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ORIGINAL PAPER

An efficient 1,3-allylic carbonyl transposition of chalcones

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Abstract A very simple, convenient, and efficient procedure is reported for the 1,3-allylic carbonyl transposition of chalcones. The transposition can be achieved by reduction of chalcones to 1,3-diarylpropan-1-ols and dehydration of the latter to give 1,3-diarylpropenes followed by benzylic/allylic oxidation.

Keywords Dehydration · 1,3-Diarylpropenes · Oxidation · Tetrahydrochalcones · Transposed chalcones

Introduction

Efficient transposition of a functional group from one carbon to another, as in 1,3-carbonyl transposition of α,β-unsaturated ketones, offers a wide degree of flexibility in synthesis design of many naturally occurring compounds [1, 2]. A number of synthesis methods and reagents are available for effecting allylic carbonyl transposition. In general, however, these methods suffer from low yields and/or multi-step manipulation of delicate intermediates and alkylation of intermediates [2]. The reported transposition of chalcones is noteworthy, not only from the viewpoint of the novelty in the reaction path, but also in view of the importance of the products (chalcones), which serve as starting materials for the synthesis of flavan-4-ols, flavanones, 3-hydroxy flavones, heterocyclic compounds, etc. [3, 4]. Chalcones are also known to possess multi-pronged activity, e.g. as antihypertensives, cardiovascular agents, bronchodilators, and immunomodulators [5, 6], and have anticancer and antibacterial activity [7–9]. Hence, there is a need for synthesis of new chalcones, which may be difficult to prepare by conventional methods owing to the non-availability of appropriate starting materials.

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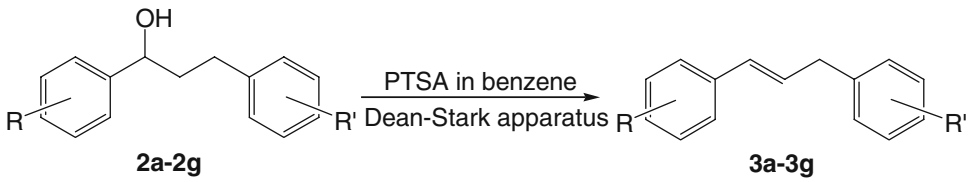
Results and discussions

We now report a new synthesis protocol wherein one chalcone can be converted to another by 1,3-allylic transposition of the carbonyl group. The transposition can be achieved by (1) reduction of chalcones to 1,3-diarylpropan-1-ols, (2) dehydration of 1,3-diarylpropan-1-ols to 1,3-diarylpropenes, and (3) oxidation of 1,3-diarylpropenes without rearrangement. Recently, we have reported that chalcones **1** can be rapidly reduced to the corresponding 1,3-diarylpropan-1-ols **2** with nickel boride, generated in situ from anhydrous nickel chloride and sodium borohydride in methanol at ambient temperature [10]. With these results in hand, we attempted dehydration of 1-phenyl-3-(4-tolyl)propan-1-ol (**2a**) with a variety of reagents known for dehydration of alcohols [11]. Dehydration with catalytic amounts of *p*-toluene sulphonic acid (PTSA) in benzene using Dean-Stark apparatus, under reflux, appeared to be the ideal procedure for these substrates. Reaction was completed in 45 min, as monitored by TLC, giving 1-phenyl-3-(4-tolyl)propene (**3a**) in 95% yield. All other 1,3-diarylpropan-1-ols (**2b–2f**) also underwent dehydration smoothly under these conditions, giving corresponding 1,3-diarylpropenes (**3b–3f**) (Scheme 1, Table 1). All the 1,3-diarylpropenes are known, and they were identified by comparison of spectral data with [12, 13].

