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A room temperature alternative of the Claisen rearrangement route to *ortho* allylated phenols: unique reactivity pattern of allylindium reagents

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Abstract—Quinol ethers and quinone monoketals are shown to undergo formal anti-Michael addition reactions with allylindium reagents at room temperature to give only *ortho* allylated phenols in good yields.

The Claisen rearrangement,[1] viewed as a [3,3] sigmatropic thermal isomerization, is a very useful carbon–carbon bond forming reaction. It has been widely used in the total synthesis of natural products.[2] Since the original report[3] by Claisen in 1912, the reaction has witnessed numerous variants such as Caroll, Ireland, Bellus, etc., which are all related to the aliphatic version of the rearrangement.[1] Surprisingly, there is no literature report on the alternatives of the aromatic Claisen rearrangement route to allylated products. The Claisen route to *ortho* allylated phenols traditionally entails two steps: *o*-allylation of phenols and thermal isomerization of the *o*-allyl derivatives. The rearrangement is typically carried out at 150–300 °C. Although the products of rearrangement are usually *ortho* isomers, *para* allylated phenols and benzofurans are often formed as side products. The rearrangement can be performed at room temperature only when alkylaluminium halides are used as catalysts.[4] However, the requirement for a large excess of highly acidic catalysts restricts the practical uses of this variant. Herein, we report an ambient temperature alternative of the Claisen rearrangement route to *o*-allylated phenols from the same set of starting materials as used in the Claisen route. This is based upon oxidative dearomatization of phenols to quinol ethers or quinone monoketals followed by their formal anti-Michael addition reaction with allylindium reagents. The two-step conversion can be carried out in one operation, by avoiding isolation and purification of the substrates from the crude reaction mixtures if they are prepared by oxidation of the corresponding phenols with phenyliodonium diacetate (PIDA).

In connection with our ongoing programme[5] on the total synthesis of angucyclines, we planned to prepare 5-allyl-4-methoxy-2-cyclohexenones (e.g., **5**) from quinol derivatives,[6] which are accessible via a variety of routes. Since there is no literature report on 1,4-addition of allylmetal reagents to quinol ethers,[7] we envisaged the preparation of compound **5** in two steps (Scheme 1), namely 1,2-addition of an allylmetal reagent to compound **2** and oxy-Cope rearrangement of the resulting product **4**. The proposed tandem methodology is well documented for acyclic systems and quinones.[8] In view of increasing interest in the use of allylindium reagents[9] and the operational simplicity associated with them, we decided to examine the Barbier type reactivity of the parent allylindium reagent **3** towards quinol ether **2** in order to obtain compound **4**.

When compound **2**,[10] prepared by oxidation of *p*-cresol with phenyliodonium diacetate in methanol, was reacted in DMF with the allylindium reagent derived from allyl bromide, a colourless liquid was isolated as the sole product after work-up of the mixture and purification of the crude product by chromatography. It was found to be 2-allyl-4-methylphenol **6**, contrary to the expected product **4** or **5** (Scheme 1). Since both 2-allyl and 3-allyl

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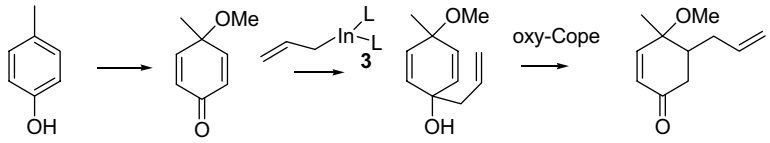
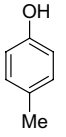
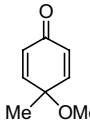
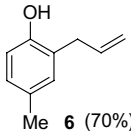
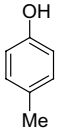
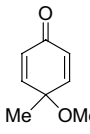
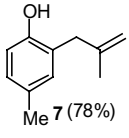
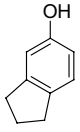
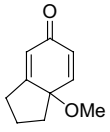
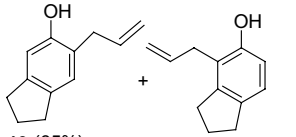
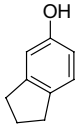
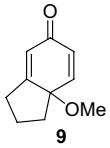
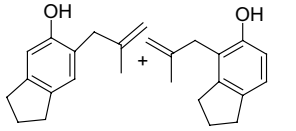
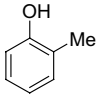
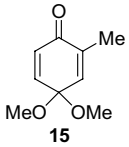
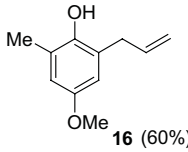
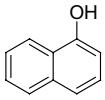
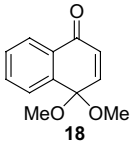
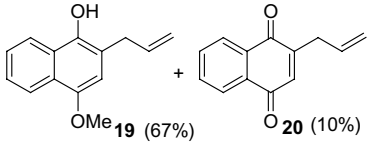
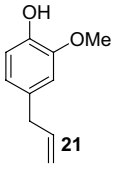
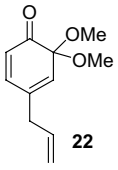
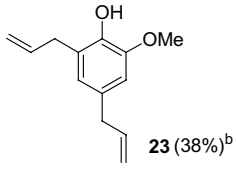


