

Heck arylation of cyclic enol ethers with aryldiazonium salts: regio- and stereoselective synthesis of arylated oxacycles

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Received (in Cambridge, UK) 8th May 2003, Accepted 23rd May 2003

First published as an Advance Article on the web 5th June 2003

Dihydropyrans and dihydrofurans bearing an aryl substituent in the 2-position are regio- and stereoselectively synthesized by Heck arylation of cyclic enol ethers with aryldiazonium salts.

Although it was discovered as early as 1977 that arenediazonium salts are extraordinarily reactive substrates for Heck reactions,¹ their application in organic synthesis² has been rather limited compared to analogous aryl iodides or triflates. Most surprisingly, the palladium-catalyzed arylation of cyclic enol ethers, which is a well established test reaction for the development of enantioselective Heck reactions,³ has, to the best of our knowledge, not been carried out with arenediazonium salts.⁴ In this contribution we report the highly regio- and diastereoselective arylation of substituted 2,3-dihydropyrans and 2,3-dihydrofurans with an electron rich arenediazonium salt. We demonstrate that these arylating agents are clearly superior in *intermolecular* Heck reactions with cyclic enol ethers. The study described herein was inspired by a project directed towards the synthesis of cyclic diaryl heptanoids. Several natural products with this structural pattern have been isolated from *Alpinia blepharocalyx* and other plants over the past few years and tested for antiproliferative activity against certain human tumor cell lines. Dihydropyran **1** and tetrahydropyran **2** are representative examples (Fig. 1).⁵

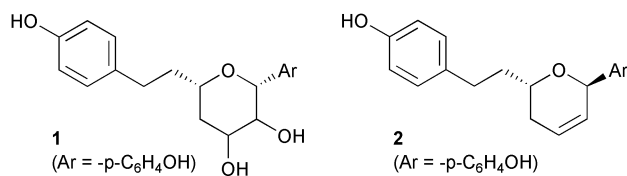
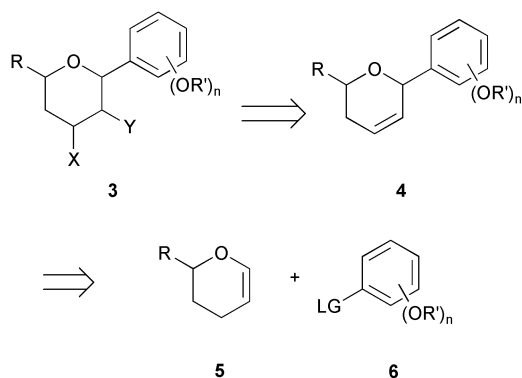


Fig. 1

The synthetic concept is outlined in Scheme 1. We considered a Heck reaction of cyclic enol ethers **3** and electron rich arylating agents **6** as the key C–C-bond forming step in the synthesis of dihydropyrans with the general formula **4**. This transformation has so far—to the best of our knowledge—only been described for the parent compound 2,3-dihydropyran (R = H) and iodobenzene or phenyl triflate. The dihydropyrans **4**



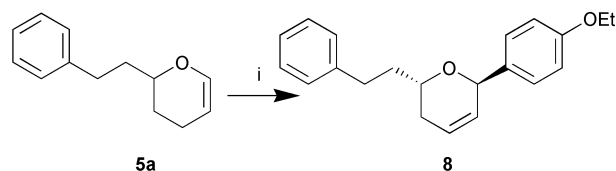
Scheme 1

should be suitable intermediates for cyclic diaryl heptanoids with a tetrahydropyran core **3**, especially hydroxylated (X = H, Y = OH or X = OH, Y = H) or dihydroxylated derivatives (X = Y = OH), such as **2**. For the synthesis of substituted 2,3-dihydropyrans **5** we wanted to apply a novel ring closing metathesis isomerization sequence recently developed independently by Snapper *et al.*^{6a} and by ourselves.^{6b} This sequence involves the olefin metathesis of allyl ethers and the formation of ruthenium hydride species *in situ*, which catalyze the isomerization subsequently to the metathesis process.

