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PII: S0040-4039(16)30947-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.07.079
Reference: TETL 47941

To appear in: *Tetrahedron Letters*

Received Date: 17 June 2016
Revised Date: 22 July 2016
Accepted Date: 26 July 2016

Please cite this article as: Bochicchio, A., Cefola, R., Choppin, S., Colobert, F., Noia, M.A.D., Funicello, M., Hanquet, G., Pisano, I., Todisco, S., Chiummiento, L., Selective Claisen rearrangement and iodination for the synthesis of polyoxygenated allyl phenol derivatives, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.07.079

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Graphical Abstract

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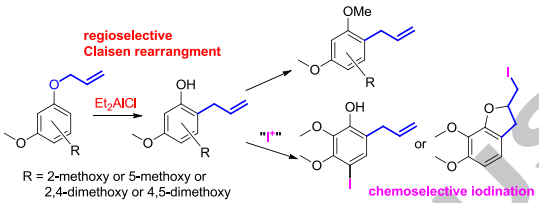

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Selective Claisen rearrangement and iodination for the synthesis of polyoxygenated allyl phenol derivatives

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Phenylpropanoids
Polyoxygenated allylbenzenes
Claisen rearrangment
Chemo-selective iodination
Antibacterial properties

ABSTRACT

Allyl aryl ethers and allyl phenol derivatives were prepared starting from commercial or synthetized phenols. Either Williamson reaction or Et_2AlCl catalyzed Claisen rearrangement were performed to obtain the polyoxygenated molecules. The pivotal allyl phenols were then modified by methylation, iodocyclization or electrophilic aromatic iodination to afford the polyoxygenated derivatives in good to excellent yields. Additionally, their antibacterial properties were also investigated against Gram-positive and Gram-negative bacteria.

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Allylbenzenes are a group of small molecules derived from the general phenylpropanoid pathway. They are key flavoring elements in many important herbs and spices, including peppercorns, cloves, nutmeg, cinnamon, allspice, pimenta, tarragon, and basil.[1] Polyoxygenated allylbenzenes extracted as essential oils from a variety of plants[2] show different biological activities,[3] including antioxidative, antifungal, or anti-inflammatory effects[4] to antitumoral [5] and antibacterial activity[6].

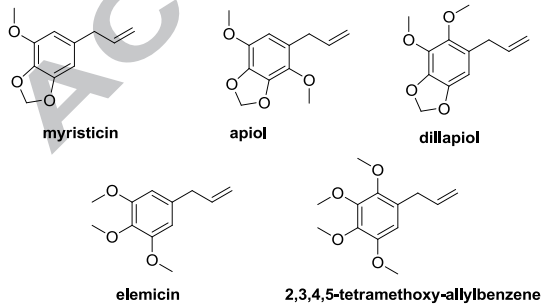

Figure 1: Natural tri- and tetra-oxygenated allylbenzenes.

Among the naturally occurring tri- and tetra-oxygenated allylbenzenes myristicin, apiol and dillapiol are largely widespread, possessing a methylenedioxyphenyl moiety, while elemicin and 2,3,4,5-tetramethoxy-allylbenzene are rather rare[7] (Figure 1).

Their interesting biological properties and their potential use as building blocks[8] prompt us to synthesize tri- and tetra-oxygenated allylbenzenes bearing an hydroxy- or a methoxy-group *ortho* to the allyl moiety. Moreover, a preliminary functionalization as iodinated compounds was studied to prepare more complex structures.

Then, considering the reported antimicrobial properties of the essential oils[6] which may be due to a synergistic effect of the mixture components, we measured the antibacterial activity against Gram-positive and Gram-negative bacteria of synthetized compounds.

In view of the interesting biological activities of the natural halogenated compounds[18a] and the reported antitubercular properties of the halogenated phenyl ethers[18b] we decided to evaluate the antimicrobial activities of the prepared compounds

Results and discussion

A series of different tri- and tetra-oxygenated benzene derivatives with the allyl group as an ether part or as a substituent of phenyl ring was prepared. The key strategic steps following an

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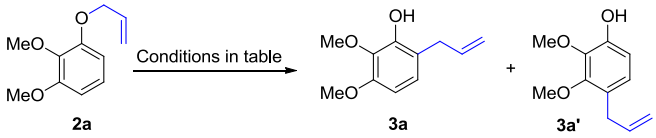
atom-economy approach are selective etherification and Claisen rearrangement.

Our investigation began with phenol **1a**, which was treated with allyl bromide under basic conditions giving quantitatively the allyl ether **2a**. The subsequent conversion of this allyl aryl ether into the allyl phenol **3a** via a Claisen rearrangement[9] was then studied. Considering that this reaction was never performed before on substrate **2a**, we decided to screen different conditions which are listed in Table 1.

