Tetrahedron 69 (2013) 839-843

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet



The Heck reaction of polymer-supported allylamine with aryl iodides

CrossMark

Tuomo Leikoski^{a,*}, Pauli Wrigstedt^a, Jussi Helminen^a, Jorma Matikainen^a, Jussi Sipilä^a, Jari Yli-Kauhaluoma^b

^a Department of Chemistry, Laboratory of Organic Chemistry, PO Box 55 (A. I. Virtasen aukio 1), University of Helsinki, FI-00014 Helsinki, Finland ^b Faculty of Pharmacy, Division of Pharmaceutical Chemistry, PO Box 56 (Viikinkaari 5 E), University of Helsinki, FI-00014 Helsinki, Finland

ARTICLE INFO

Article history: Received 22 June 2012 Received in revised form 23 September 2012 Accepted 15 October 2012 Available online 8 November 2012

Keywords: Heck Solid-phase Polymer Palladium Allylamine Cinnamylamine

ABSTRACT

The Heck reaction of Wang resin-bound allylamine with aryl iodides produces various, substituted cinnamylamines. The catalyst and additive system consisting of palladium(II) acetate, n-Bu₄NOAc and potassium chloride, in addition to potassium carbonate in N_i -dimethylformamide, accomplishes a regioselective γ -arylation. By utilising the easily formed and stable carbamate linker on Wang resin, the incompatibility of free amines with the palladium catalyst is avoided. The cinnamylamine products are cleaved from the resin with trifluoroacetic acid under mild conditions and are converted into chromatographically separable acetamides. Our solid-phase method offers a new alternative for the synthesis of cinnamylamine derivatives, as biologically interesting compounds and useful synthetic intermediates. © 2012 Elsevier Ltd. All rights reserved.

1. Introduction

Arylated allylamines, such as cinnamylamines, are important synthetic intermediates and key structural units in many biologically active compounds. Conn and co-workers discovered a modified cinnamylamine that acts as an inhibitor of bovine plasma semicarbazide-sensitive amine oxidase.¹ Lermer and co-workers studied the use of synthetic oligonucleotides in the catalytic cleavage of RNA, where uracil was substituted in its 5-position, with the γ carbon atom of allylamine.² Robin and Rousseau used arylated allylamines as precursors in 4-*endo trig* cyclisations to form azetidines.³

The Heck reaction is a powerful and modern palladiumcatalysed method for generation of carbon–carbon bonds between unsaturated entities, and it has been extensively utilised in arylation and vinylation of olefins.^{4–7} Though widely studied since its independent introduction by Heck and Mizoroki, in the early 70's,^{8,9} there are no straightforward rules to assess reaction conditions for a particular type of coupling reaction. As a result, finding satisfactory conditions for an individual reaction typically requires thorough screening and optimisation. For example, in terms of general reactivity and regioselectivity, the use of electron-rich alkenes as substrates has been shown to be particularly challenging and allylamine derivatives are representative examples of such compounds.^{10–22} In addition, an extra concern in the preparation of such compounds, by Heck coupling, is caused by the strong interaction between amine nitrogens and palladium atoms.^{10,11,18,23,24} As such, in most trials amines have to be protected as less coordinating derivatives.

Compared to the vast amount of research conducted on the Heck reaction, the number of publications about its solid-phase version are relatively limited. There are however examples where either the olefin or the halide component has been attached to a polymeric support.^{25–35} In addition, solid-phase methods have been utilised in intramolecular Heck reactions.^{36–42} Even the palladium catalyst complexes have been bound covalently to polystyrene, while keeping all the other reactants in solution.^{43,44} Frei and Blackwell attached the olefinic component covalently to cellulose, with the help of a Rink-amide linker, to produce stilbenes, which were cleaved from cellulose with trifluoroacetic acid (TFA) vapour.⁴⁵ Kopylovich and coworkers absorbed reaction mixtures onto silica gel and performed microwave-assisted Heck reactions in the absence of solvent.⁴⁶

The incompatibility of free amines with palladium catalysis was established in the early years of the Heck reaction. As an example, the unsubstituted allylamine yielded only mixtures of unidentified products, instead of the desired aryl amine.^{13,18,21,22} However, some exceptions exist. A very typical example is the intramolecular Heck reaction of *N*-allyl-*o*-haloaniline derivatives, which has been utilised



^{*} Corresponding author. Tel.: +358 50 554 3682; fax: +358 9 191 50366; e-mail address: tuomo.leikoski@helsinki.fi (T. Leikoski).