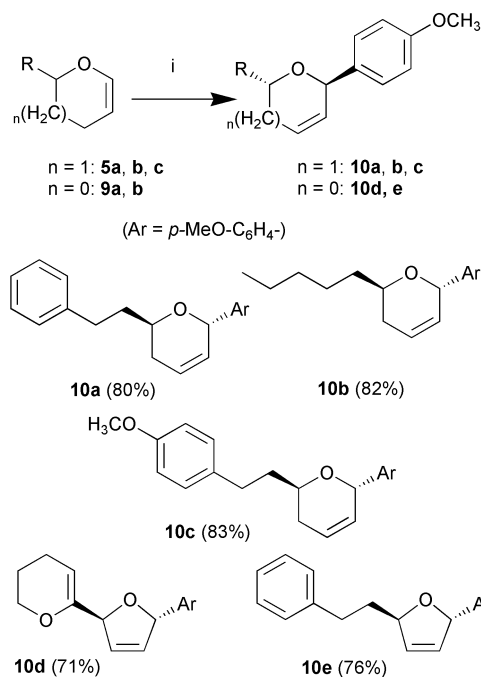
A major difficulty in intermolecular Heck arylation reactions of cyclic enol ethers is the subsequent double bond migration reaction initiated by readdition of palladium hydride species to the C–C-double bond of the product.⁷ It has been described in the literature that addition of excess amounts of iodide scavengers such as Ag₂CO₃^{8a} or Ti₂CO₃^{8b} not only enhances the reactivity of aryl iodides in Heck reactions, but also suppresses undesired double bond migration reactions by removing iodide from the coordination sphere of the palladium. We first investigated the Heck reaction of **5a** with *p*-ethoxyiodobenzene (**7**) using conditions similar to those previously described by Larock *et al.*⁹ for the synthesis of platelet-activating factor antagonists. The desired dihydropyran **8** was formed in 32% yield if a threefold excess of the aryl iodide and 5 mol% of Pd(OAc)₂ were used. A large excess of Ag₂CO₃ (three equivalents) was necessary to obtain preparatively useful rates of conversion (Scheme 2). Even under these conditions, conversion remained incomplete in all experiments. Purification of the reaction mixture turned out to be a major drawback. It was not only very difficult to remove unreacted starting materials, especially the aryl iodide, furthermore, several unidentified byproducts were formed in the course of the reaction and purification of the product turned out to be very laborious. The diastereoselectivity appears to be very high, however, it is not possible to give a reliable ratio of diastereomers from the crude reaction mixture.

With the corresponding iodomethoxybenzene separation and purification problems became even worse. To avoid the problems observed for aryl iodides in the intermolecular Heck arylation, especially the comparatively low reactivity, we considered arenediazonium salts as an alternative. With these reagents, we also saw a good chance to avoid undesired double bond migration reactions if no strongly coordinating counterions were present. Thus, the corresponding tetrafluoroborate was chosen, which has the additional advantage of being stable and easily prepared in larger quantities.¹⁰

It was indeed possible to circumvent all problems observed for the arylation of **5a** with aryl iodides by using an



Scheme 2 Reagents and conditions: **1**, **7** (3.0 equiv.), Ag₂CO₃ (3.0 equiv.), PPh₃ (10 mol%), Pd(OAc)₂ (5 mol%), acetonitrile, 80 °C (32%).



Scheme 3 Reagents and conditions: i, $[\text{N}_2\text{C}_6\text{H}_4\text{OCH}_3]\text{BF}_4$ (**11**) (1.2 equiv.), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (2.0 mol%), NaOAc (3.0 equiv.), CH_3CN , 20 °C.

aryldiazonium tetrafluoroborate **11**, the $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ catalyst and NaOAc as a base. We investigated the reaction of dihydropyrans **5a–c** with **11** to give **10a–c**, and the reaction of dihydrofurans **9a,b** with **11** to give **10d,e**, respectively (Scheme 3).[†]

The following points are noteworthy: a) the reaction is fast at ambient temperature in the presence of 1–2 mol% of the palladium catalyst and leads to complete conversion of the starting material; b) byproducts are formed only in very minor amounts, and these can be removed by chromatography; c) only a slight excess of aryldiazonium salt is required (10–20%), larger excess leads to an increasing amount of unidentified byproducts; d) no products resulting from additional double bond migration could be detected; e) the Heck reaction proceeds with high *trans*-diastereoselectivity (> 12 : 1).

The starting materials **5a–c** and **9a,b** required for this study were obtained *via* the novel RCM-isomerization sequence using our protocol.^{6b} This sequence allows the convenient preparation of enantiomerically pure or enriched starting materials by using established enantioselective allylation methodology. For example, **5a** was obtained in 90% ee in two steps from the homoallylic alcohol synthesized by enantioselective allylboration of 3-phenylpropanal with diisopinacampheyl chloride and allylmagnesium bromide.¹¹

The relative configuration of Heck reaction products **10** was elucidated by gradient selected one-dimensional NOE-experiments at 600 MHz as shown in Fig. 2 for **10c**.