Table 1. Claisen rearrangement of compound **2a**



2a **3a** **3a'**

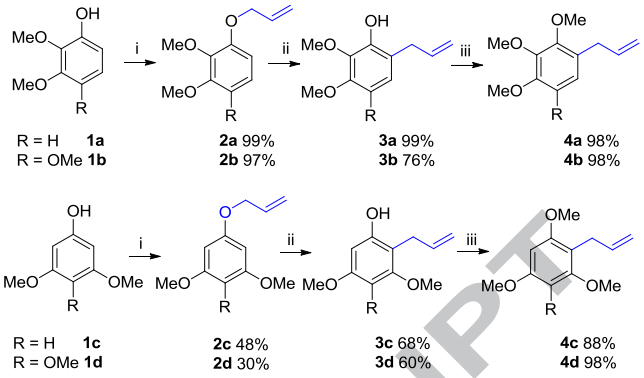
Entry	Conditions	conv (%)[a]	Ratio (**3a:3a'**)[a]
1	DMF, oil bath, 120°C, 1h	s.m.	- : -
2	DMF, MW (330W), 200°C, 1h	5	- : -
3	*N*,*N*-dimethylaniline, oil bath, 190°C, 25h	100	65 : 35
4	NMP, oil bath, 180°C, 48h	s.m.	- : -
5	neat, MW (330W), 200°C, 1h	31	71 : 29
6	neat, heat gun, 1h	95	65 : 35
7	neat, oil bath, 180°C, 8h	95	67 : 33
8	AcOH, oil bath, 120°C, 7h	s.m.	- : -
9	DIBAL, DCM, rt, 1h, 3.5h	s.m.	- : -
10	Et_2AlCl, hexane, 0°C, 1.5h	100	100 : -
11	Me_2AlCl, hexane, 0°C, 1.5h	100	100 : -

[a] Conversion and regioisomeric ratio were evaluated by ^{1}H-NMR spectroscopic analysis.

Initially compound **2a** was rearranged using DMF[10] as the solvent but no reaction occurred with the use of an oil bath or microwave (MW)[11] (entries 1 and 2). Using tertiary aromatic amines[12] (entry 3) a complete conversion of starting material was observed but as a mixture of two inseparable regioisomers with the *ortho* rearranged compound **3a** as the major product. The use of *N*-methylpyrrolidone (NMP)[13] allowed the recovery only starting material (entry 4). *O*-allyl phenol was next used in neat[14] form, modifying just the heating source (entries 5, 6 and 7). The use of MW gave rise to a slightly better regioisomeric ratio between **3a** and **3a'** with moderated conversion of the starting material (31%) while using heat gun or oil bath, we noticed a total conversion with the two possible regioisomers in a ratio of 66:33. Moreover using Brønsted acid[15] and di*iso*butylaluminium hydride (DIBAL) [9b], **2a** was quantitatively recovered (entries 8 and 9). Finally, attempts with Et_2AlCl and Me_2AlCl gave rise to the complete conversion of **2a** and the only desired regioisomer **3a**.[16]

Notably, the presence of the aluminium atom strongly activated the rearrangement and allowed the reaction to work at low temperature avoiding the deprotection of the methyl ether in position 2.

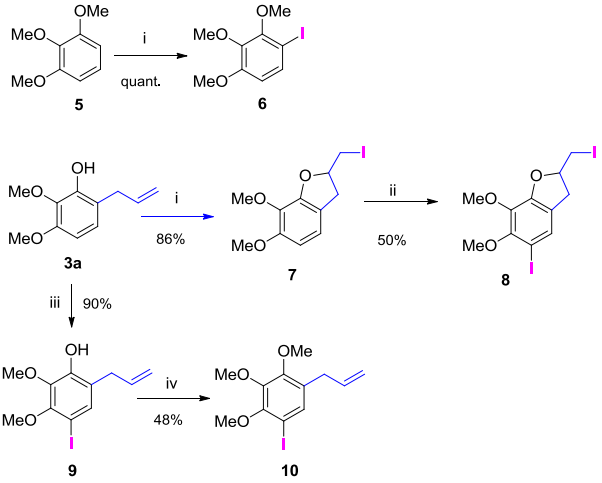
These optimized conditions were applied to the Claisen rearrangement of the allyl ethers **2b-d**, affording the corresponding allyl phenols **3b-d** in good yields (60-76%) and lower reaction times (above 2h).[17] Quantitative methylation of the allyl phenols **3a-d** afforded compounds **4a-d** (Scheme 1).



Scheme 1: [a]*Reagents and conditions*: (i) allyl bromide, K_2CO_3, acetone, reflux; (ii) Et_2AlCl, hexane, 0 °C; (iii) MeI, K_2CO_3, acetone, rt

Iodinated derivatives were also prepared as functionalized compounds and the antibacterial activities were evaluated considering the interesting biological properties of the natural halogenated compounds.[18]

Depending on the polyoxygenated starting compounds and the iodination conditions different products were obtained. Indeed starting from 1,2,3-trimethoxybenzene **5** the iodination occurred in high yield and led to compound **6** using *N*-iodosuccinimide (NIS) and a catalytic amount of trifluoroacetic acid (TFA)[19] (Scheme 2). Performing the same reaction on compound **3a** without TFA, an iodocyclization occurred furnishing selectively mono-iodinated compound **7** in 86% yield. Adding 1,5 equiv. of I_2 and catalytic amount of silver triflate (AgOTf) in dichloromethane (DCM) to compound **7** gave rise to the dihydrobenzofuran derivative **8**.



