Synthesis of diarylacetylenes and benzofuran derivatives

summary

Márton Csékei
MSc in chemistry

Supervisor: Dr. András Kotschy
associate professor

Chemistry PhD School
Head: Dr. György Inzelt
professor

Synthetic chemistry, materials science and biomolecular chemistry PhD program
Head of the program: Dr. István Tamás Horváth
professor

Eötvös Loránd University
Institute of Chemistry

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1. Introduction

Cross-coupling reactions are very important methods among the transition metal catalyzed processes. A member of this reaction class is the Sonogashira reaction of aryl halides and terminal alkynes,\(^1\) which is a powerful tool for the construction of acetylene derivatives. The introduction of a triple bond between two aromatic cores can be achieved using aryl halides and a masked acetylene, in a coupling-deprotection-coupling sequence. The most frequently used masked acetylenes are ethynyltrimethylsilane,\(^2\) and 2-methyl-3-butyn-2-ol.\(^3\) Using the latter one, our research group recently developed an efficient ‘one-pot’ method for the preparation of diarylacetylenes.\(^4\) Our aim was to introduce a new acetylene source, 1-ethynyl-cyclohexanol in the ‘one-pot’ synthesis of diarylacetylenes.

\[
\text{ArX} + \text{PG} \xrightarrow{\text{Pd(0)L}, \text{Cu(I)}, \text{base}} \text{Ar} \xrightarrow{\text{ArPG'}} \text{Ar}'
\]

1. Scheme. Synthesis of diarylacetylenes using masked acetylenes in a sequential Sonogashira coupling

In certain cases the product of a Sonogashira coupling can be an intermediate in the synthesis of condensed heterocycles. For example the ring closure of orto-arylethynyl-phenol derivatives (VII) leads to the formation of 2-arylbenzofurans (VIII).\(^5\) Our goal was to develop a ‘one-pot’ method for the synthesis of benzofurans, starting from an aryl halide (I), an acetylene source (II) and a 2-halophenol derivative (VI).

\[
\text{Ar} + \text{PG} \xrightarrow{\text{Pd(0)L}, \text{Cu(I)}, \text{base}} \text{ArPG'O} + \text{ArX}
\]

2. Scheme. The strategy of the synthesis of 2-arylbenzofuran derivatives

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2. Results

2.1. The application of 1-ethynyl-cyclohexanol in the synthesis of diarylacetylenes

We investigated the application of 1-ethynyl-cyclohexanol (IX) in the synthesis of diarylacetylenes. These compounds can be synthetized in a sequential or a domino coupling. In the sequential coupling the arylethynyl-cyclohexanol intermediates (X) were isolated, while in the domino process the three steps were performed in one pot. The cleavage of the cyclohexanonone protecting group requires a base. The best results were achieved when potassium hydroxide was used in diisopropylamine.

\[
\text{Ar} \quad \text{Ar} \quad \text{Ar'} \\
\text{OH} \quad \text{OH} \quad \text{OH} \\
\text{ArX} \quad \text{Ar} \quad \text{Ar'}
\]

3. Scheme. The application of 1-ethynyl-cyclohexanol in sequential and domino couplings

2.1.1. The sequential coupling of aryl halides and 1-ethynyl-cyclohexanol

The Sonogashira coupling of aryl bromides and 1-ethynyl-cyclohexanol (IX) gave the appropriate arylethynyl-cyclohexanols (X) in good yield (75-87%), while using aryl iodides we achieved excellent results (91-99%). During the second step of the sequential coupling the cyclohexanon protecting group was released, and the \textit{in situ} formed terminal acetylene (IV) reacted with the second aryl halide (I') to give a diarylacetylene (V). In general the products were isolated in good yield, except when one or both of the aromatic cores were electron rich. Coupling of the arylethynyl-cyclohexanols bearing the electron rich aromatic group with less electron rich aryl halides gave substantially higher yields than the other way around. Except for this limitation the sequential coupling performed reliably well (61-95%). Neutral and electron deficient aryl bromides and iodides gave comparable yields. Both five and six membered heterocycles can be included in the process and the presence of an \textit{ortho}-substituent on the aryl halide had no significant influence on the efficiency of the coupling.

