One Pot O-alkylation/Wittig Olefination of Hydroxybenzaldehydes in DMSO [†]

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Abstract: Hydroxybenzaldehydes are submitted to a one pot O-alkylation/Wittig olefination in dimethyl sulfoxide (DMSO) to give alkyl alkoxycinnamates. The reaction is carried out facilely and gives the products in high yield.

Keywords: Wittig olefination; one pot reaction; O-alkylation; cinnamates

1. Introduction

In our endeavor to develop one-pot transformations involving Wittig olefination reactions with stabilized phosphoranes leading to substituted cinnamates [1,2] and cinnamic acids [3], we have recently turned to running etherification and Wittig olefination reactions with (carbomethoxymethylene)triphenylphosphorane (1a) (Figure 1) in one pot. The following contribution describes the scope of such procedures and gives experimental details.

Figure 1. Carbalkoxymethylenetriphenylphosphoranes as stabilized Wittig reagents (**1**) and target compounds alkoxycinnamates (**2**).

2. Materials and Methods

2.1. 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 and a Perkin Elmer Spectrum Two spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 NMR spectrometer (1H 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. Column chromatography, where necessary, was performed on recycled silica gel (S, 0.063 mm–0.1 mm, Riedel de Haen and Merck grade 9385).
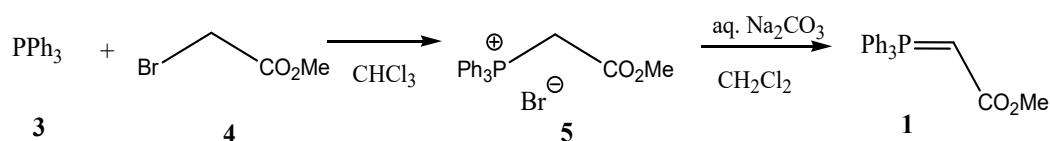
2.2. Starting Materials

Triphenylphosphine (**3**, Aldrich, Germany), iodomethane (**7**, Sigma-Aldrich, Germany), iodoethane (**7b**, BDH, UK), 1-iodopropane (**7c**, Alfa Products, USA), 1-iodobutane (**7d**, Merck-Schuchardt, Germany), 4-bromobenzyl bromide (**7e**, Aldrich, Germany), methyl bromoacetate (**4**, Aldrich, Germany), 3-hydroxy-4-methoxybenzaldehyde (**11**, Aldrich, Germany), 4-hydroxybenzaldehyde (**6**, BDH, UK), 2-hydroxybenzaldehyde (**9**, salicylaldehyde, Merck-Schuchardt, Germany), potassium hydroxide (KOH, Merck, Germany), chloroform (CHCl$_3$-Sigma Aldrich, Germany), dichloromethane (CH$_2$Cl$_2$, Sigma-Aldrich, Germany) were acquired commercially. (Carbomethoxymethylene)triphenylphosphorane (**1**) was prepared by the reaction of methyl bromoacetate (**4**) with triphenylphosphine (**3**, CHCl$_3$, precipitated upon addition of diethyl ether) with the subsequent reaction of carbomethoxymethyltriphenylphosphonium bromide (**5**) in a biphasic system of aq. Na$_2$CO$_3$ and CH$_2$Cl$_2$ (Scheme 1) [4].

Scheme 1. Preparation of stabilized phosphorane **1** as starting material.