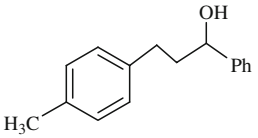
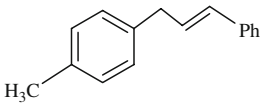
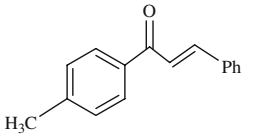
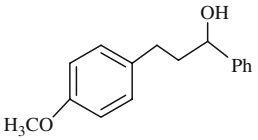
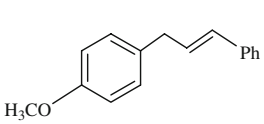
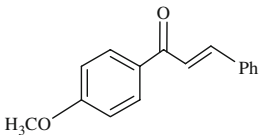
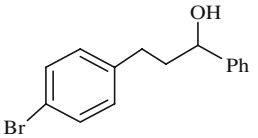
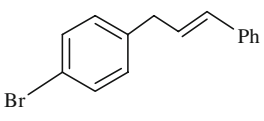
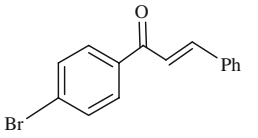
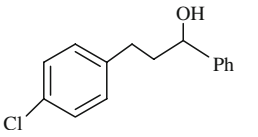
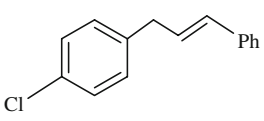
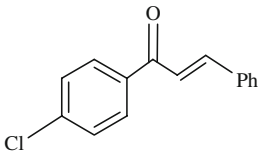
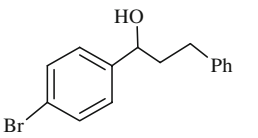
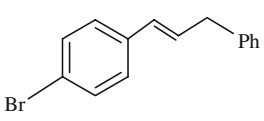
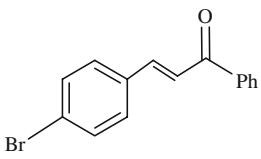
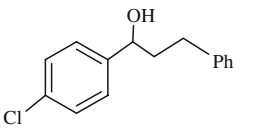
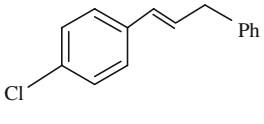
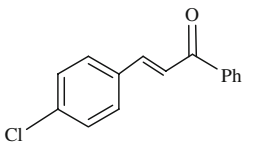
Allylic oxidation of 1,3-diarylpropenes posed some problems. Oxidation of **3a** was attempted with CrO_3/AcOH/H_2O, NBS/DMSO, NBS/THF/H_2O, DDQ/dioxane,

Scheme 1



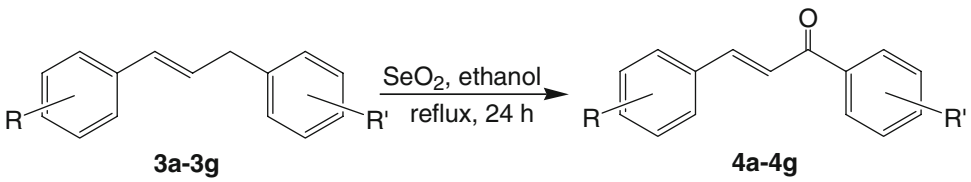
2a-2g **3a-3g**

Table 1 Dehydration of **2** to **3** and oxidation of the latter to transposed product **4**

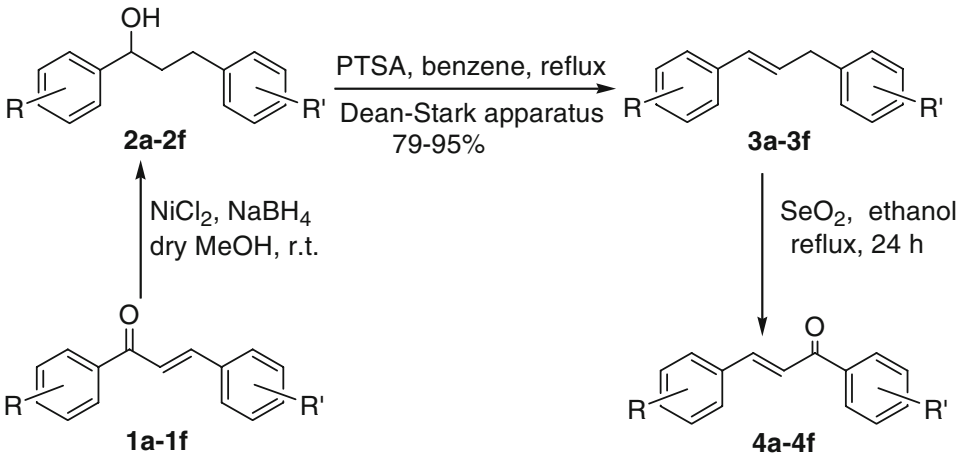
S.No.	**2**	**3**	**3** Yield/% (**2** to **3**)	**4**	**4** Yield/% (**3** to **4**)
a			95		50
b			83		58
c			84		53
d			79		51
e			89		58
f			87		54

DDQ/dioxane/pyridine and DDQ/$CHCl_3$/H_2O, but in none of these cases was the desired product obtained. The reaction of **3a** with DDQ in $CHCl_3$/H_2O/reflux was sluggish, and none of the products corresponded to the desired one. When **3a** was heated under reflux with 3 equiv. of DDQ in CH_3COOH, the reaction was complete in 3 h. but the product obtained was the completely rearranged product, **1a** (starting chalcone), and not the desired product, **4a**. Similarly, reaction of **3b** also gave the rearranged product, **1b**, under these conditions, implying that oxidation of allylic/benzylic $–CH_2–$ was proceeding along with the rearrangement. The reaction of **3a** with DDQ (2 equiv.) in

Scheme 2



Scheme 3



CH_2Cl_2/H_2O (4:1) at room temperature yielded a nearly 1:1 mixture of **4a** and **1a**, but it proved impossible for us to separate the two chalcones. Neither increasing the amount of water from 5% to 50% nor higher molar ratios of substrate to DDQ changed the reaction rate appreciably and increased the concentration of **4a** noticeably. Other solvents such as methanol and methanol–water were also of no help.