1-Ethynyl-cyclohexanol was succesfully applied in the synthesis of hexadehydro-tribenzo[12]annulene (XII). The deprotection of 1-((o-bromophenyl)ethynyl-cyclohexanol (XI)
gave o-bromophenylacetylene, which in situ went through a sequential homocoupling to give the desired product (XII). The obtained yield is in line with other reported synthetic approaches.6

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\begin{align*}
\text{Br} & \quad \text{OH} \\
\text{XI} & \quad \text{PdL}_2\text{Cl}_2 \\
& \quad \text{CuI, KOH} \\
& \quad \text{toluene, 100°C} \\
\end{align*}
\]

\[
\begin{align*}
\text{L: } & \text{PPh}_3 \ Y: 20\%; \text{ PCy}_3 \ Y: 32\%
\end{align*}
\]


2.1.2. The domino coupling of aryl halides and 1-ethynyl-cyclohexanol

During the domino coupling of aryl halides (I) and 1-ethynyl-cyclohexanol (IX) the formed 1-arylethynyl-cyclohexanols (X) were not isolated, and after the deprotection step the formed terminal alkynes (IV) were reacted with the next aryl halide (I'). The 'one-pot' process resulted in similar yields to the sequential couplings. The significancy of the order of the addition of aryl halides was also observed. In comparison with the use of the analogous 2-methyl-3-butyn-2-ol this method was found to work equally well or even better on the substrates tested.

2.2. The synthesis of 2-arylbenzofurans

The formerly introduced strategy was extended to synthetize 2-arylbenzofuran derivatives (VIII). Iodobenzene was coupled with ethynyltrimethylsilane, 2-methyl-3-butyn-2-ol and 1-ethynyl-cyclohexanol. After deprotection the formed phenylacetylene was coupled with 2-iodophenol, but the desired product was formed only when using TMS-acetylene (65%). The protection of the phenol was necessary when using carbinol based acetylene sources. Using triisopropylsilyl protected 2-iodophenol after addition of tetrabutylammonium fluoride the formed diarylacetylene derivatives (VII) went through a spontaneous ring closure to give the desired products (VIII).

5. Scheme. The 'one-pot' synthesis of 2-arylbenzofurans with different acetylene sources

The five step synthesis (coupling – deprotection – coupling – deprotection – ring closure) gave 2-phenylbenzofuran in 76% yield using methylbutynol, and 87% yield when using 1-ethynyl-cyclohexanol, and none of the intermediates were isolated. In the further studies we used 1-ethynyl-cyclohexanol.

To test the strategy, several aryl halides and protected iodophenol derivatives were coupled. Using electron rich and electron poor, ortho, meta and para substituted aryl halides the desired 2-arylbenzofurans (VIII) were obtained in good yield (62-87%). The 2-arylethynyl-O-triisopropylsilylphenol (VII) intermediates could also be isolated in good yield (69-89%), to give an opportunity for further transformations.

2.3. The synthesis of biologically active benzofuran derivatives

The formerly introduced strategy was applied in the synthesis of two biologically active benzofuran derivatives: a drug candidate, which is in preclinical development\(^7\) (XVI), and a natural product called vignafuran\(^8\) (XX).

The benzofuran derivative on Scheme 6., 4-(E-2-(2-(benzofuran-2-yl)phenyl)-vinyl)benzoic acid (XVI) was synthetized via the Heck coupling of 2-(2'-bromophenyl)benzofuran (XIII) and methyl 4-vinylbenzoate (XIV). For the synthesis of key intermediate XIII the formerly introduced strategy was applied. Starting from 2-bromo-iodobenzene, TIPS protected 2-iodophenol and 1-ethynyl-cyclohexanol the 5 step procedure gave 2-(2'-bromophenyl)-benzofuran (XIII) in 62% yield. The Heck coupling gave selectively the trans

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product (XV), which was isolated in 72% yield. The saponification was performed in the presence of lithium hydroxide, and the desired product (XVI) was isolated in quantitative yield.

6. Scheme. The synthesis of 4-(E-2-(2-(benzofuran-2-yl)phenyl)vinyl)benzoic acid

Summarizing the results, starting from 2-bromo-iodobenzene we synthetized the product in seven steps with 45% overall yield using chromatographic purification only twice.

The ‘one-pot’ strategy was also successful in the total synthesis of vignafuran (XX). The starting TIPS protected iodo-methoxyphenol isomers (XVII, XVIII) were obtained through the iodination and silylation of O-methyl-resorcinol.
7. Scheme. The total synthesis of vignafuran

The domino coupling of the protected resorcinol isomers (XVII, XVIII) and 1-ethynyl-cyclohexanol (IX) gave the XIX acetylene derivative. After deprotection and ring closure vignafuran (XX) was isolated in 69% yield. The yields achieved in the synthesis of these biologically active compounds demonstrate nicely the usefulness and efficiency of the procedure.
3. Publications, oral presentations, posters

Publications

1. A zöld kémia tizenkét alapelve (The twelve principles of green chemistry)
   Barta Katalin; Csékei Márton; Csihony Szilárd; Mehdi Hasszán; Horváth István Tamás; Pusztai Zoltán; Vlád Gábor
   *Magyar Kémikusok Lapja* 2000, 55, 173.