2.3. General Procedures

2.3.1. Preparation of methyl 4-bromobenzyloxycinnamate (**8e**)

Potassium hydroxide (KOH, 0.84 g, 15 mmol) was ground in a mortar under pentane to give a fine powder. This was added to dimethyl sulfoxide (DMSO, 10 mL), stirred for 10 min. After that, 4-hydroxybenzaldehyde (**6**, 1.22 g, 10 mmol) was added. The reaction mixture was stirred at rt. Then, 4-bromobenzyl bromide (**7e**, 3.0 g, 12.0 mmol) was added to the mixture (exothermic reaction). After 10 min, (carbomethoxymethylene)triphenylphosphorane (Ph$_3$P=CHCO$_2$Me, **1**, 5.15 g, 14.9 mmol) was added. The reaction was heated at 80 °C for 1 h, thereafter stirred at rt for another 5 h. The resulting mixture was poured into cold water (75 mL) and extracted with CHCl$_3$ (3 × 50 mL). The organic phase was separated and dried over anhydrous MgSO$_4$. The residue was subjected to column chromatography on silica gel (CH$_2$Cl$_2$) to give **8e** as a colorless solid (3.33 g, 96%); IR υ (KBr, cm^{-1}): 2948, 2918, 2862, 1721, 1641, 1604, 1510, 1285, 1251, 1175, 1009, 983, 821, 551, 530, 497; δ_H (400 MHz, CDCl$_3$) 3.79 (3H, s, OCH$_3$), 5.03 (2H, s, OCH$_2$), 6.94 (2H, d, ^3J = 8.8 Hz), 6.31 (1H, d, ^3J = 16.0 Hz), 7.29 (2H, d, ^3J = 8.8 Hz), 7.46 (2H, d, ^3J = 8.0 Hz), 7.51 (2H, d, ^3J = 8.0 Hz), 7.64 (1H, d, ^3J = 16.0 Hz); δ_C (100.5 MHz, CDCl$_3$) 51.6 (OCH$_3$), 69.2 (OCH$_2$), 115.2 (2CH), 115.6 (CH), 122.1 (C$_{quat}$), 127.5 (C$_{quat}$), 129.1 (2C, CH), 129.8 (2C, CH), 131.8 (2C, CH), 135.5 (C$_{quat}$), 144.4 (CH), 160.2 (C$_{quat}$), 167.7 (C$_{quat}$, CO).

2.3.2. Preparation of methyl 3-ethoxy-4-methoxycinnamate (**12b**)

Potassium hydroxide (KOH, 0.84 g, 15 mmol) was ground in a mortar under pentane to give a fine powder. This was added to dimethyl sulfoxide (DMSO, 10 mL). After that, 3-hydroxy-4-methoxybenzaldehyde (**11**, 1.52 g, 10 mmol) was added, and the solution was stirred for 10 min at rt. Then, iodoethane (2.45 g, 1.4 mol) was added dropwise. The resulting mixture was stirred at rt. for 10 min, whereby the color of the solution turned yellow. The reaction produced heat. (Carbomethoxymethylene)triphenylphosphorane (**1**, 5.15 g, 15.4 mmol) was added to the mixture. The reaction was heated at 80 °C for 1 h, thereafter stirred at rt for another 5 h. The resulting mixture was poured into cold water (75 mL) and extracted with CHCl$_3$ (3 × 50 mL). The organic phase was separated and dried over anhydrous MgSO$_4$. The residue was subjected to column chromatography on silica gel to give methyl 3-ethoxy-4-methoxycinnamate (**12b**, trans/cis: > 95:5) as a pale yellow solid (2.11 g, 90%); IR υ (KBr, cm^{-1}): 3448, 3028, 2978, 2836, 2609, 2503, 2285, 2050, 1948, 1891, 1813, 1696, 1627, 1592, 1516, 1350, 1226, 1031, 984, 799, 699, 538; δ_H (400 MHz, CDCl$_3$)

1.47 (3H, t, ^3J = 7.2 Hz), 4.11 (2H, q, ^3J = 7.2 Hz), 3.78 (3H, s, OCH$_3$), 3.89 (3H, s, OCH$_3$), 6.28 (1H, d, ^3J = 16.0 Hz), 6.85 (1H, d, ^3J = 8.0 Hz), 7.04 (1H, d, ^4J = 2.0 Hz), 7.09 (1H, dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 7.61 (1H, d, ^3J = 16.0 Hz); δ_C (100.5 MHz, CDCl$_3$) 14.7 (CH$_3$), 51.6 (OCH$_3$), 56.0 (OCH$_3$), 64.3 (OCH$_2$), 110.9 (CH), 111.1 (CH), 115.3 (CH), 122.5 (CH), 127.2 (C$_{quat}$), 144.9 (CH), 148.4 (C$_{quat}$), 151.4 (C$_{quat}$), 167.7 (C$_{quat}$, CO).

