Versatile Synthesis of 3-Arylindan-1-ones by Palladium-Catalyzed Intramolecular Reductive Cyclization of Bromochalcones

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Received 5 July 2004; revised 22 September 2004

Abstract: We have developed a novel and versatile synthesis of racemic 3-arylindan-1-ones by palladium-catalyzed intramolecular reductive cyclization of bromochalcones. This method is especially attractive because it avoids strong acidic conditions and consequently a larger number of sensitive functional groups are accepted during synthesis compared with existing methods.

Key words: 3-arylidan-1-ones, palladium, reductive cyclization, chalcone, intramolecular

3-Arylindan-1-ones 1 (Figure 1) are versatile key intermediates in the syntheses of a number of biologically active compounds.

Prominent examples are the antidepressant indatraline (2),1 the antipsychotic tefludazine (3),2 the drug tolterodine (4),3 and many others.3–8 Furthermore, 3-aryl-1-indanones can also be used directly as anti-inflammatories, antipyretics or analgesics.9 Previously, 4 different routes to 3-arylidan-1-ones have mainly been applied (Scheme 1).10

The routes A–C (Scheme 1) all utilize intramolecular electrophilic aromatic substitution under rather harsh and strongly acidic conditions from 3,3-diphenylpropionic acids (5A), 3,3-diphenylpropionyl chlorides (5B) and 1,3-diphenylpropenones (chalcones, 6), respectively. Even in the versatile ‘enamine route’ (Route D), where a methyl 3-
amino-1-phenyl-1-cyano-1H-indene-2-carboxylate is assembled by nucleophilic aromatic substitution of an aryl acetonitrile on an ortho-halogen-substituted cyano aramote followed by alkylation with methyl chloroacetate and subsequent intramolecular Dieckmann-type reaction to the enamine 7, the final 3-arylindan-1-ones are obtained only after heating under strongly acidic conditions. Recently, a stereoselective synthesis of an (S)-3-arylindan-1-one 1a from a 3-arylinden-1-one 9a was described by Clark et al. via stereoselective reduction of the intermediate keto group in 9a and subsequent base-induced stereoselective sigmatropic hydrogen rearrangement of the allylic alcohol 10a (Scheme 2).6a Recently, Clark et al. also described a stereoselective synthesis of (S)-3-arylindan-1-one 1a from 3-arylinden-1-one 9a by enantioselective reduction of the intermediate alkene moiety in 9a.6b Although the two different stereoselective syntheses described by Clark et al. are very elegant, they have only been shown to work with electron-donating aromatic substituents.

Furthermore, the methods described by Clark et al. only give access to the (S)-3-arylindan-1-one contrary to many of the CNS active 3-arylindanes which posses the (R)-3-aryl configuration.4,11,12 The indene 9a was synthesized by Clark et al. from 2¢-bromochalcone 8a by an intramolecular Heck reaction.6a During our work on the syntheses of CNS-active compounds like 2 and 3 we attempted the analogous Heck-reaction, but besides the expected indene 9 (Scheme 3) we observed also small and variable amounts of the reduced racemic indanone 1.

In order to avoid the two-step cyclization and reduction from 8 over 9, we decided to try to develop a direct indanone synthesis from the 2¢-bromochalcone 8. The 2¢-bromochalcones 8b–j are easily available by condensing 2¢-bromoacetophenone with various substituted benzaldehydes under basic conditions.