Selenium dioxide proved to be the most reliable reagent for the direct insertion of oxygen at the allylic carbon regioselectively to give the desired products. We attempted reactions of **3a** by changing molar ratios of substrate to SeO_2 and solvents to achieve the desired transformation. The reaction of **3a** with SeO_2 in ethanol gave *p*′-methyl chalcone **4a** in 50% yield. Other 1,3-diarylpropenes **3b–3f** were oxidized under identical conditions to transposed chalcones (Scheme 2, Table 1). All the products are known, and they were identified by comparison of their spectral data with those in [14–18].

In conclusion, the successful 1,3-allylic carbonyl transposition of chalcones had been achieved in moderate-to-good yields. The reaction sequence and conditions represent significant improvement over existing methodologies (Scheme 3).

Experimental

All the melting points were recorded on Tropical Labequip apparatus. IR spectra were recorded on Perkin-Elmer FT-IR SPECTRUM-2000. NMR spectra were recorded on an FT-NMR model R-300 Hitachi (300 MHz) with TMS as the internal standard. All the products were well known and were identified by co-TLC, m.p., mixed m.p. (wherever applicable), IR, NMR, and mass spectra with the authentic sample. Literature melting points are cited from [15–18].

*General procedure for the reduction of chalcones **1** with nickel boride*

In a typical experiment, 1.0 g *p*-methyl chalcone (**1a**) (4.50 mmol), 1.16 g anhydrous nickel chloride (9.0 mmol), and 25 cm^3 dry methanol were stirred magnetically under a nitrogen atmosphere. Sodium borohydride (1.02 g, 27.02 mmol) was added to the mixture carefully, and the contents were stirred vigorously. TLC analyses (petroleum ether:ethyl acetate 95:5, v/v) showed complete reduction after 5 min. The reaction mixture was filtered through a celite pad (~2.5 cm). The filtrate was diluted with ca. 50 cm^3 water. It was extracted with 3 × 10 cm^3 CH_2Cl_2, washed with ca. 10 cm^3 water, dried over anhydrous sodium sulfate, and concentrated in a Büchi rotary evaporator. The crude product was purified by column chromatography on neutral alumina (petroleum ether:ethyl acetate 92:8, v/v). 1-Phenyl-3-(4-tolyl)propan-1-ol (0.814 g, 80%) (**2a**) was obtained as a white solid, m.p. 54–56° C ([16] 56 °C).

*General procedure of dehydration of 1,3-diarylpropan-1-ols **2** with PTSA*

In a typical reaction, a solution of 0.5 g 1-phenyl-3-(4-tolyl)propan-1-ol (**2a**) (2.40 mmol) in 50 cm^3 of benzene

and a catalytic amount of PTSA (0.01 g) was refluxed for 45 min in a 100-ml round-bottomed flask fitted with a Dean-Stark apparatus. The progress of the reaction was monitored by TLC (petroleum ether:ethyl acetate 95:5, v/v). The reaction mixture was cooled and neutralized with 25 cm^3 of saturated $NaHCO_3$ solution. The benzene layer was separated and dried over anhydrous sodium sulfate. The solvent was removed in a rotary evaporator, and the product was purified by column chromatography using neutral alumina and petroleum ether, to yield 1-phenyl-3-(4-tolyl)propene (**3a**) (0.437 g, 95%) as a colourless oil identical to the product described in [12].

The reactions can also be carried out successfully in toluene under the same reaction conditions.

*General procedure of oxidation of 1,3-diarylpropenes **3** with SeO_2*

In a typical reaction, a mixture of 0-phenyl-3-(4-tolyl)propene (**3a**) (1.92 mmol), 3.17 g SeO_2 (28.8 mmol) and 25 cm^3 ethanol was heated under reflux for 24 h. The mixture was cooled and filtered through a celite pad ($\sim$2.5 cm). The filtrate was diluted with ca. 50 cm^3 water and extracted with 2 $\times$ 10 cm^3 CH_2Cl_2. The CH_2Cl_2 layer was washed with 25 cm^3 of saturated $NaHCO_3$ solution, dried over anhydrous sodium sulfate, and concentrated in a Büchi rotary evaporator. The crude product was purified by column chromatography on neutral alumina using petroleum ether:ethyl acetate (97:3, v/v) as eluent. *p'*-Methylchalcone (**4a**) (0.1707 g, 50%), based on the consumption of starting material, was obtained as a yellow solid, m.p. 73 °C ([12] 75 °C).

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