2.3.3. Preparation of methyl 3-(4-bromobenzyloxy)-4-methoxycinnamate (**12e**)

Potassium hydroxide (KOH, 0.84 g, 15 mmol) was ground under pentane to give a fine powder. This was added to dimethyl sulfoxide (DMSO, 10 mL) and stirred for 10 min. After that, 3-hydroxy-4-methoxybenzaldehyde (**11**, 1.52 g, 10 mmol) was added. The reaction mixture was stirred at rt. Then, 4-bromobenzyl bromide (**7e**, 3.0 g, 12 mmol), was added to the mixture (exothermic reaction). After 10 min, (carbomethoxymethylene)triphenylphosphorane (Ph$_3$P=CHCO$_2$Me, **1**, 5.15 g, 15.4 mmol) was added. The reaction was heated at 80 °C for 1 h, thereafter stirred at rt for another 5 h. The resulting mixture was poured into cold water (75 mL) and extracted with CHCl$_3$ (3 × 50 mL). The organic phase was separated and dried over anhydrous MgSO$_4$. The residue was subjected to column chromatography on silica gel to give methyl 3-(4-bromobenzyloxy)-4-methoxycinnamate (trans/cis: > 95:5) as a pale yellow solid (**12e**, 3.53 g, 93.4%). IR υ (KBr, cm^{-1}): 3016, 2934, 2838, 1727, 1634, 1600, 1514, 1434, 1305, 1268, 1158, 1141, 101, 846, 808, 767, 610, 481 ; δ_H (400 MHz, CDCl$_3$) 3.78 (3H, s, OCH$_3$), 3.90 (3H, s, OCH$_3$), 6.88 (1H, d, ^3J = 8.4 Hz), 5.10 (2H, s, OCH$_2$), 6.23 (1H, d, ^3J = 16.0 Hz), 7.03 (1H, d, ^4J = 1.6 Hz), 7.12 (1H, dd, ^3J = 8.4 Hz, ^4J = 1.6 Hz), 7.32 (2H, d, ^3J = 8.4 Hz), 7.50 (2H, d, ^3J = 8.4 Hz), 7.57 (1H, d, ^3J = 16.0 Hz); δ_C (100.5 MHz, CDCl$_3$) 51.6 (OCH$_3$), 56.1 (OCH$_3$), 70.3 (OCH$_2$), 111.5 (CH), 112.6 (CH), 115.6 (CH), 122.0 (C$_{quat}$), 123.1 (CH), 127.2 (C$_{quat}$), 129.0 (2C, CH), 131.8 (2C, 2 CH), 135.7 (C$_{quat}$), 144.6 (CH), 148.0 (C$_{quat}$), 151.7 (C$_{quat}$), 167.6 (C$_{quat}$, CO).

3. Results and Discussion

Among other things, cinnamates are used as UV-B sunscreens and are present in over 90% of the commercial sunscreen products [5,6]. Cinnamates can be prepared by esterification of cinnamic acid and by Claisen reaction of benzaldehyde with alkyl acetates in the presence of Na. The Wittig reaction of benzaldehydes with the stabilized carbalkoxymethylenetriphenylphosphoranes have also been used in the synthesis of cinnamates. Carbalkoxymethylenetriphenylphosphoranes such as **1**, as stabilized phosphoranes, are reactive enough to undergo Wittig olefination reactions with both aldehydes and ketones, but are not sensitive towards water (and oxygen/air) and tolerate a number of solvent systems that include THF, DMSO, DME, and CHCl$_3$, aqueous systems [2], aqueous/organic solvent mixtures and even solventless conditions [1]. On the other hand, one of the best reaction systems for the alkylation of phenols by Williamson ether synthesis is the utilization of KOH in DMSO as initially forwarded by Johnstone and Rose [7]. Particularly with methyl halides, the alkylation of phenolates sometimes leads to ring alkyation, especially in ortho position of the phenolic function, but also in para position, however, the system KOH/DMSO, RX is known for its high O-alkylation versus C-alkylation selectivity [8].

