One pot reactions of benzaldehydes to cinnamic acids and arylpropiolic acids in aqueous medium

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Abstract: Benzaldehydes undergo Wittig olefination with alkoxycarbonylmethylidenephosphorane in 10w% aqueous NaOH. The cinnamates are hydrolysed under the conditions and cinnamic acids are obtained after simple extractive work-up. Under the same conditions, benzaldehydes react with alkoxycarbonylbromomethylidenephosphorane to give arylpropiolic acids.

Introduction

Cinnamic acids and their derivatives have found a range of applications such as as antifungal agents,[1a] as firming agents for the skin in cosmetic formulations, and as a stabilizer in the food industry. Our interest[2a,b] in cinnamic acids and their derivatives stems from the fact that cinnamic acids[2c] and especially dihydroxycinnamic acid derivatives can be viewed as potential anti-tumour agents.

There are a number of common ways to prepare cinnamates and cinnamic acids, among them the reaction of benzaldehydes with malonic acid (for cinnamic acids, Knoevenagel reaction with subsequent decarboxylation[3a,b]) or with alkoxymalonates (for alkyl cinnamates[3a,b]), of benzaldehydes with acetic anhydride/sodium acetate (Perkin reaction[3c]), and of iodoarenes with acrylates via Heck reaction[3d] with subsequent hydrolysis. Nevertheless, for the preparation of cinnamic acid derivatives, the Wittig olefination reaction of benzaldehydes with the stabilized alkoxymethylidenetriphenylphosphorane has been used extensively, too.[4]

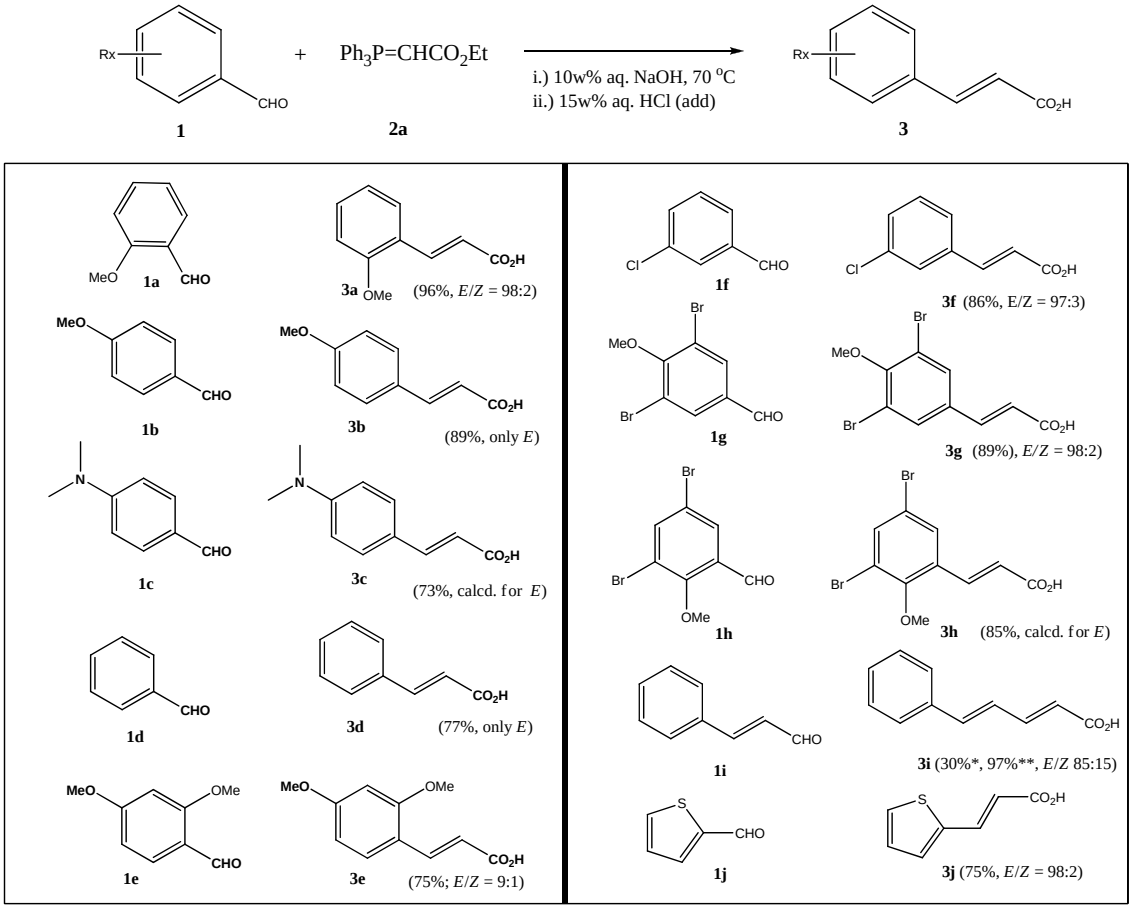
Traditionally, Wittig reactions with stabilized phosphoranes have been run in thermally heated organic solvents such as THF and benzene, often under acid catalysis.[5] More recently, they have been performed under non-classical reaction conditions, such as solventless[6] or in ionic liquids,[7] often combined with the use of microwave irradiation

