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Protected Indanones by a Heck−Aldol Annulation Reaction

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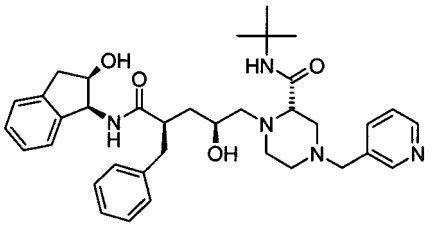
Abstract: Monoprotected 3-hydroxyindan-1-ones have been prepared in moderate to good yields by a new tandem reaction involving salicylaldehyde triflates and commercially available 2-hydroxyethyl vinyl ether. This one-pot annulation reaction proceeds in the presence of a palladium bidentate catalyst and results in the formation of two new ring systems.

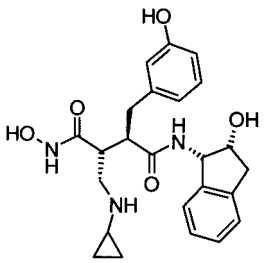
Indan structures are important components in many bioactive compounds. Two examples of protease inhibitors that contain the indan fragment are the aspartyl protease inhibitor indinavir,[1] an anti-HIV agent in clinic, and the orally available matrix metalloprotease (MMP) inhibitor[2] in Figure 1. In a medicinal chemistry program, where carbohydrates are used as precursors for C2-symmetric HIV-1 protease inhibitors,[3] we require access to acetals of 3-hydroxyindan-1-ones (**3**). These 1,3-difunctionalized indan derivates should serve as suitable starting structures for further modification into a diverse array of P2/P2′ residues.

Derivatives of 3-hydroxyindan-1-one have previously been prepared by a more elaborate procedure involving an intramolecular Friedel−Craft-type cyclization,[4] a reaction sequence that was not applicable for our purposes. Aldol reactions with strong bases have been employed to generate the 3-hydroxyindan-1-one system in some complex molecules,[5] but examples that lack substituents in the 2-position are rare. The synthesis of the parent 3-hydroxyindan-1-ones from the correspondning *o*-formyl acetophenones by an aldol reaction has, to the best of our knowledge, not been reported.

We herein report that triflates (**1**) of salicylic aldehydes[6] can be conveniently converted to 1,1-(ethylenedioxy)-3-hydroxyindans (**3**) by an internal Heck arylation



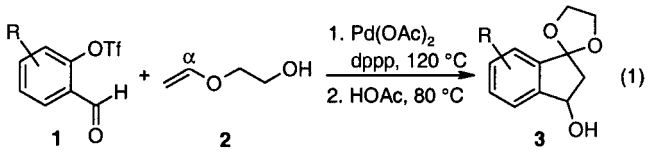
Indinavir



MMP-inhibitor

FIGURE 1. Bioactive compounds containing indan structures.

of the commercially available 2-hydroxyethyl vinyl ether (**2**) and subsequent ring-closure (eq 1). This one-pot annulation offers a new route to monoprotected hydroxy indanones.



(1)

Initially we attempted to prepare **3a** (R = H) via an aldol reaction of *o*-formyl acetophenone, followed by a ketalization reaction (Scheme 1). Thus, the triflate **1a** was reacted with butyl vinyl ether in the presence of a palladium-dppp catalyst.[7] According to LC/MS the internal arylation smoothly produced the enol ether **4**, but the acid-mediated generation of the *o*-formyl acetophenone was not successful. Only 3-hydroxyindanone (**5**) could be isolated in low yield from the complex product mixture. In fact, no *o*-formyl acetophenone was traced as deduced from LC-MS.

Fortunately, by using 2-hydroxyethyl vinyl ether[8,9] as the olefin instead of butyl vinyl ether, the outcome of the reaction was significantly improved. Following this modification not only was the annulation accomplished, but also the protection of the ketone was achieved concomitantly (Scheme 2).

A mixture of the salicylic triflate (**1**) (1.0 equiv), the hydroxyethyl vinyl ether (**2**) (3.0 equiv), and palladium acetate/dppp (1,3-bis(diphenylphosphino)propane) (0.01/0.02 equiv) with triethylamine or 1,2,2,6,6-pentamethylpiperidine (PMP) (2.2 equiv) as base and DMF as

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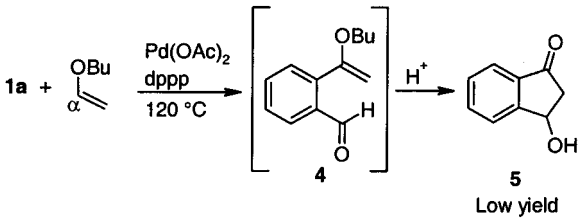
SCHEME 1. α-Arylation of Butyl Vinyl Ether Followed by Cyclization