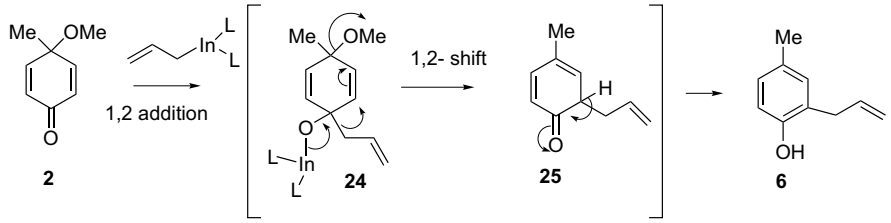
Scheme 1. The proposed route for the preparation of cyclohexenone **5**.

derivatives of 4-methylphenol **1** have very similar ^{1}H NMR spectra, the structure of compound **6** was confirmed by spectroscopic comparison with an authentic sample prepared from *p*-cresol in two steps by the published method.[11] This unusual reactivity of quinol ether **2** prompted us to look into the scope of the reaction and thus several substrates were examined under similar conditions. The results are summarized in Table 1. When the indium reagent derived from 2-methylallyl bromide was examined with quinol ether **2**, the *ortho* allylated phenol **7**[12] was obtained as the sole product in 78% yield. The result with quinol ether **9**[5a] was different as expected. The allyl derivative **10** was formed in 65% yield along with its regioisomer **11** in 14% yield. Though

Table 1. Allylation of quinol ethers and quinone ketals with allylindium reagents[18]

Entry	Phenol	Enone	Metal, allyl bromide	Product (% yield)[a]
1				 **6** (70%) (45%)[b]
2				 **7** (78%)
3	 **8**	 **9**		 **10** (65%) **11** (14%)
4		 **9**		 **12** (70%) **13** (10%)
5	 **14**	 **15**		 **16** (60%)
6	 **17**	 **18**		 **19** (67%) **20** (10%)
7	 **21**	 **22**		 **23** (38%)[b]

[a] Yields are unoptimized and refer to the allylation step.
[b] Yields refer to a one-pot process.



Scheme 2. Mechanistic proposal for the formation of *o*-allylphenol from quinol ethers.

not separable by chromatography, their structures could be ascertained from the ^{1}H NMR spectrum of the mixture. The observed regioselectivity with ether **9** can be explained in terms of a hyperconjugative effect of the alkyl chain of the cyclopentane ring. A similar result was obtained with the 2-methylallylindium reagent and quinol ether **9** (entry 4).

Several quinone monoketals were next examined to broaden the scope of the reaction. The monoketal **15**,[13] when submitted to the reaction with allylindium reagent **3** at room temperature, provided compound **16** as the only product. 1,4-Naphthoquinone monoketal **18** yielded methoxy-substituted allylnaphthol **19** together with 2-allyl-1,4-naphthoquinone **20**. The latter might have been formed by aerial oxidation of **19** during work-up of the reaction. It should be noted that partially protected naphthols are useful intermediates for the synthesis of pyranonaphthoquinone antibiotics.[14] The only example of an *ortho* quinone monoketal studied was compound **22**. This was prepared from eugenol **21** in accordance with the reported procedure[10] and was treated with allylindium reagent **3** to furnish a complex mixture of products. Though the formation of the desired product **23** was revealed by examination of the ^{1}H NMR spectrum of the mixture, it was too complex for further investigation.

