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Palladium mediated total synthesis of *o*-acetylphenylacetic acids: a general route to indolo[2,3-*b*]naphthalene-6,11-diones

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Abstract—Here we describe a new, efficient general synthesis of *o*-acetylphenylacetic acids by Heck palladium-catalyzed arylation of *n*-butyl vinyl ether with *o*-bromophenylacetic acids, and its application to the synthesis of indolo[2,3-*b*]naphthalene-6,11-diones.

2-Hydroxy-1,4-naphthoquinones[1] **5** have received considerable attention on account of their biological properties,[2] their industrial applications[3] and their potential as intermediates in the synthesis of nitrogenated and oxygenated heterocycles such as indolonaphthoquinones **7** (Z = NH) and benzofuronaphthoquinones[4] **7** (Z = O). Hitherto, however, synthetic approaches to these compounds have been onerous and/or of limited scope; although alkyl-2-acetylphenylacetates (**3**) can be transformed into 2-hydroxy-1,4-naphthoquinones quickly and efficiently by mixed Claisen condensation followed by oxidation of the resulting cyclized products,[5] the generality of this route has been restricted by the methods used to prepare the *o*-acetylphenylacetate intermediates (intra-[5] or intermolecular[6] Friedel–Crafts acylation).

Noting that acetylbenzenes have been efficiently obtained by Heck coupling[7] of *n*-butyl vinyl ether (BVE) and halobenzenes (α-selectivity being attributed to the inclusion of TlOAc and a chelating phosphine in the reaction medium), we reasoned that a similar Heck coupling reaction might give easy access to *o*-acetylphenylacetic acids (**3**). This hypothesis was confirmed when reaction of BVE with methyl *o*-bromophenylacetate **1a** under the conditions used by Cabri et al.[8] (Table 1, entry 1), produced the desired α-arylated compound **2a**, which upon treatment for 1 h with 10% aq. HCl in THF at room temperature afforded an almost quantitative yield of ketoester **3a**[9]. No formation of the β-arylated product expected for classical Heck conditions (no TlOAc) was detected by ^{1}H NMR. Coupling of BVE to the electron-rich bromophenylacetate **1b** gave a lower yield of **3b**, even when more catalyst and a much longer reaction times were used (entry 2), but regioselectivity was again total. To our surprise, similar regiochemical purities were obtained when these reactions were carried out using classical Heck conditions,[7a,10] which required longer reaction times but have the advantage of not involving toxic TlOAc (entries 3 and 4).

Table 1. Coupling of *o*-bromophenylacetates to *n*-butyl vinyl ether (BVE)[a]

Entry	Compound	Catalyst	Additive	Solvent	Reaction time	Reaction product
1	**1a** (R = H)	$Pd(OAc)_2$/DPPP (7.5 mol%)	TlOAc	DMF	4 h	**3a** (90%)
2	**1b** (R = OMe)	$Pd(OAc)_2$/DPPP (10 mol%)	TlOAc	DMF	1 week	**3b** (75%)
3	**1a** (R = H)	$Pd(OAc)_2$/Ph_3P (7.5 mol%)	–	CH_3CN	16 h	**3a** (91%)
4	**1b** (R = OMe)	$Pd(OAc)_2$/Ph_3P (10 mol%)	–	CH_3CN	1 week	**3b** (65%)

[a] All experiments were carried out at 100°C.

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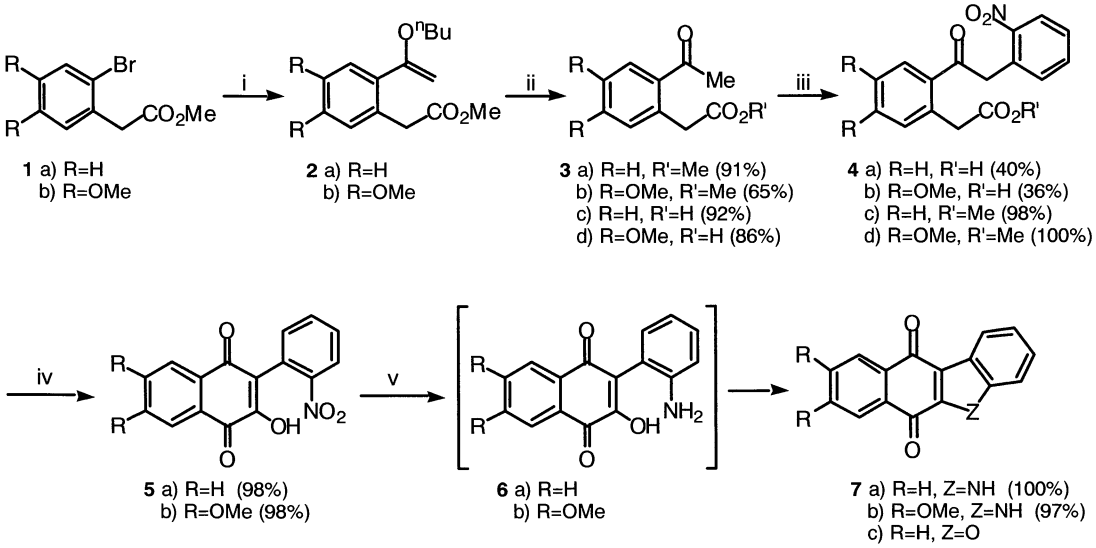