When hydroxybenzaldehydes **6/9/11** are reacted with alkyl iodides/bromides in the presence of KOH as base in DMSO as a solvent with the subsequent addition of phosphorane **1**, the alkoxycinnamates **8/10/12** are formed in high yields (Schemes 2–4). The workup is a simple aqueous extraction followed by a chromatographic separation of the reaction mixture, where the cinnamates can easily be purified from the accompanying triphenylphosphine oxide. Only, in the case of the preparation of the methylated products can small amounts of side products stemming from C-alkylation of the aromatic system be found. The Wittig-olefination is deemed to be a reaction of poor atom-economy as triphenylphosphine oxide is lost to the material yield of the product. This "deficiency" could be overcome by recycling of the triphenylphosphine oxide [9–11]. Studies on how such a recycling step can be incorporated in the above process are currently underway.
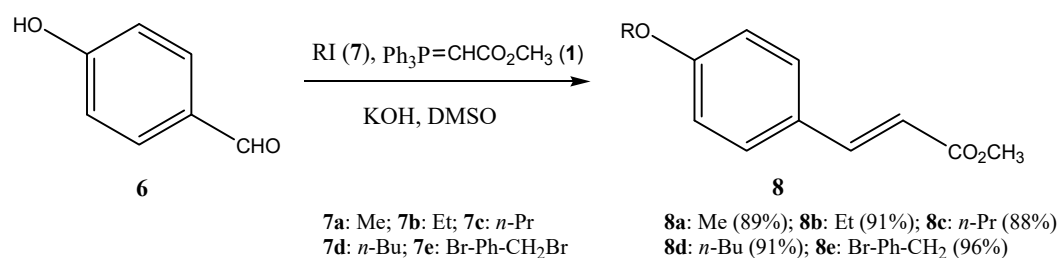
Scheme 2. One pot Wittig olefination—etherification of 4-hydroxybenzaldehyde (**6**).
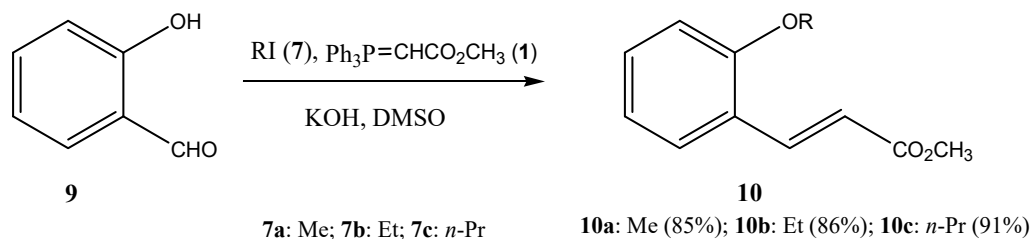
Scheme 3. One pot Wittig olefination—etherification of 2-hydroxybenzaldehyde (**9**).
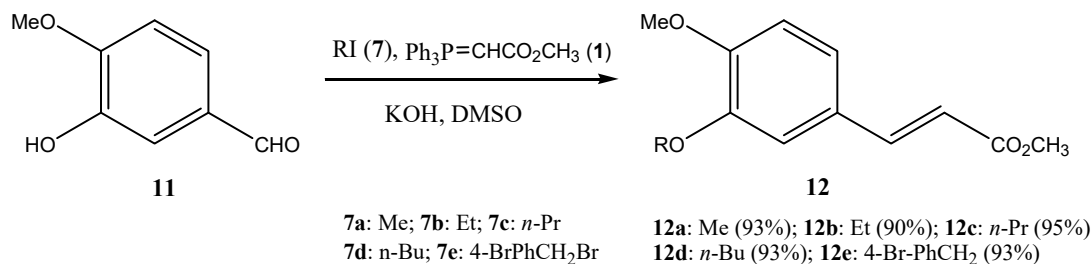
Scheme 4. One pot Wittig olefination—etherification of 3-hydroxy-4-methoxybenzaldehyde (**11**).