Several reports in the literature have dealt with the synthetic challenge of intermolecular palladium-catalyzed hydroarylation reactions of α,β-unsaturated carbonyl compounds and aryl halides (formal conjugate Michael addition).13 It is apparent from these literature reports, that there is generally a competition between vinylic substitution resulting in the Heck reaction and hydroarylation resulting in the conjugate addition. When translating this into the indane-based substrates, it corresponds to a competition between formation of products 3-arylinden-1-one 9 (Heck product) and 3-arylindan-1-one 1 (hydroarylation product). We observed that we could push the balance towards the hydroarylated conjugate addition product 1 as the main product when using an organic base, e.g. triethylamine as opposed to an inorganic base, e.g. K2CO3. Presumably, triethylamine acts here as a hydride source as is well known for Pd-catalyzed reactions.13 From earlier reports it appears that the balance between Heck and hydroarylation depends on an intriguing combination of steric, electronic and medium effects.14 Realizing this, we decided to approach the problem by multivariate analysis. We used the chalcone 8b derived from 4-fluorobenzaldehyde as a substrate because electron-deficient olefins are known to be the most difficult substrates. When using electron-deficient chalcones, we generally observed as the main product the dehalogenated reduced ketone 11 (Scheme 4). Hence, we reasoned that if we could optimize the reaction with the difficult electron-withdrawing fluoro substituent, we would expect the reaction to work also with more ‘easy’ substrates. We used DoE (modde 6.0) to design 60 experiments, which were carried out on a 1 mmol scale and analyzed by GC-MS. In these experiments triethylamine was used as the only base and di-
methylnonacetamide (DMA) was used as the solvent. Various Pd sources [Pallacycle, PdCl₂, Pd(dpdp)₂, Pd(OAc)₂, Pd(PPh₃)₂Cl₂, POPd₁, POPd, PdCl₂MeCN₂, Pd-103 and PD-dba] combined with different phosphine ligands [none, PPh₃, P(o-Tol), P(terr-Bu)₃, P(furfuryl)₃ and P(OPh)₃] were screened. The semi-optimized procedure obtained this way, was: Pd(PPh₃)₂Cl₂ (1 mol%), DMA as solvent (0.1 M), triethylamine (2 equiv) as base and a temperature of 140 °C. However, when these reaction conditions were used to try to ring-close the chalcone derived from 3,4-dichlorobenzaldehyde (8e), we surprisingly observed that no product was formed. A closer inspection of the reaction set-up revealed, that the most likely cause was that triethylamine (bp 89 °C) was not efficiently refluxed back into the reaction mixture. We therefore decided to screen a number of higher boiling amines. The two best turned out to be tributylamine (NBu₃) and cyclohexylamine. Since the latter performed slightly better, this was chosen as the preferred base. Furthermore, it was found that DMF and DMA performed equally well and since DMF is easier to remove by evaporation, DMF was chosen as the preferred solvent. Finally the temperature was increased to 155 °C in order to speed up the reaction. Furthermore, we also investigated the effect of the type of halogen used and observed no difference in cyclization efficiency using either 2'-bromo- or 2'-iodochalcone. Thus, the chalcone derived from condensing 2'-iodochalcone to 4-fluorobenzaldehyde gave the same purified yield of indanone 8b as using 2'-bromoacetophenone (69% versus 72%). The optimized procedure obtained this way (Method A) was: Pd(PPh₃)₂Cl₂ (1 mol%), DMF as solvent (0.5 M), N,N-dimethylcyclohexylamine (2 equiv) as base and a temperature of 155 °C. The isolated yields using Method A were satisfactory ranging from 58–83% (Table 1). We were able to further optimize the reaction conditions by using microwave conditions (Method B). Thereby the reaction time was decreased from approximately 1–2 hours to 15 minutes. Generally, we did not observe any major differences in the yields between the two heating methods.

The yields using Method B were satisfactory ranging from 33–83% (Table 1). Generally, we observed a very good functional group compatibility accepting both electron-withdrawing and electron-donating substituents. Indanones incorporating chloro (1e), amide (1g), ester (1h), and nitrile (1i) functional groups were all formed in acceptable yields. Only 1j (containing the nitro group) could not be prepared by these methods. The method is quite sensitive to steric effects. This is seen for the 2-methoxychalcone 8f which is cyclized to the indanone 1f in only 33% yield – the major side product being the partially reduced ketone 11 (compare entry 3 and 5, Method B).