***Conditions**: i) See Table 1. ii) 10% aq. HCl, r.t., 1 h. iii) 20% aq. H_2SO_4, dioxan, reflux, 2 h; t-BuOK,o-fluoronitrobenzene, DMF, reflux, 5 h. H_2SO_4, MeOH, reflux, 2 h. iv) 10% aq. NaOH, MeOH, reflux, 1 h. v) $NaBH_4$, i-PrOH, r.t., 2 h.*

The high and unexpected α-regioselectivity achieved with classical Heck conditions suggests that the carboxymethyl group of aryl halides **1** interacts with the palladium complex to give a chelate facilitating α-arylation,[11] a mechanism different from the one hypothesized by Cabri et al.[8] for arylation of BVE in the absence of TlOAc. In our work, Cabri coupling conditions facilitated reaction, but were not necessary for α-selectivity.

The easy preparation of methyl phenylacetates **3** allowed us to develop a general synthesis of indolonaphthoquinones **7** (Z = NH). Nucleophilic attack of the enolate of acetylphenylacetic acid **3d** on *o*-nitrofluorobenzene gave 2-(2′-nitrophenylacetyl)phenylacetic acid **4b**, the methyl ester of which, **4d**, was transformed into indolonaphthoquinone **7b** via nitrophenylnaphthoquinone **5b**, as previously described.[12] The final cyclization of this sequence presumably takes place via the aminophenylnaphthoquinone intermediate **6b**, the amino group attacking C_4. Similarly, reaction of acetylphenylacetic acid **3c** with *o*-nitrofluorobenzene gave nitroketoacid **4a**, which was converted to its methyl ester **4c**; treatment of **4c** with aq. sodium hydroxide in refluxing methanol for 1 h afforded nitrophenylnaphthoquinone **5a**; and reduction of the latter with $NaBH_4$ in isopropanol at rt gave an 88% yield of unsubstituted indolonaphthoquinone **7a**, presumably through amino attack at C_4.

In conclusion, we have established an efficient method for the preparation of *o*-acetylphenylacetic acids that seems to provide unrestricted access to indolonaphthoquinones **7** (Z = NH). Work is now in progress to synthesize a variety of indolonanaphthoquinones for chemical and biological studies. We are also exploring additional synthetic applications of ketoacids **3**, including the general synthesis of 2-phenylacetylphenylacetic acids, application of which to the synthesis of a number of carbocyclic and heterocyclic derivatives of chemical and biological interest has previously been restricted to compounds that can be prepared by Friedel–Crafts acylations.

Acknowledgements

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9. All new compounds gave satisfactory analytical and spectroscopic data. Selected ^{1}H NMR spectroscopic data (δ, ppm): **compound 3a**, 2.58 (s, 3H, -OCH_3), 3.68 (s, 3H, -$COCH_3$), 7.22–7.26 (m, 1H, Ar-H), 7.34–7.48 (m, 2H, 2×Ar-H) and 7.80 (dd, $J=1.6$ and $J=7.7$ Hz, 1H, Ar-H); **compound 3c**, 2.53 (s, 3H, -OCH_3), 3.89 (s, 3H, -$COCH_3$), 7.39–7.59 (m, 3H, 3×Ar-H) and 7.84 (dd, $J=1.0$ and $J=7.7$ Hz, 1H, Ar-H); **compound 4a**, 3.80 (s, 3H, -OCH_3), 4.70 (s, 2H, -CH_2-), 5.95 (s, 1H, -COOH), 7.40 (m, 7H, Ar-H), 8.10 (m, 1H, 2×Ar-H); **compound 5a**, 7.51–7.58 (m, 2H, 2×Ar-H), 7.66–7.82 (m, 3H, 3×Ar-H), 8.10–8.16 (m, 3H, 3×Ar-H); **compound 7a**, 7.25–7.35 (m, 2H, 2×Ar-H), 7.55–7.57 (m, 2H, 2×Ar-H), 7.78–7.84 (m, 1H, Ar-H), 7.95–8.07 (m, 3H, Ar-H), 12.94 (bs, 1H, NH).
10. General procedure. A solution of 1.2 mmol of **1**, 6 mmol of BVE, 0.09 mmol of $Pd(OAc)_2$ (7.5 mol%), 0.18 mmol of Ph_3P (Pd/ligand ratio 1:2) and 1.44 mmol of Et_3N in 2.5 mL of dry degassified acetonitrile was heated at 100°C in a screw-capped Pyrex tube for the stated time. The solution was cooled, filtered through Celite and washed with water (25 mL). The solvents were evaporated and a sample was examined by ^{1}H NMR. The crude was dissolved in a 1:1 mixture of 10% aq. HCl and THF (40 mL) and stirred for 1 h at rt. The THF was removed under vacuum, and the residue was extracted with CH_2Cl_2. The extracts were washed with water until pH 7 was reached and dried with anhydrous Na_2SO_4, and the solvents were removed. The stated yield of the reaction is the yield after purification by flash chromatography on silica gel.
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