or ultrasonication. Also, water soluble phosphoranes[8] were developed to carry out the reactions in aqueous solutions. Subsequently, Wittig olefination reactions with stabilized and semi-stabilized, non-water soluble phosphoranes have been performed in water.[9,10] These reactions could even be run in one pot with other reactions, such as with Suzuki Miyaura cross coupling reactions.[11] Nevertheless, the work-up in almost all cases still involved extractions with organic solvents and in some cases even chromatographic separation using organic solvents as eluents. Often, such type of work-up involves the use of more organic solvents than does the reaction itself, if it were run in organic medium. Previously, the authors had developed a biphasic reaction system for the Wittig olefination with stabilized and semi-stabilized phosphoranes, which uses water and hexane as solvents.[12] Here, the reaction takes place mostly at the solvent interface. Triphenylphosphine oxide is only sparingly soluble in hexane and in water and can be filtered off after the reaction. Then, the organic (hexane) phase can be concentrated *in vacuo* to give the products in reasonable purity. Hexane could be recycled. This reduces the use of organic solvents significantly.

Results and Discussion

In the following, the authors portray the synthesis of cinnamic acids **3** and of arylpro-

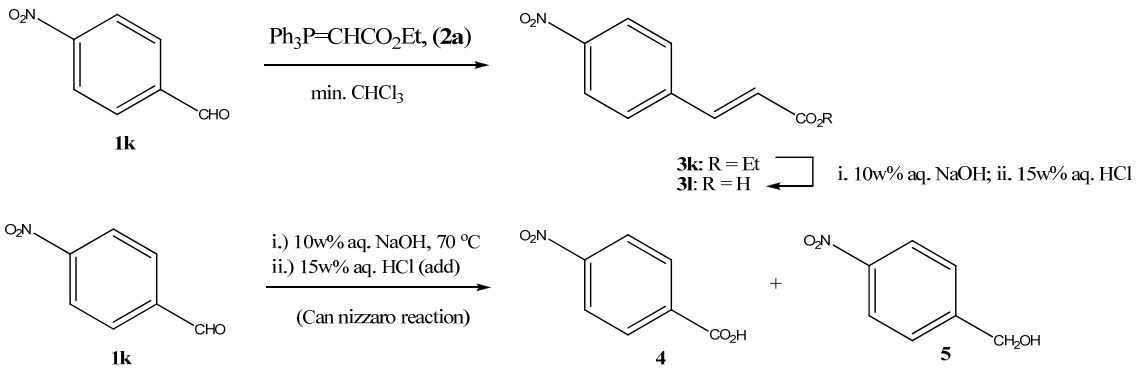
piolic acids **4** from (substituted) benzaldehydes **1** in one pot, circumventing the use of organic solvents in both reaction and work-up. When a mixture of (substituted) benzaldehyde **1** and ethoxymethylidenetriphenylphosphorane (**2a**, 1.3 eq.) is heated in a 10w% aq. NaOH solution, sodium cinnamates are formed by Wittig olefination and subsequent ester hydrolysis. Upon neutralization of the aqueous solutions with 15w% aq. HCl, the cinnamic acids **3** can be obtained by simple filtration and air-drying of the solids. In this way, a number of cinnamic acids **3** could be isolated (Table 1).