SCHEME 2. Reaction Sequence for the Heck−Aldol Reaction

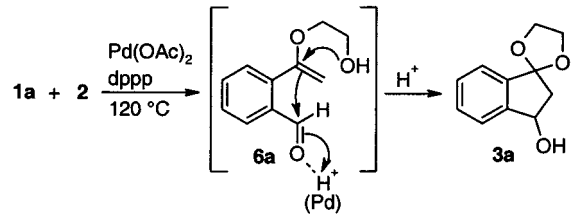
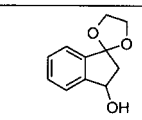
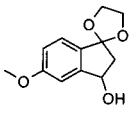
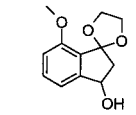
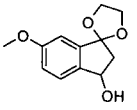
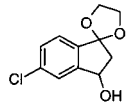
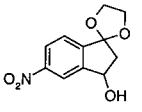


TABLE 1. One-Pot Synthesis of Monoprotected 3-hydroxyindanones (3)[a]

Entry	Product		Isolated Yield (%)[b]	Isolated Yield (%)[c]
1		**3a**	51	39
2		**3b**	78	38
3		**3c**	52	50
4		**3d**	57[d]	0[e]
5		**3e**	47	24
6		**(3f)**	-	0[e]

[a] Reaction scale: 200 μmol **1a**−**f**. [b] With PMP as base. [c] With Et_3N as base. [d] Slow ring closure; 50 μL (4.3 equiv) acetic acid and 100 °C for 24 h. [e] No product was detected.

solvent was heated for 1−2 h at 120 °C. Following the complete consumption of **1**, acetic acid (2.6 equiv) was routinely added and the reaction was stirred overnight at 80 °C. The results of the preparative reactions with a small series of salicylic triflates are outlined in Table 1. As is apparent, the isolated yields of the tricyclic products were higher after employing the sterically hindered base PMP, compared to the more classical Heck conditions in which triethylamine was used. Analysis of the reaction mixture revealed that the reaction was more selective when PMP was used. No ring closure occurred with the inorganic base potassium carbonate.

Overall, moderate to good yields were encountered except in cases where very electron-deficient aryl triflates were subjected to the reaction conditions. For example, the triflate of 4-nitrosalicylic aldehyde (entry 6) completely failed to deliver indans of type **3**. A low conversion of the aryl triflate to the internally arylated vinyl ether in the Heck reaction accounts for this result.[10] In the two examples in which methoxy groups were meta to the formyl group (entries 2 and 3), most of the cyclization occurred prior to the addition of acetic acid with both amine bases. For the preparation of **3d**, where the electron-releasing methoxy group is located in the para position to the formyl group, the acetic acid addition was absolutely essential to promote cyclization/ketalization (entry 4). To achieve a reasonable reaction rate, an extra amount of acetic acid (4.3 equiv) and a higher temperature (100 °C) were employed. In fact, when triethylamine was used as the base no tricyclic **3d** was obtained at all.

The Heck arylation of vinyl ethers with aryl triflates and bidentate ligands is proposed to proceed via charged aryl palladium species.[7,11,12] The insertion process is electronically controlled leading to α-arylation of the electron-rich olefin. We believe that **3** is formed by a reaction sequence similar to that shown in Scheme 2. Despite the fact that the 2-hydroxyethyl vinyl ether has previously been used successfully for preparation of ketals of acetophenones,[8] no monocyclic 2-aryl-2-methyl-1,3-dioxolane was detected after the Heck reaction in the annulation reaction.[8,9,13] In attempts to better understand factors of importance for the annulation step, the intermediate **6a** was isolated and used as the starting material for a series of model experiments. The experiments demonstrated that catalytic amounts of palladium acetate promote cyclization under acidic conditions. In addition, a slow ring-closure was observed when acetic acid was used and the palladium catalyst was omitted. No cyclization occurred without addition of acid. The fact that the corresponding α-arylated butyl vinyl ether (**4**) undergoes slower and less selective cyclization than **6a** under identical conditions suggests that the terminal hydroxyl group plays an active role in the carbon−carbon bond formation by stabilization of the partial positive charge that builds up on the α-carbon as ring closure occurs. Related neighboring group participations have been proposed in other aldol-type condensation-like reactions involving vinyl ethers and aldehydes.[14] We therefore postulate that the formation of **3** proceeds via a tandem reaction in which the two ring systems are formed after a highly regioselective palladium(0)-catalyzed arylation

(10) It is known that electron-poor aryl triflates react sluggishly in internal Heck arylations. Larhed, M.; Andersson, C. M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285−304.

