Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 82 (12) 1335–1341 (2017)
JSCS–5044
UDC 547.384+542.913:547..7+
547.944/.945:66.095.11
Original scientific paper

Synthesis of substituted allyl acetates from heterocyclic dienes by a Pd-promoted arylation–acetoxylation cascade

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(Received 17 March, revised 3 April, accepted 10 April 2017)

Abstract: Pd-catalysed arylation–acetoxylation cascade, a previously reported methodology, was applied in the functionalisation of unsymmetrical dienes. Both explored classes of compounds, isoquinoline and β-carboline-derived dienes, afforded single regioisomers. Although further improvements of the process are necessary, primarily due to lower yields, the described functionalisation of the studied compounds might be useful in the synthesis of emetine and related naturally occurring compounds.

Keywords: heterocycles; synthesis; emetine-like compounds; Pd-catalysis; regioselectivity.

INTRODUCTION

Allylic acetates are an important class of organic compounds employed in various chemical transformations.[1–5] Their reactions promoted by different transition metals are of particular interest.[6–13] Amongst them, Pd-catalysed processes stand as the most intensively studied methodologies frequently used in the synthesis of various organic molecules, including naturally occurring substances.[14–22] The most common way to access allylic acetates utilizes allyl alcohols as starting materials, which are widely accessible *via* addition of vinyl-nucleophiles on aldehydes or ketones or simple nucleophilic additions on α,β-unsaturated equivalents.[23–26]

Some alternative processes usually based on the acetoxylation of alkenes or related compounds have also been developed.[27–31] To this end, the arylation of dienes/allenes with concomitant acetoxylation promoted by Pd-complexes as a way to produce substituted allyl acetates, Scheme 1, was recently reported.[32,33]

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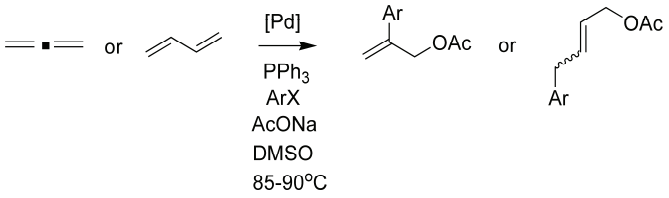
https://doi.org/10.2298/JSC170317046S

Although the product itself is a Pd-substrate, the reaction conditions favoured the formation of the acetate in moderate to good yields.

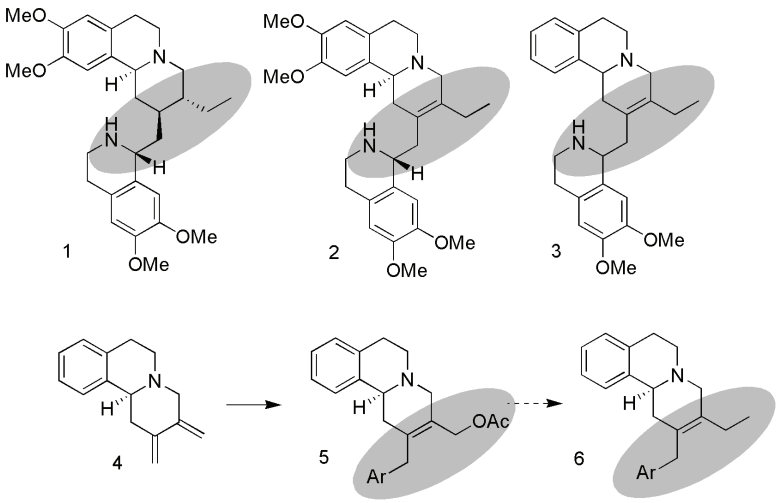


Scheme 1. Pd-promoted arylation/acetoxylation of dienes or allenes.