* no additive; ** tetramethylammonium bromide (0.15 eq. Bu_4NBr) added

The anilinic nitrogen in **3c** is not basic enough to be protonated on careful neutralization

of the reaction solution and solid **3c** can be filtered off from the neutralized solution without problem. In most cases, a good *E*-selectivity for the cinnamic acids is observed. Only for phenylpenta-2,5-dienoic acid (**3i**) and 2,4-dimethoxycinnamic acid (**3e**), an appreciable amount of Z-isomer is formed. 4-Nitrobenzaldehyde (**1k**), however, does not give an adequate result. With ease, 4-nitrobenzaldehyde (**1k**) and ethoxymethylidenetriphenylphosphorane (**2a**) undergo Wittig olefination, when the reaction is run in chloroform (Scheme 1).



Scheme 1

The ester hydrolysis of **3k** in 10w% aq. NaOH proceeds normally, and **3l** is obtained, which can be filtered off and dried after acidification of the reaction solution. In 10 w% aq. NaOH, 4-nitrobenzaldehyde (**1k**), however, undergoes a rapid Cannizzaro reaction, which would be expected to be the general competing reaction for benzaldehydes in basic aq. solutions. In case of the other benzaldehydes used, the Cannizzaro reaction is not

found to be a main side reaction. The reason for this may be that the Wittig olefination proceeds rapidly in the lipophilic droplets of benzaldehyde and phosphorane mixture, initially suspended in the aqueous solution. 4-Nitrobenzaldehyde (**1k**) in 10w% aq. NaOH, however, quickly forms a deep red homogenous solution, from which one of the Cannizzaro products, 4-nitrobenzoic acid (**4**), can easily be obtained by extraction with CH_2Cl_2 and acidification of the aqueous phase with subsequent extraction of the phase and crystallization of **4**.[13]

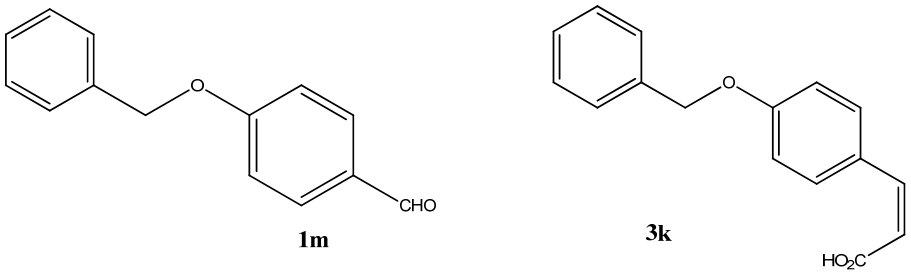


Figure 1

In the case of **1m** (Figure 1), only (*Z*)-*p*-benzyloxycinnamic acid (**3k**) was noted as a cinnamic acid fraction. The corresponding *E*-isomer was not detected. As at 70 °C triphenylphosphine oxide and Wittig product form (liquid) hydrophobic micelles and much of the hydrolysis of the esters takes place at the micelle boundary, it may be that the ethyl (*E*)-*p*-benzyloxycinnamate, more facilely forming intermolecular layers within the micelle, is not as readily accessible as the *Z*-isomer. It must also be noted that under the strongly basic conditions, the benzyloxy function is not stable enough and is cleaved off to provide the hydroxy-substituted compound. That micelles play a role in the out-

come of the ester hydrolysis can be seen in the fact that for alkyl cinnamates with larger residues, such as in the case of ethyl phenylpenta-2,4-dienoate, the addition of tetramethylammonium bromide [$(CH_3)_4NBr$] led to a higher yield of the phenyl-penta-2,4-dienoic acid (**3i**).