Scheme 2: [a]*Reagents and conditions*: (i) NIS, (with TFA for **6**) acetonitrile, rt.; (ii) I_2, AgOTf, DCM, 18h; (iii) *t*BuNH_2, I_2, toluene, DCM, rt; (iv) MeI, K_2CO_3, acetone, rt.

Meanwhile treatment of **3a** with iodine, in the presence of *tert*-butylamine (*t*BuNH_2) in toluene[20] for 30 min, led regioselectively to compound **9**[21] (90% yield) which was methylated affording compound **10** (48% yield).

With compounds **2-4** and **6-10** in hand, *in vitro* antibacterial properties of which were screened against both Gram positive (*Bacillus subtilis ATCC 6633*) and Gram negative (*Escherichia coli ATCC 25922*) bacterial strains using gentamicin and kanamycin sulfate as the reference drugs. The minimum

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inhibitory concentrations (MIC) of the synthesized compounds were determined and the results are reported in Table 2.

Table 2. MIC (mg/mL) values of polyoxygenated allyl benzenes (**2-4**) and iododerivatives (**6-10)**.

compound	MIC (mg/mL)		compound	MIC (mg/mL)	
	B.subtilis	*E. coli*		*B.subtilis*	*E. coli*
2a	>1.2	>1.2	**4a**	>1.2	>1.2
2b	>1.2	>1.2	**4b**	>1.2	>1.2
2c	>1.2	>1.2	**4c**	>1.2	>1.2
2d	>1.2	>1.2	**4d**	ND	ND
3a	1.2	1.2	**6**	>1.2	>1.2
3b	1.2	1.2	**7**	ND	ND
3c	1.2	1.2	**8**	ND	ND
3d	1.2	1.2	**9**	**0.128**	>1.0
			10	ND	ND

ND not determined.

All compounds were solubilized in dimethyl sulfoxide (DMSO), and added in the final reaction mixture containing the different microorganisms as described in the experimental section. Unfortunately, MICs of compounds **4d**, **7, 8** and **10** were not determined because they are insoluble under the conditions used for the assay.

The antibacterial screening revealed that allyl aryl ethers **2a-d** and methoxy allyl benzenes **4a-c** did not inhibit the growth of *B. subtilis* and *E. coli*. In contrast the presence of the free hydroxyl group on aromatic ring (**3a-d** compounds) led to enhanced antibacterial effect confirming the key role of phenolic part for the antimicrobial activity.[22-24]

It should be stressed that the similar behavior of phenolic compounds on *E. coli* and *B. subtilis* has suggested a broad-spectrum antimicrobial effect of the tested compounds, but it is not easy to propose a mechanism. It has been reported that phenolic compounds could interact with the cell membrane of microorganisms,[25] by leading to permeability changes of cations like H^+ and K^+.[23,26] The resulting dissipation of ion gradients could affect cell viability causing cell death.

Interestingly, the greatest effect was measured in the presence of compound **9** for *B. subtilis* (0.128 mg/mL), while *E. coli* remained insensitive to this compound. The reason of this toxicity against Gram positive bacteria is not clear but the iodine atom on the phenol ring appears to be important.

In conclusion, a synthetic and efficient methodology to obtain regioselectively functionalized polyoxygenated allyl phenols has been successfully achieved *via* Et_2AlCl-mediated Claisen rearrangement. Moreover, chemoselective iodinations *via* NIS or tBuNH$_2$/I$_2$ complex on the same starting phenol **3a** have provided iodo-dihydrobenzofuran or iodinated aromatic compounds, respectively.

Finally, according to biological studies on a very small library of synthesized compounds, one can speculate that the allyl aryl ethers (**2a-d**) as well as the polymethoxy allylbenzenes (**4a-c**) show a negligible antibacterial activity while phenols **3a-d** had a modest activity towards both Gram positive and Gram negative bacteria. The functionalization of phenolic ring of **3a** with an iodine in *para* position leads to higher antibacterial activity on Gram positive.

Essays are under investigation in order to evaluate how the presence of iodine atom and its position on the phenol ring could influence the antibacterial activity.

Acknowledgments

Financial support has been provided by Università degli Studi della Basilicata.

Authors would like to thank Prof. Antonio Rosato of University of Bari –"Aldo Moro" for providing microorganisms used in this study.

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Supplementary Material

Supplementary material is available. Experimental section and copies of ^{1}H and ^{13}C NMR spectra are reported .

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Highlights

- Polyoxygenated phenol synthesis *via* Williamson reaction and Claisen rearrangement.
- Methylation and iodination were performed to obtain polyoxygenated derivatives.
- Antibacterial properties against Gram-positive and Gram-negative were tested.
- Regioselective rearrangement and chemoselective iodination were performed.

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