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of **2** and a protonation (or palladium(II) activation) of the formyl group.[15]

In summary an efficient tandem annulation reaction that delivers monoblocked 1,3-difunctionalized indans from electron-rich or neutral salicylic aldehydes has been developed. The synthetic method merits special attention as for the simplicity of the one-pot experimental procedure and the use of readily accessible starting materials.

Experimental Section

General. The triflates were prepared according to a fast microwave procedure.[6] All other chemicals used are commercially available. The reactions were monitored with reversed phase LC/MS utilizing electrospray ionization (ESI). ^{1}H NMR and ^{13}C NMR were recorded with $CDCl_3$ or DMSO-d_6 as solvent on a 400 MHz spectrometer. Mass spectra were recorded on a GC-MS, equipped with a nonpolar capillary column, utilizing electron impact (EI) at an ionizing energy of 70 eV. All compounds **3** were pure according to NMR.

General Procedure for the Synthesis of 1,1-(Ethylenedioxy)-3-hydroxyindans (3). The aryl triflate (200 μmol) was dissolved in DMF (1.0 mL) in a reaction tube. 2-Hydroxyethylvinyl ether (600 μmol, 54 μL), $Pd(OAc)_2$ (2,0 μmol, 20 μL 1.0 M stock solution in DMF), and dppp (4,0 μmol, 40 μL 1.0 M stock solution in DMF) were added. Either triethylamine (440 μmol, 58 μL) or PMP (440 μmol, 80 μL) was also added. The tube was flushed with N_2 and sealed with a screw cap. The reaction mixture was stirred at 120 °C for 1−2 h. The temperature was reduced to 80 °C and acetic acid (30 μL) was added. After 18 h the reaction mixture was extracted with 10% K_2CO_3 (aq) and EtOAc. The organic phases were combined and evaporated.

Purification Procedure 1 (Et_3N as Base). A prepacked column with 5 g of silica gel was flushed with EtOAc/*i*-hexane (1:1, 2% Et_3N) (eluent A). The crude product was dissolved in eluent A and applied to the column. The column was rinsed with eluent A and EtOAc. The obtained product was left under vacuum overnight.

Purification Procedure 2 (PMP as Base). The crude product, dissolved in H_2O/MeOH (1:1, 3 mL), was added to a 20-g C18 column and washed through with pure MeOH. Compounds **3a**,**d**−**e** were purified further according to purification procedure 1.

Only the yields from the reactions that were carried out with PMP as base are reported below.

1,1-(Ethylenedioxy)-3-hydroxyindan (3a). The title compound was obtained in 51% yield (19.6 mg) as an orange syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (br s, 1H), 2.19 (dd, J = 4.4, 13.8 Hz, 1H), 2.70 (dd, J = 6.7, 13.8 Hz, 1H), 4.05−4.12 (m, 2H), 4.16−4.22 (m, 2H), 5.20 (dd, J = 4.4, 6.7 Hz, 1H), 7.36−7.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.9, 65.3, 65.5, 72.0, 114.6, 123.1, 124.6, 129.2, 130.3, 141.6, 145.1. MS (EI, 70 eV) *m*/*z* 192 (M^+, 1), 175 (13), 149 (100), 131 (16). IR (neat) 3413 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C 68.7, H 6.3. Found: C 68.7, H 6.4.

1,1-(Ethylenedioxy)-3-hydroxy-5-methoxyindan (3b). The title compound was obtained in 78% yield (35.5 mg) as an orange syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (dd, J = 4.7, 13.7 Hz, 1H), 2.38 (br s, 1H), 2.67 (dd, J = 6.7, 13.7 Hz, 1H), 3.81 (s, 3H), 3.99−4.10 (m, 2H), 4.13−4.21 (m, 2H), 5.13 (dd, J = 4.7, 6.7 Hz, 1H), 6.89 (dd, J = 2.2, 8.3 Hz, 1H), 6.93 (d, J = 2.2 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.4, 55.6, 65.1, 65.4, 71.8, 108.3, 114.3, 116.5, 124.2, 133.4, 147.0, 161.7. MS (EI, 70 eV) *m*/*z* 222 (M^+, 31), 205 (31), 179 (100), 161 (28). IR (neat) 3435 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_4$: C 64.9, H 6.4. Found: C 64.9, H 6.1.