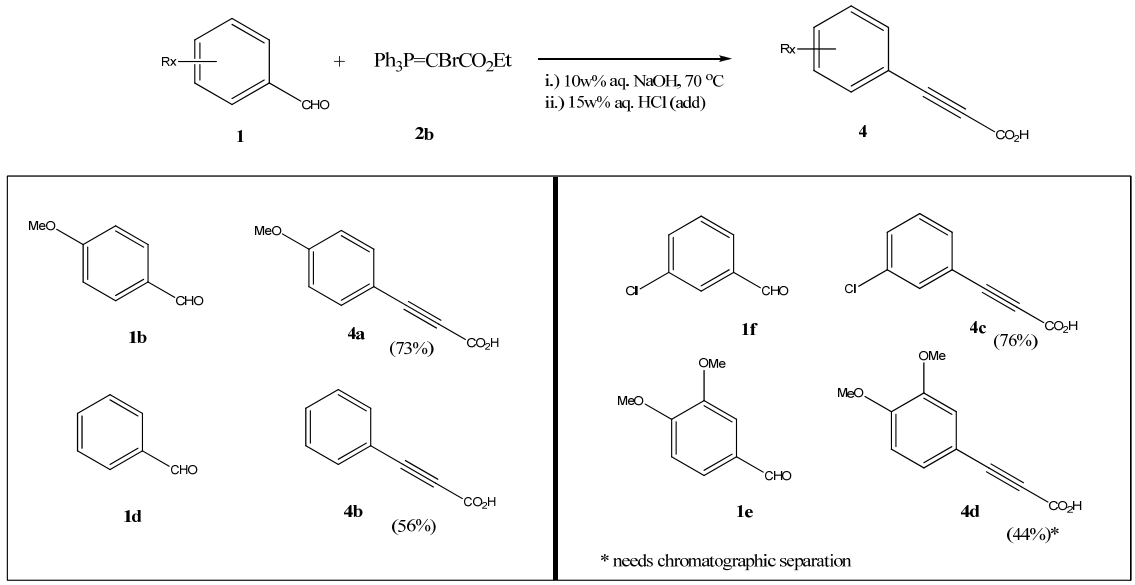


Table 2 Arylpropiolic acids from benzaldehydes in a one pot synthesis in aqueous solutions

When a mixture of (substituted) benzaldehyde **1** and ethoxybromomethylidenetriphenylphosphorane (**2b**, 1.3 eq.) is heated in a 10w% aq. NaOH solution, arylpropiolic acids **6** can be isolated upon careful neutralization of the aqueous solution (Table 2). In this case, the Wittig olefination is followed by ester hydrolysis and base catalysed dehydrobromination. Phenylpropiolic acids are usually prepared by bromination and dehydrobromination of cinnamic acids[14a] or by Sonogashira coupling of haloarenes with propiolates.[14b] In the present communication, we are

showing a facile one-pot procedure to phenylpropiolic acids with a simple extractive work-up. For certain derivatives, cinnamic acids have been found as side-products and the scope of this procedure is still under investigation.

In conclusion, we have developed two procedures from benzaldehydes to cinnamic acids and to phenylpropiolic acids, respectively, utilizing a modified Wittig-olefination protocol. The reactions and the work-up are performed without any organic solvents.