^{0040-4020/\$ –} see front matter @ 2012 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tet.2012.10.092

in syntheses of indoles.^{24,47} The suitability of anilines, as reactants, is obviously associated with conjugation of the lone pair on the nitrogen with the aromatic π -electron system, whereas the effective reactions observed with some tertiary allylamines^{15,17,19} might be explained by steric hindrance on the nitrogen atom. A general strategy in the Heck reactions of allylamine derivatives is protection of the amino group, for example, as phthalimides,^{11,18,21,22} tri-fluoroacetamides^{11,13,14} or carbamates,^{10–13,16,18,20,21} which simultaneously renders the olefin less electron-rich and therefore more reactive. Noteworthy successful reactions have been performed with N,N-diprotected allylamines containing а carbamate moiety.^{10–13,16,20,21} Very recently Jiang and co-workers utilised *N*,*N*- $(t-BOC)_2$ -allylamine, as an efficient substrate in a regioselective and stereoselective reaction with various aryl bromides.¹⁰

An additional challenge with the Heck reaction of allylamine derivatives is regioselectivity. It is possible to obtain β as well as γ arylated allylamines, depending on the direction of migratory insertion, of the arylpalladium halide, into the C=C bond. There are examples in the literature where the Heck reaction of allylamine derivatives has been performed with excellent regioselectivity, in respect to either β^{17-19} or γ^{10-13} arylation. In the Heck reaction of three-carbon units in general, rearrangement of the double bond is possible as well, as there are hydrogen atoms in two distinct positions available in the organopalladium intermediate, during the β hydride elimination step.^{12,48} Formation of regioisomers is shown as a simplified cascade of reactions, in Scheme 1.



Scheme 1. Regiochemistry in the Heck reaction of three-carbon units.

Based on our previous results on the Sonogashira coupling of polymer-bound propargylamine, with aryl iodides,⁴⁹ we decided to study whether cinnamylamines could similarly be synthesised, by the Heck reaction of polymer-bound allylamine. In addition to developing new methods for the synthesis of this interesting group of

compounds, we also wanted to synthesise intermediates that could be hydrogenated to the corresponding 1,3-arylaminopropanes.

We attached allylamine, like propargylamine in our Sonogashira studies,⁴⁹ through a carbamate linker onto the polymeric support. This polymer-supported amine is easily prepared by a two-step procedure, starting from the commercially available Wang resin via the 4-nitrophenyl carbonate resin intermediate (Scheme 2). Previously, the carbamate method has been used successfully in the syntheses of low molecular-mass compounds, such as 1,2,3-triazoles,⁵⁰ and in the solid-phase synthesis of oligomeric peptides.⁵¹ In addition to the easy attachment, with the simultaneous protection of amines and to the stability of the linker in neutral and basic conditions, this method enables fast and quantitative cleavage of the amine product, with 50% trifluoroacetic acid in dichloromethane. Herein, we report our results on the Heck reaction of Wang resin-bound allylamine with aryl iodides, the cleavage and isolation of the cinnamylamine products, and their purification as chromatographically separable acetamides.

2. Results and discussion

Finding satisfactory Heck conditions, for our test reaction system with Wang resin-bound allylamine and iodobenzene, was much more difficult than originally anticipated. We tested palladium acetate, $Pd_2(dba)_3$ and Herrmann's palladacycle,^{52–54} as catalysts and triethylamine, sodium acetate, caesium acetate, potassium carbonate, sodium hydrogen carbonate, caesium carbonate, pyrrolidine and 1,1,3,3-tetramethylguanidine, as bases. We performed experiments with or without tri-*o*-tolylphosphine, additives, e.g., potassium chloride and caesium chloride,⁵⁵ and ionic mediators, such as *n*-Bu₄NCl, *n*-Bu₄NBr and *n*-Bu₄NOAc. For solvents we tested *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide, *N*-methylpyrrolidone and even oxygen-free water, as co-solvent. The temperature range of our reactions was 50–130 °C.

In most of our experiments the yields were very low, or the cinnamylamine product was not formed at all. However, we applied successfully the solution phase method of Battistuzzi and coworkers, with palladium(II) acetate (5 mol %), potassium carbonate, *n*-Bu₄NOAc and potassium chloride in DMF.⁴⁸ The reaction of Wang resin-bound allylamine, with iodobenzene at 85 °C for 22 h, gave a 44% yield of *N*-cinnamylacetamide, after cleavage with 50% TFA in dichloromethane, liberation of the amine product from its TFA salt with triethylamine, acetylation with acetic anhydride, triethylamine and *N*,*N*-dimethylaminopyridine (DMAP) (Scheme 2) and purification by flash chromatography. This Heck procedure was originally developed to control the β hydride elimination of the organopalladium intermediate (see Scheme 1), in the synthesis of cinnamaldehydes from acrolein diethyl acetal and aryl halides.⁴⁸ Because allylamine is similarly a relatively electron-rich olefin, having two β hydrogens prone to elimination, the selectivity of the β hydride elimination for its part might well be responsible for the success of our reaction.



Scheme 2. Loading of allylamine to Wang resin, the Heck reaction, cleavage and acetylation.

Download English Version:

https://daneshyari.com/en/article/5218925

Download Persian Version:

https://daneshyari.com/article/5218925

Daneshyari.com