During the reaction the indenone 9b seemed to be an intermediate, as judged by LC-MS. It was believed then that 9b is reduced to the indanone 1b. However, when Method A conditions were applied to the indenone 9b (synthesized from 8b using a slightly modified method as described in Ref.6), the conversion to 1b was very slow (6 h instead of 1 h). We therefore believe that two different reaction paths are possible, one leading to the indenone 9b and the other to the indanone 1b. Notably, the ring closure is formally a 5-endo-trig cyclization, which according to Baldwin is disfavored. Based on analogy with the intermolecular reaction,13 we therefore suggest the mechanism outlined in Scheme 4. After oxidative insertion of the aryl halide to palladium(0) resulting in the complex 12 followed by double bond insertion, the adduct 13 normally would have been expected to undergo reductive elimination with formation of the styrene 9 according to the well known Heck reaction. However, because of the nature of the syn addition to the double bond, the resulting cis-complex 13 does not readily undergo β-elimination. This is because the rigid trans configuration of the β-hydrogen and palladium atom hinders elimination of the hydropalladium halide. Therefore, the complex 13 can be forced to undergo a Cᵦ-Pd heterolytic bond cleavage followed by rapid protonation of the anionic moiety 14 by trialkylammonium bromide resulting in the racemic indanone 1. This suggested mechanism is in line with what has been suggested for palladium-catalyzed intermolecular conjugate addition of aryl iodides with α,β-unsaturated ketones by Cacchi et al.13b In order not to terminate the catalytic cycle, the reduction of palladium(II) to palladium(0) is achieved by the tertiary amine as described in the literature.13 Hence, the use of an organic amine base is crucial in order to direct the reaction towards conjugate addition since the amine serves both as a reducing agent towards

Scheme 4  Suggested mechanism for the catalytic Pd cycle leading to the Heck product 9 or hydroarylation product 1. A compound with reduced double bond and reduced bromine 11 have also been observed when R = electron-withdrawing or ortho-substituents.
Palladium(II) and the corresponding ammonium ion serves as the hydrogen source. This explanation is also consistent with the observation that the Heck reaction path is dominant when an inorganic base like potassium carbonate is used.

Preliminary attempts towards a stereoselective synthesis using chiral phosphine ligands were also carried out. Probably because of the stringent requirement of the reaction conditions (most notably the high temperature 155 °C), these attempts have so far not been successful. In these preliminary experiments only \((R)-\) and \((S)-\)BINAP seems to be able to catalyze the ring closure properly, whereas \((R)-\)Tol-Binap, \((R,R)-\)Me-DuPhos, and \((R)-\)Phanephos are much less efficient. Unfortunately, no stereoselectivity has so far been detected. Furthermore, the stereochemical outcome might depend strongly on the substrate and especially the aromatic substitution pattern possibly preventing development of a general procedure.

In conclusion we have developed a simple non-moisture sensitive and rapid synthesis of racemic 3-arylindan-1-ones. This method tolerates acid sensitive groups and reduction sensitive groups like the methoxy, nitrile and ester groups, which are partly degraded when using the more harsh acidic procedures. Furthermore, the starting materials (chalcones) are easy to synthesize from commercially available aryl aldehydes. The major limitation is that nucleophilic moieties (e.g. pyridine) are not tolerated in the reactants (chalcones) since they would be prone to self-condensation by 1,4-addition to these enones. Reactions were carried out in a Carousel reaction station (from Radley discovery) in 30 mL reaction tubes under argon. Microwave reactions were carried out in a single mode cavity (from Prolabo) operating at 2450 MHz under argon but not under high pressure (open system). Flash chromatography was carried out using silica gel 60 (0.04–0.063 mm). NMR analysis was performed on a BRUKER instrument operating at 500.1 MHz \((^1\text{H NMR})\) and 125.8 MHz \((^1\text{C NMR})\). Samples were dissolved in CDCl₃ and peaks were referenced to TMS. Chemicals and solvents were bought from Aldrich.