Experimental

General remarks. - Melting points were measured on a Stuart SMP 10 melting point apparatus and are uncorrected. Infrared spectra were measured with a Thermo/Nicolet Nexus 470 FT-IR ESP Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 NMR spectrometer (^{1}H at 395.7 MHz, ^{13}C at 100.5 MHz). The assignments of the carbon signals were aided by DEPT 90 and DEPT 135 experiments (DEPT = Distortionless Enhancement by Polarisation Transfer). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer. Column chromatography, where necessary, was performed on silica gel S (0.063 mm – 0.1 mm, Riedel de Haen).

2-Methoxybenzaldehyde (**1a**) and 2,4-dimethoxybenzaldehyde (**1e**) were prepared from

the corresponding, commericially available hydroxybenzaldehydes (KOH, DMSO, CH_3I).[15] Benzaldehydes **1g** and **1h** were synthesized by bromination (NBS, DMF, rt) of 2-hydroxy- and 4-hydroxybenzaldehydes, respectively, followed by alkylation (KOH, DMSO, CH_3I). Phosphoranes **2a**[16a] and **2b**[16b] were prepared according to literature procedures.

Typical procedures:

(*E*)-Cinnamic acid (**3d**). – To a mixture of benzaldehyde (**1d**, 1.60 g, 15.1 mmol) and ethoxycarbonylmethylidenetriphenylphosphorane (**2a**, 6.82 g, 19.5 mmmol) was given an aq. NaOH solution (10 w%, 3.5 g (87.5 mmol) NaOH in 35 mL H_2O) and the resulting suspension was stirred at 75 °C for 23h. Triphenylphosphine oxide was filtered off the cooled solution. Thereafter, the filtrate was acidified carefully with 15w% aq. HCl. The resulting suspension was cooled and filtered. The solid obtained was dried in air to give cinnamic acid (**3d**, 1.89 g, 77%) as a colorless solid; mp. 132 °C [Lit. 133 – 134 °C]; ν_{max} (KBr/cm^{-1}) 1690, 1631, 1454, 1312, 1290, 1225, 771, 714; δ_H (270 MHz, DMSO-d^6) 6.51 (1H, d, ^3J = 16.0 Hz), 7.39 (2H, m), 7.57 (1H, d, ^3J = 16.0 Hz), 7.59 – 7.66 (3H, m), 12.35 (1H, bs); δ_C (67.8 MHz, DMSO-d^6) 119.7, 128.6 (2C), 129.3 (2C), 130.7, 134.7, 144.4, 168.0; MS (EI, 70 eV) m/z (%) 148 (M^+) (100), 77 (40).

Phenylpropiolic acid (**4b**). - To a mixture of benzaldehyde (**1d**, 763 mg, 7.2 mmol) and ethoxycarbonylbromomethylidenetriphenylphosphorane (**2b**, 4.0 g, 9.4 mmol) was given aq. NaOH solution (10 w%, 1.8 g NaOH in 18 mL H_2O) and the resulting suspension was stirred at 85 °C for 16h. Triphenylphosphine oxide was filtered off the cooled solution. Thereafter, the filtrate was acidified carefully with 15w% aq. HCl. The resulting suspension was cooled and filtered. The solid obtained was dried in air to give phenylpropiolic acid (**4b**, 589 mg, 56%) as a colorless solid. An analytical sample gave mp. 133 °C [Lit. 135 – 137 °C] - ν_{max} (KBr/cm^{-1}) 3200 – 2500 (bs, OH), 2238, 2201, 1670, 1489, 1417, 1305, 1208, 919, 753, 683, 610, 533, 509; δ_H (400 MHz, $CDCl_3$) 7.39 – 7.42 (2H, m), 7.46 – 7.48 (1H, m), 7.60 – 7.62 (2H, m), 10.1 (bs, OH); δ_C (100.5 MHz, $CDCl_3$) 80.2 (C_{quat}), 88.8 (C_{quat}), 119.1 (C_{quat}), 128.8 (2C, +, CH), 131.1 (+, CH), 133.3 (2C, +, CH), 158.4 (C_{quat}, CO); MS (EI, 70 eV) *m/z* (%) 146 (M^+) (100), 76 (30).

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