RESULTS AND DISCUSSION

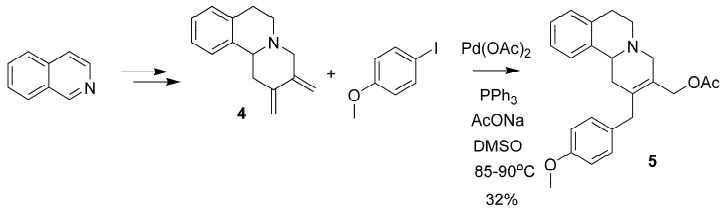
In order to explore further this methodology, the present interest lay in functionalisation of heterocyclic, unsymmetrical diene **4**, which would be potentially useful to access emetine **1** and its derivatives, such as dehydroemetine **2** or biologically active compound **3**.[34–36] In addition, related to these are also protoemetine or protoemetinol.[36]

A potential synthetic strategy towards these natural compounds is outlined in Scheme 2. Functionalisation of the diene moiety followed by the acetate to methyl transformation would provide a core skeleton, while further structural manipulation would lead towards the target compounds.[37–40] Obviously, the first issue with this approach is the regioselectivity of the arylation/acetoxylation process and initial results related to this concern are outlined in this report. Starting from isoquinoline, diene **4** was prepared in several high yielding steps as reported previously.[41,42]



Scheme 2. Emetine and some related derivatives.

Synthesis of corresponding allylic acetate was performed under typical conditions employing $Pd(OAc)_2/PPh_3$ as the catalytic system and an excess of NaOAc (5 equivalents) in DMSO as a solvent (Scheme 3). A single product was isolated in 32 % yield after column chromatography. Analysis of the $^1H/^{13}C$--NMR spectra confirmed the structure of the isolated derivative with the IR and mass spectra corroborating its formation. Full signal assignment in the ^1H-NMR (Fig. 1) and ^{13}C-NMR (Supplementary material to this paper) spectra was based on 2D experiments (H–H/C correlations), while the reaction regioselectivity was unambiguously established by examining the NOESY and HMBC spectra (Supplementary material).



Scheme 3. Synthesis of heterocyclic allyl acetate.

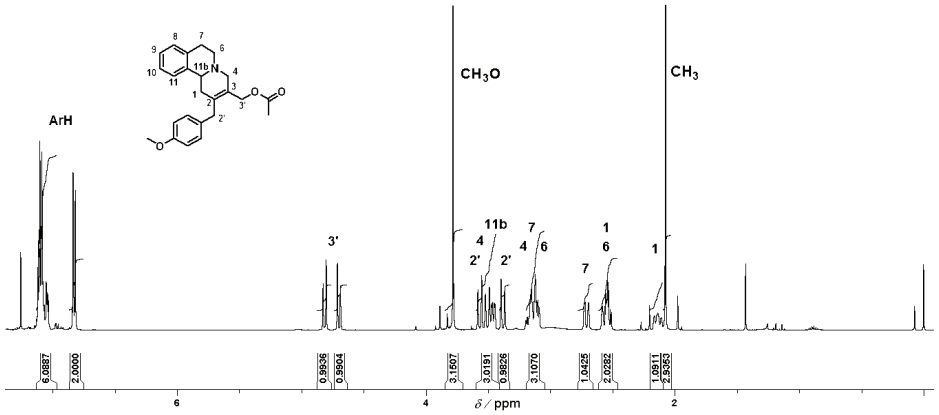


Fig. 1. ^1H-NMR spectrum of allyl acetate **5**.

Analysis of NOESY spectrum showed weak interactions between H-1/H-2′ and H-4/H-3′ hydrogens, supporting the proposed structure (Fig. 2).

Additionally, examination of HMBC spectrum (Supplementary material) led to same conclusion since it showed correlations C-4/H-3′ and C-1/ H-2′ (Fig. 2). The isolation of only one regioisomeric product came as a surprise but detailed analysis of the ^1H-NMR spectrum (200 MHz) of the crude reaction mixture, including careful TLC analysis did not reveal the presence of any other distinctive compound. Furthermore, several additional reactions, as outlined in Scheme 4, were performed.