The most significant NOE-interaction occurs between the *ortho* protons of one aromatic substituent and one α -proton of the dihydropyran core. A NOE-interaction between the two α -protons of the dihydropyran core, which is normally observed for *cis*-configured dihydropyrans, was not detected.¹² In conclusion, this contribution describes the facile and highly regio- and diastereoselective palladium(0)-catalyzed arylation of substituted cyclic enol ethers with an arenediazonium salt.

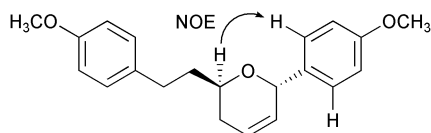


Fig. 2

The protocol avoids the problems of reduced reactivity and undesired double bond isomerization often observed in the intermolecular Heck reaction of 2,3-dihydrofurans and 2,3-dihydropyrans. Extension of the methodology to acyclic enol ethers and other aryldiazonium salts, including electron-deficient systems, and its application in target molecule oriented synthesis are currently under investigation.

Generous financial support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Department of Chemistry, University of Dortmund, is gratefully acknowledged.

Notes and references

[†] Representative procedure: (2*R*, 6*S*)-6-(4-Methoxyphenyl)-2-phenethyl-3,6-dihydro-2*H*-pyran (**10a**): To a solution of (*R*)-**5a** (0.80 g, 4.2 mmol, 90% ee) in acetonitrile (20 mL) was added **11** (1.04 g, 4.7 mmol), NaOAc (1.23 g, 15.0 mmol) and $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (86 mg, 2 mol%). After a short induction period, vigorous gas evolution was observed. The mixture was stirred until the starting material was fully consumed (TLC, cyclohexane–MTBE 10 : 1 (v/v)) and the gas evolution had ceased. The reaction mixture was diluted with MTBE (30 mL), washed with brine, dried with MgSO_4 and filtered. All volatiles were removed *in vacuo*, and the dark residue was purified by flash chromatography on silica to give **10a** (0.99 g, 80%). ¹H-NMR (500 MHz, CDCl_3): δ 7.36 (d, 2H, $J = 8.5$, Ar), 7.17–7.10 (3H, Ph), 6.92 (d, 2H, $J = 8.8$, Ph), 6.91 (d, 2H, $J = 8.5$, Ar), 6.04 (ddm, 1H, $J = 10.2$, 5.0, H4), 5.97 (dm, 1H, $J = 10.2$, H5), 5.27 (s(br), 1H, H6), 3.85 (s, 3H, OCH₃), 3.51 (m, 1H, H2), 2.71 (ddd, 1H, $J = 13.7$, 8.7, 5.0, $-\text{CH}_2\text{CH}_2\text{Ph}$), 2.50 (ddd, 1H, $J = 13.7$, 8.2, 8.2, $-\text{CH}_2\text{CH}_2\text{Ph}$), 2.08 (dddd, 1H, $J = 17.5$, 9.7, 2.5, 2.5, 2.5, H3), 1.98 (dm, 1H, $J = 17.5$, H3'), 1.86 (dddd, 1H, $J = 14.0$, 9.0, 9.0, 5.2, $-\text{CH}_2\text{CH}_2\text{Ph}$), 1.66 (dddd, 1H, $J = 14.0$, 8.2, 8.2, 3.7, $-\text{CH}_2\text{CH}_2\text{Ph}$). ¹³C-NMR (125 MHz, CDCl_3): δ 159.2 (0), 142.1 (0), 133.2 (0), 129.8 (1), 128.5 (1), 128.1 (1), 127.6 (1, C5), 125.9 (1, C4), 125.4 (1), 113.5 (1), 73.7 (1, C6), 65.7 (1, C2), 55.2 (3, OCH₃), 37.4 (2), 31.5 (2), 31.1 (2, C3). IR (film) $\nu = 3028$ (m), 2927 (s), 1610 (s), 1509 (s). MS (EI, 70 eV) m/z (I_{rel}) 294 (71, M⁺), 135 (100). $[\alpha]_{20}^D -66$ (c 1.68, CH_2Cl_2) for 90% ee.

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