(ii) *Using Ra-Ni and dihydrogen:* A magnetically stirred solution of the relevant β-(*o*-nitrophenyl)-α,β-unsaturated aldehyde **4** (0.1 mmol) in ethanol (20 mL) was treated with a suspension of Ra-Ni in ethanol (10 mL). Dry dihydrogen was gently bubbled through the mixture and after 2 h the solid was removed by filtration. The filtrate was concentrated under reduced pressure and the residue subjected to preparative thin layer chromatography. Extraction of the appropriate band afforded the corresponding quinoline **5**.

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14. *Selected spectral data*: Compound **4k**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 6.70 (d, $J = 8.0$ Hz, 1H), 7.16 (m, 4H), 7.47 (dd, $J = 8.0$ and 1.5 Hz, 1H), 7.69 (tm, $J = 8.0$ Hz, 1H), 7.77 (tm, $J = 8.0$ Hz, 1H), 8.24 (dm, $J = 8.0$ Hz, 1H), 9.40 (br d, $J = 8.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 125.2, 125.9, 127.1, 129.5, 130.2, 132.0, 133.0, 133.3, 134.3, 141.4, 148.2, 158.4, 191.6; IR ν_{max} (neat)/cm^{-1} 2923, 2852, 1667, 1591, 1526, 1345, 1132, 818; MS *m*/*z* (EI) 267 ($M^{+\cdot}$, 28%), 252 (22), 238 (100), 210 (99), 91 (77); HRMS found $M^{+\cdot}$, 267.0890; $C_{16}H_{13}NO_3$ requires $M^{+\cdot}$, 267.0895.
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20. *Selected spectral data*: Compound **5k**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.31–7.38 (complex m, 3H), 7.39–7.45 (complex m, 2H), 7.49 (m, 1H), 7.72 (m, 1H), 7.94 (dm, $J = 8.4$ Hz, 1H), 8.18 (dm, $J = 8.4$ Hz, 1H), 8.93 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 121.0, 125.6, 126.2, 126.5, 128.9(7), 128.9(9), 129.1, 129.5, 134.7, 138.0, 148.2, 148.4, 149.6; IR ν_{max} (neat)/cm^{-1} 3028, 2922, 1614, 1586, 1502, 1460, 1421, 1390, 1022, 819, 763, 674, 662; MS *m*/*z* (EI) 219 ($M^{+\cdot}$, 100%), 218 (88), 204 (78), 109 (42); HRMS found $M^{+\cdot}$, 219.1049; $C_{16}H_{13}N$ requires $M^{+\cdot}$, 219.1048.
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