1,1-(Ethylenedioxy)-3-hydroxy-7-methoxyindan (3c). The title compound was obtained in 52% yield (23.1 mg) as an orange syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (dd, J = 4.6, 13.9 Hz, 1H), 2.26 (br s, 1H), 2.67 (dd, J = 6.8, 13.9 Hz, 1H), 3.85 (s, 3H), 3.97−4.06 (m, 2H), 4.19−4.26 (m, 2H), 5.09 (dd, J = 4.6, 6.8 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 7.35 (dd, J = 7.5, 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.0, 55.5, 66.07, 66.13, 71.4, 110.9, 115.2, 116.7, 128.4, 131.9, 147.8, 155.8. MS (EI, 70 eV) *m*/*z* 222 (M^+, 24), 205 (20), 179 (100), 161 (33). IR (neat) 3427 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_4$: C 64.9, H 6.4. Found: C 64.3, H 6.2

1,1-(Ethylenedioxy)-3-hydroxy-6-methoxyindan (3d). The synthesis was conducted according to the general method but at 100 °C with 50 μL of acetic acid and for 24 h instead of at 80 °C, with 30 μL acetic acid, and for 18 h. The title compound was obtained in 57% yield (25.1 mg) as an orange syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (dd, J = 3.9, 13.9 Hz, 1H), 2.22 (br s, 1H), 2.66 (dd, J = 6.6, 13.9 Hz, 1H), 3.82 (s, 3H), 4.02−4.12 (m, 2H), 4.14−4.23 (m, 2H), 5.13 (dd, J = 3.9, 6.6 Hz, 1H), 6.84 (d, J = 2.5 Hz,1H), 6.95 (dd, J = 2.5, 8.3 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.3, 55.6, 65.4, 65.5, 71.4, 106.9, 114.6, 117.7, 125.7, 137.5, 143.0, 160.8. MS (EI, 70 eV) *m*/*z* 222 (M^+, 10), 204 (17), 179 (100), 161 (16). IR (neat) 3418 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_4$: C 64.9, H 6.4. Found: C 64.5, H 6.5.

1,1-(Ethylenedioxy)-3-hydroxy-5-chloroindan (3e). The title compound was obtained in 47% yield (21.3 mg) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (br s, 1H), 2.17 (dd, J = 5.0, 13.9 Hz, 1H), 2.69 (dd, J = 6.8, 13.9 Hz, 1H), 4.03−4.11 (m, 2H), 4.14−4.21 (m, 2H), 5.15 (dd, J = 5.0, 6.8 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.34 (dd, J = 8.1, 1.8 Hz, 1H), 7.43 (d, J = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.1, 65.3, 65.6, 71.5, 113.9, 124.4, 124.9, 129.5, 136.2, 140.0, 146.9. MS (EI, 70 eV) *m*/*z* 226 (M^+, 5), 209 (11), 183 (100), 165 (20). IR (neat) 3311 cm^{-1}. Anal. Calcd for $C_{11}H_{11}ClO_3$: C 58.3, H 4.9. Found: C 58.2, H 5.0.

2-[1-(2-Hydroxyethoxy)vinyl]benzaldehyde (6a). The aryl triflate **1a** (1.0 mmol, 254 mg) was dissolved in DMF (4.0 mL) in a reaction tube. 2-Hydroxyethylvinyl ether (3.0 mmol, 269 μL), $Pd(OAc)_2$ (10 μmol, 100 μL 1.0 M stock solution in DMF), dppp (20 μmol, 200 μL 1.0 M stock solution in DMF), and K_2CO_3 (2.2 mmol, 304 mg) were added. The tube was flushed with N_2 and sealed with a screw cap. The reaction mixture was stirred at 120 °C for 1 h and then extracted with 10% K_2CO_3 (aq) and EtOAc. The organic phases were combined and evaporated. Purification on silica gel according to purification procedure 1 gave the acid- and air-sensitive compound **6a** (24.1 mg) with around 90% purity. The instability of **6a** prevented further purification.[16] The structure was verified with ^{1}H NMR and high-resolution MS. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91−3.95 (m, 2H), 4.01−4.03 (m, 2H), 4.39 (d, 1H), 4.53 (d, 1H), 7.46−7.59 (m, 3H), 7.89−7.91 (m, 1H), 10.22 (s, 1H). HRMS calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0785.

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(15) An alternative mechanism, as pointed out by a referee, might be that initially a Wacker-type dioxolane formation takes place leading to a σ-Pd intermediate, which then intramolecularly reacts in an insertion reaction with the carbonyl group to give the product **3**.

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