### 3-Arylindan-1-ones 1: General Procedures

**Method A (Conventional Heating):** This method is identical to method B, except that conventional heating was used for 2 h instead of microwave heating.

**Method B (Microwave Heating):** The chalcone (5 mmol), \((\text{Ph}_3\text{P})_2\text{PdCl}_2\) (35 mg, 0.05 mmol) and \(N,N\)-dimethylcyclohexylamine (1.27 g, 10.0 mmol) were dissolved in DMF (10 mL). The reaction container was fitted with a normal reflux condenser and an argon atmosphere was established. Microwave irradiation was used to increase the temperature to 160 °C in 3 min and this temperature was maintained for a further 12 min. The solvent was evaporated off and the residue was taken up in EtOAc (100 mL) and aq 2 M HCl (50 mL). The phases were separated and the organic phase was washed with aq 2 M HCl (50 mL), brine and dried (Na₂SO₄). The crude product was purified by chromatography using a gradient of EtOAc in heptane.

<table>
<thead>
<tr>
<th>R</th>
<th>Reactant (Chalcone)</th>
<th>Product (Indanone)</th>
<th>Conventional Heating (Method A)(^a)</th>
<th>Microwave Heating (Method B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-F</td>
<td>8b</td>
<td>1b</td>
<td>72 (43)(^b)</td>
<td>78 (73)(^a)</td>
</tr>
<tr>
<td>H</td>
<td>8c</td>
<td>1c</td>
<td>65 (38)(^b)</td>
<td>66 (72)(^a)</td>
</tr>
<tr>
<td>4-OMe</td>
<td>8d</td>
<td>1d</td>
<td>83 (65)(^b)</td>
<td>87 (82)(^c)</td>
</tr>
<tr>
<td>3,4-Cl₂</td>
<td>8e</td>
<td>1e</td>
<td>58 (0)(^b)</td>
<td>83 (58)(^c)</td>
</tr>
<tr>
<td>2-OMe</td>
<td>8f</td>
<td>1f</td>
<td>n.d.</td>
<td>33</td>
</tr>
<tr>
<td>4-NHCOCH₃</td>
<td>8g</td>
<td>1g</td>
<td>n.d.</td>
<td>45</td>
</tr>
<tr>
<td>4-CO₂Et</td>
<td>8h</td>
<td>1h</td>
<td>n.d.</td>
<td>57</td>
</tr>
<tr>
<td>4-CN</td>
<td>8i</td>
<td>1i</td>
<td>n.d.</td>
<td>64</td>
</tr>
<tr>
<td>4-NO₂</td>
<td>8j</td>
<td>1j</td>
<td>n.d.</td>
<td>0</td>
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\(^{a}\) n.d. = not detected.  
\(^{b}\) Numbers in parentheses indicate yields with Et₃N as base instead of \(N,N\)-dimethylcyclohexylamine.  
\(^{c}\) 5 mol% \((\text{Ph}_3\text{P})_2\text{PdCl}_2\) catalyst was used (instead of 1 mol%).

### Table 1 Reduction Cyclization of Bromochalcones 8b–j

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Anal. Calcd for C_{15}H_{10}Cl_{2}O: C, 65.01; H, 3.64. Found: C, 65.34; H, 3.13, 130.2, 129.7, 128.5, 128.4, 127.1, 123.3, 45.9, 42.9.

3-(4-Cyanophenyl)indan-1-one (1i)
Mp 110–112 °C (Lit.11 mp 113–115 °C).

3-(3,4-Dichlorophenyl)indan-1-one (1e)

3-(2-Methoxyphenyl)indan-1-one (1f)

3-(4-Methoxyphenyl)indan-1-one (1d)

4-(3-Oxoindan-1-yl)benzoic Acid Ethyl Ester (1h)

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Syntheses of 3-Arylindan-1-ones by Intramolecular Cyclization of Bromochalcones

Anal. Calcd for C_{16}H_{11}NO: C, 82.38; H, 4.76; N, 6.01 Found: C, 82.37; H, 4.82; N, 5.89.

References