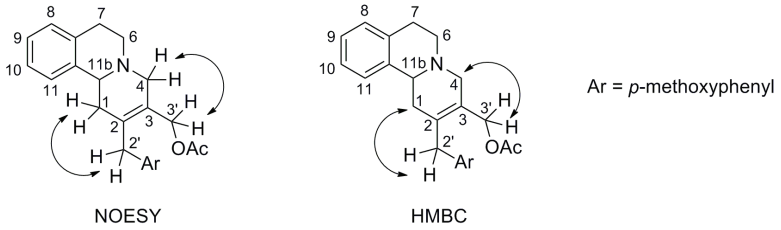
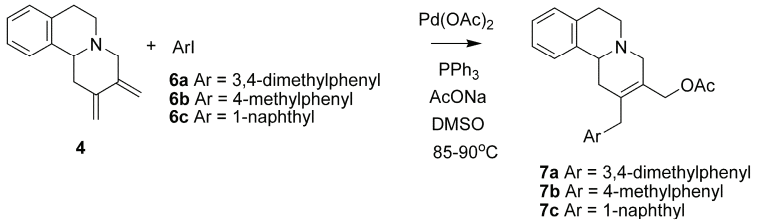
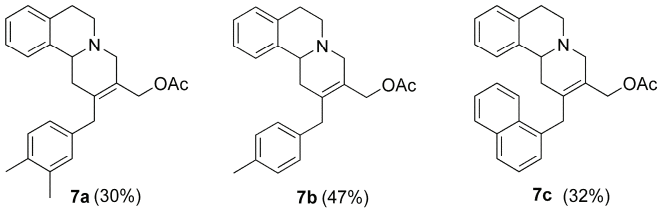


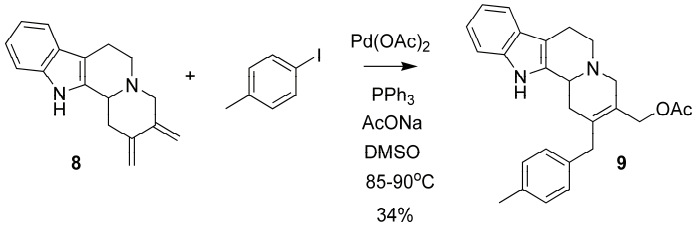
Fig. 2. Key correlations in the NOESY/HMBC spectra of allyl acetate **5**.





Scheme 4. Synthesis of isoquinoline derived allyl acetates.

All transformations were performed as already described producing a single isolatable isomer in all reactions in yields of up to 47 %. The final example was performed using *β*-carboline derived diene **8** that, under the described conditions, produced acetate **9**, a compound structurally related to naturally occurring pseudo-tubulosine (Scheme 5).[36] The indole N–H bond does not seem to influence the reaction pathway and the product was isolated in a yield similar to those outlined in Scheme 4.



Scheme 5. Synthesis of the *β*-carboline derived allyl acetate.

Although the formation of the other regioisomer in all the studied reactions cannot be ruled out completely, it was not observed during the reaction or work-up and purification procedure. At present, it is difficult to rationalise the exclusive formation of the observed products. It is not clear whether the other isomer was not formed at all or it was formed but decomposed during the reaction course. The fact that the yields were relatively low might suggest the second options but it remains to be explored further.

EXPERIMENTAL

General

The NMR spectra were recorded on a Bruker Avance III (500 MHz) spectrometer. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as the internal standard. Deuterochloroform was used as the solvent. Mass spectral data were recorded using an Agilent MSD TOF spectrometer coupled with Agilent 1200 HPLC or Agilent Technologies 5975C MS coupled with Agilent Technologies 6890N GC. The IR spectra were recorded on an IR Thermo Scientific Nicolet iS10 (4950) spectrometer. Silica gel 60 (230–400 mesh) was employed for the flash chromatography while thin layer chromatography was performed using alumina plates with 0.25 mm silica layer (Kieselgel 60 F_{254}, Merck). The compounds were visualised by staining with alkaline potassium permanganate solution. The solvents were purified by distillation before use.