The unanticipated result with eugenol **21** and the exceptional stability of allylindium reagents to protic solvents led us to explore the possibility of abbreviating the two-step preparation of allylated phenols to a single-step operation, thus adding synthetic usefulness to the method. The reaction mixture resulting from addition of PIDA to a methanolic solution of *p*-cresol **1** was treated as such with a solution of the allylindium reagent prepared as previously described. Work-up of the reaction mixture followed by purification of the crude product provided compound **6** in 45% yield. The superiority of the one-step version was remarkable for the preparation of allyleugenol **23**. When quinol derivative **22** was directly used for allylation without isolation, the expected allyl derivative **23** was obtained in 38% overall yield, which was better than that observed in the two-step sequence. This higher yield may be a consequence of avoidance of dimerization of the unstable quinol ether **22** during chromatographic purification.

In stark contrast to the established multimodal reactivity pattern of quinol derivatives, the reactivity of quinol ethers or quinone monoketals with allylindium reagents is unique and without any precedents. The closest similarity can be found in the reaction of allylmagnesium bromide with quinone monoketal derivatives as reported by Swenton and co-workers.[15] To account for the unusual formation of 2-allyl-4-methylphenol **6**, we were initially tempted to invoke intermolecular S_N2' displacement[16] of the methoxy group in **2** by an allylmetal nucleophile. However, considering the high propensity[9d] for 1,2-addition of allylindium reagents to carbonyl compounds, we propose an anionic vinylogous semipinacol[17] type rearrangement (Scheme 2) of the initially formed 1,2-adduct **24** to **25**. The indium salts formed during the reaction, being acidic in nature, probably trigger displacement of the methoxy group with concomitant migration of the allyl group. Attempts to isolate the 1,2-adduct **24** and thereby substantiate the proposed mechanism were of no avail.

In conclusion, this study has revealed a formal anti-Michael addition mode for the reactivity of quinol ethers and quinone monoketals towards allylindium intermediates, and has increased their synthetic utility. It has also established the possibility of further developing the more convenient alternative of the aromatic Claisen rearrangement. Resolution of the obvious questions generated by this initial finding with respect to substrate specificity and reaction mechanism is under investigation.

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18. *Typical procedure*: to a stirred solution of In metal (191.7 mg, 1.67 mmol) and NaI (250 mg, 1.67 mmol) in DMF at room temperature, was added dropwise allyl bromide (0.21 mL, 2.47 mmol). When the indium had completely dissolved to form a homogeneous solution, a solution of quinol ether or quinone monoketal (1.59 mmol) in DMF (1.5 mL) was added. The resulting mixture was stirred at ambient temperature until complete consumption of the substrate (usually 12–24 h) and was then quenched by addition of 3 N HCl (5 mL). It was then extracted with ether (3×20 mL) and the combined organic extracts were washed with aqueous sodium thiosulfate, brine, dried and concentrated. Chromatographic (silica gel) purification (1:10 mixture of ethyl acetate and petroleum ether) of the resulting residue furnished the product.
Selected data: compound **12** (oil): δ_H ($CDCl_3$): 6.93 (1H, s), 6.71 (1H, s), 4.92 (1H, s), 4.86 (1H, s), 3.34 (2H, s), 2.70–3.00 (4H, m), 1.95–2.15 (2H, m), 1.75 (3H, s); HRESIMS (*m*/*z*): 187.1118, calcd for $C_{13}H_{15}O$ ($[M-H]^+$): 187.1123. Compound **19** (oil): δ_H ($CDCl_3$): 8.00–8.25 (2H, m), 7.35–7.60 (2H, m), 6.56 (1H, s), 5.95–6.20 (1H, m), 5.10–5.35 (2H, m), 3.96 (3H, s), 3.50–3.60 (2H, m). Compound **23** (oil): δ_H ($CDCl_3$): 6.73 (1H, s), 6.63 (1H, s), 5.75–6.05 (2H, m), 5.42 (1H, br s), 4.85–5.15 (4H, m), 3.85 (3H, s), 3.20–3.35 (4H, m).