4. Conclusions

The reaction of hydroxybenzaldehydes with alkyl iodides/bromides in DMSO, in the presence of KOH as base, leads after addition of (carbomethoxymethylene)triphenylphosphorane to O-alkylated cinnamates in high yield.

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References

1. Thiemann, T.; Watanabe, M.; Tanaka, Y.; Mataka, S. One-Pot Wittig-olefination/Suzuki-reaction—The Compatibility of conjugated phosphoranes in Pd(0) catalysed C-C-bond forming reactions. *New J. Chem.* **2006**, *30*, 359–369.
2. Yamamoto, K.; Watanabe, W.; Ideta, K.; Mataka, S.; Thiemann, T. Combined Suzuki coupling—Wittig olefination reaction in aqueous medium. *Z. Nat. B* **2005**, *60*, 1299–1307.
3. Thiemann, T.; Elshorbagy, M.; Ahmadani, S.; Al Jasem, Y.; Al Azani, M.; Al-Sulaibi, M.; Al Hindawi, B. Facile, direct reaction of benzaldehydes to 3-phenyl-prop-2-enoic acids and 3-arylprop-2-ynoic acids in aqueous medium. *Int. J. Org. Chem.* **2016**, *6*, 126–141.
4. Thiemann, T. Solventless Wittig reactions with fluorinated benzaldehydes. *J. Chem. Res.* **2007**, *31*, 336–341.
5. Cantrell, A.; McGarvey, D.J.; Truscott, T.G. Photochemical and photophysical properties of sunscreens. In *Sun Protection in Man*; Giacomoni, P.U., Ed.; Elsevier Science, B.V: Amsterdam, The Netherlands, 2001; Volume 26, pp. 495–519.

6. Nunes, A.R.; Vieira, I.G.P.; Queiroz, D.B.; Leal, A.L.A.B.; Morais, S.M.; Muniz, D.F.; Calixto-Junior, J.T.; Coutinho, H.D.M. Use of flavonoids and cinnamates, the main photoprotectors with natural origin. *Adv. Pharmacol. Pharm. Sci.* **2018**, *2018*, 5341487.

7. Johnstone, R.A.W.; Rose, M.E. A rapid, simple, and mild procedure for alkylation of phenols, alcohols, amides and acids. *Tetrahedron* **1979**, *35*, 2169–2173.

8. Abdel-Magid, A.F. Potassium hydroxide-dimethyl sulfoxide. In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd.: Chichester, UK, 2001; pp. 1–2.

9. Horner, L.; Hoffman, H.; Beck, P. Phosphororganische Verbindungen, XVI. Wege zur Darstellung primärer, sekundärer und tertiärer Phosphine. *Chem. Ber.* **1958**, *91*, 1583–1588.

10. Keglevich, V.; Fekete, M.; Chulununbaatar, T.; Dobó, A.; Harmat, V.; Töke, L. One-pot transformation of cyclic phosphine oxides to phosphine–boranes by dimethyl sulfide-borane. *J. Chem. Soc. Perkin Trans. 1* **2000**, *24*, 4451–4455.

11. Al Jasem, Y.; El-Esawi, R.; Thiemann, T. Wittig- and Horner-Wadsworth-Emmons-olefination reactions with stabilised and semi-stabilised phosphoranes and phosphonates under non-classical conditions. *J. Chem. Res.* **2014**, *38*, 453–463.