General procedure for the synthesis of allyl acetate from dienes and aryl iodide

A mixture of diene (0.1 mmol) and aryl iodide (0.15 mmol, 1.5 eq), $Pd(OAc)_2$ (10 mol %), Ph_3P (20 mol %) and NaOAc (0.5 mmol, 5 eq) in DMSO (2 mL) was heated at 85–90 °C (bath temperature) under a nitrogen atmosphere for 12 h. The reaction mixture was then cooled to room temperature, Et_2O (20 mL) was added and the mixture washed with H_2O (3×5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (petroleum ether, diethyl ether) to afford the required product.

*[2-(4-Methoxybenzyl)-1,6,7,11*b*-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-3-yl]methyl acetate (**5**).* The compound was synthesised from diene **4** and 1-iodo-4-methoxybenzene following the general procedure. Flash chromatography (SiO_2, 3:2 diethyl ether/petroleum ether volume ratio) afforded **5** (32 %) as a yellow oil.

*[2-(3,4-Dimethylbenzyl)-1,6,7,11*b*-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-3-yl]methyl acetate (**7a**).* The compound was synthesised from diene **4** and 1-iodo-3,4-dimethylbenzene following the general procedure. Flash chromatography (SiO_2, 1:1 petroleum ether/diethyl ether volume ratio) afforded the **7a** (30 %) as a pale yellow oil.

*[2-(4-Methylbenzyl)-1,6,7,11*b*-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-3-yl]methyl acetate (**7b**).* The compound was synthesised from diene **4** and 4-iodotoluene following the general procedure. Flash chromatography (SiO_2, 2:3 petroleum ether/diethyl ether volume ratio) afforded the product **7b** (47 %) as a pale yellow oil.

*[2-(Naphthalen-1-ylmethyl)-1,6,7,11*b*-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-3-yl]-methyl acetate (**7c**).* The compound was synthesised from diene **4** and 1-iodonaphthalene following the general procedure. Flash chromatography (SiO_2, 1:1 petroleum ether/diethyl ether volume ratio) afforded **7c** (32 %) as a pale yellow oil.

*[2-(4-Methylbenzyl)-1,4,6,7,12,12*b*-hexahydroindolo[2,3-*a*]quinolizin-3-yl]methyl acetate (**9**).* Compound was synthesised from diene **8** and 4-iodotoluene following the general

procedure. Flash chromatography (SiO_2, 2:3 diethyl ether/petroleum ether volume ratio) afforded **9** (34 %) as a yellow oil.

CONCLUSION

In conclusion one can say the reactions of unsymmetrical heterocyclic dienes in the arylation–acetoxylation cascade afforded allyl acetate highly regioselective products. Although further improvement of the process is necessary, the described methodology may be potentially useful in the synthesis of a series of natural products or their derivatives.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgement. Financial support from the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. 172009) is greatly appreciated.

ИЗВОД

СИНТЕЗА АЛИЛНИХ АЦЕТАТА ИЗ ХЕТЕРОЦИКЛИЧНИХ ДИЕНА КАСКАДОМ АРИЛОВАЊА И АЦЕТОКСИЛОВАЊА ПРОМОВИСАНОМ ПАЛАДИЈУМОМ

МИЛЕНА Р.СИМИЋ, МИЛОШ Р. ПЕТКОВИЋ, ПРЕДРАГ М. ЈОВАНОВИЋ, ГОРДАНА Д. ТАСИЋ и ВЛАДИМИР М. САВИЋ

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У овом раду проучаване су функционализације несиметричних диена у Pd-катализованим процесима заснованим на каскади ариловање/ацетоксиловање. Диенски изохинолински деривати, као и деривати који садрже β-карболински структурни фрагмент у поменутим трансформацијама дају само један региоизомер. Мада процес захтева даљу оптимизацију, пре свега због нижих приноса, методологија може наћи примену у синтези еметина и сродних природних производа.

(Примљено 17. марта, ревидирано 3. априла, прихваћено 10. априла 2017)

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