2. Selective Nucleophilic Substitutions on Tetrazines
   Zoltán Novák; Beatrix Bostai; Márton Csékei; Krisztián Lőrincz; András Kotschy
   *Heterocycles* 2003, 60, 2653-2668.

3. The ‘one-pot’ preparation of substituted benzofurans
   Márton Csékei; Zoltán Novák; Géza Timári; András Kotschy

4. The palladium-catalyzed preparation of condensed tetracyclic heterocycles and their application to the synthesis of rac-Mangochinine
   Zoltán Vincze; A. Beatrix Bíró; Márton Csékei; Géza Timári; András Kotschy
   *Synthesis* 2006, 1375-1386.

5. Ethynyl-cyclohexanol: an efficient acetylene surrogate in Sonogashira coupling
   Márton Csékei; Zoltán Novák; András Kotschy
   *Tetrahedron* 2008, 64, 975-981.

6. Development of a One-Pot Sequential Sonogashira Coupling for the Synthesis of Benzofurans
   Márton Csékei; Zoltán Novák; András Kotschy
   *Tetrahedron* 2008, 64, in press.

Oral presentations, lectures

1. Transition Metal Catalyzed Synthesis of Heterocyclic Compounds
   Beatrix Bostai, Márton Csékei, János Faragó, Zoltán Novák, Zoltán Vincze and András Kotschy

2. Transition Metal Catalyzed Synthesis of Heterocyclic Compounds
   Beatrix Bostai, Márton Csékei, János Faragó, Zoltán Novák, Zoltán Vincze and András Kotschy
   *Green Chemistry in Hungary Symposium, Budapest, 2002*.

3. Átmenetifém-katalízis a heterociklusos kémiában
   Bostai Beatrix, Csékei Márton, Faragó János, Nagy András, Novák Zoltán, Vincze Zoltán, Timári Géza és Kotschy András
   MTA Bruckner room lecture, Budapest, 2002.

4. Heterociklusos vegyületek átmenetifém-katalizált színtezise
   Novák Zoltán, Vincze Zoltán, Csékei Márton, Varga Balázs, Timári Géza, Kotschy András
   *MKE National Chemistry Conference, Hajdúszoboszló, 2003*.

5. Tetrazinok szelektív átalakításai nukleofilekkel
   Bostai Beatrix, Faragó János, Csékei Márton, Novák Zoltán, Kotschy András
6. Biológiailag aktív heterociklusok szintézise és molekuláris felismerése
Novák Zoltán, Kele Péter, Csékei Márton, Timári Géza és Kotschy András

7. Benzofürán vázas vegyületek palládiumkatalizált előállítása
Novák Zoltán, Csékei Márton, Timári Géza, Kotschy András
MTA Flavanoidchemistry division meeting, Budapest, 2003.

8. Benzofürán származékok palládiumkatalizált szintézise
Csékei Márton, Novák Zoltán, Timári Géza, Kotschy András

9. Nitrogén heterociklusok palládiumkatalizált előállítása
Bíró A. Beatrix, Vincze Zoltán, Csékei Márton, Kotschy András

10. Tandem Sonogashira coupling: an efficient tool in the synthesis and functionalization of heterocycles
Zoltán Novák, Márton Csékei, András Kotschy

11. Organic moieties as metal surrogates in cross-coupling reactions
András Kotschy, Zoltán Novák, A. Beatrix Bíró, András Nagy, Márton Csékei

12. Metal poor and domino cross-coupling reactions as benign synthetic routes
András Kotschy, Zoltán Novák, Márton Csékei, A. Beatrix Bíró, András Nagy

13. Heterociklusos vegyületek palládiumkatalizált szintézise
Kotschy András, Novák Zoltán, Csékei Márton, Bíró A. Beatrix, Vincze Zoltán, Nagy András

14. Ciklohexanon-védett acetilének alkalmazása Sonogashira-kapcsolásokban
Csékei Márton, Novák Zoltán, Kotschy András
MTA Flavanoidchemistry division meeting, Budapest, 2006.

Posters
Tandem Sonogashira coupling: an efficient tool in the synthesis and functionalization of heterocycles
Márton Csékei, Zoltán Novák, Géza Timári, András Kotschy

Organic moieties as metal surrogates in cross-coupling reactions
András Kotschy, Zoltán Novák, A. Beatrix Bíró, András Nagy, Márton Csékei
1st European Chemistry Congress, Budapest, 2006, Abstract p.239.