Two Variations of Solvent-Reduced Wittig Olefination Reactions – Comparison of Solventless Wittig Reactions to Wittig Reactions under Ultrasonication with Minimal Work-up [1]

Masataka Watanabe[a], Goreti Ribeiro Morais[b,c], Shuntaro Mataka[b], Keiko Ideta[b], and Thies Thiemann[b]

[a] Interdisciplinary Graduate School of Engineering Sciences and
[b] Institute of Materials Chemistry and Engineering, Kyushu University, Fukuoka 816-8580, Japan
[c] Centro de Estudos Farmaceuticos, Faculdade de Farmacia, Universidade Coimbra, P-3000-295 Coimbra, Portugal

Reprint requests to T. Thiemann. E-mail: thies@cm.kyushu-u.ac.jp

Z. Naturforsch. **60b,** 909 – 915 (2005); received May 13, 2005

Stabilized and semi-stabilized phosphoranes can be subjected to solventless Wittig reactions with carbaldehydes. Simple heating of a mixture of added components at 100 °C in an electric oven gives the corresponding olefins in good yield. Alternatively, the Wittig reactions can be carried out in a biphasic medium under ultrasonication. In this case, the Wittig products can be isolated by simple evaporation of the organic phase without additional work-up.

Key words: Wittig Olefination, Ultrasound, Solventless Reaction

A number of criteria have to be considered when setting reaction conditions for a chemical transformation. While in former times such criteria as product yield, simplicity of operation, cost of starting materials and reagents were considered, recently, further evaluation points such as the toxicity of the reagents and solvents used, energy requirements and waste production have been added to the list, even when performing reactions at laboratory scale. A further important factor that is not to be underestimated is the amount of time needed for the synthetic step or sequence. For many chemical transformations, a multitude of different reaction conditions have been published, from which it is important to choose carefully for the individual transformation in question. One such transformation, which offers a choice of reaction conditions, is the Wittig olefination of carbaldehydes with stabilized and semi-stabilized ylides. In former times the reaction was carried out in organic solvents such as DME [2a], chloroform [2b], benzene [2c,d] or toluene [2e], often under reflux conditions and in the presence of additives such as acids [2c,d, 3] or salts [4]. More recently, waste-saving alternatives have been explored such as performing the reactions in solventless systems [1, 5] utilizing special techniques such as microwave irradiation [5b,c,d,f] and ball-mill mixing [5e]. In the following, two procedures for the Wittig olefination will be discussed, which are characterized by reduced use of solvents and simplicity of operation, no special equipment being needed.

We observed that many aromatic and heteroaromatic carbaldehydes undergo exothermic olefination reactions with stabilized Wittig reagents, when one reaction partner is added to the other, resulting in solventless Wittig olefination reactions without the necessity of microwave irradiation (Table 1). Liquid aryl- and hetarylcarbaldehydes, such as **1c** and **1e**, form uniform melts with the phosphoranes. Aldehydes with low melting points, such as **1i**, mix equally well with the phosphoranes as the heat released can generate temperatures of 60 – 70 °C. In cases, where the aldehydes have a higher melting point, the mixture of aldehyde and phosphorane is heated at 100 °C for 10 min – 2 h. to produce the olefinic products in good yield. Alkoxycarbonylmethylidenetriphenylphosphoranes **2a,b** and aroylmethylidenetriphenylphosphoranes **2c – e** can be used in these reactions. With these stabilized phosphoranes, the olefins formed are predominantely *E*-configurated. As in solution, also under solventless conditions the reactivity of alkoxymethylidenephosphoranes is higher than that of aroylmethylidenephosphoranes which is reflected in the shorter reaction times needed. Nevertheless, the alkoxymethylidenetriphenylphosphoranes **2a,b** react selectively with the

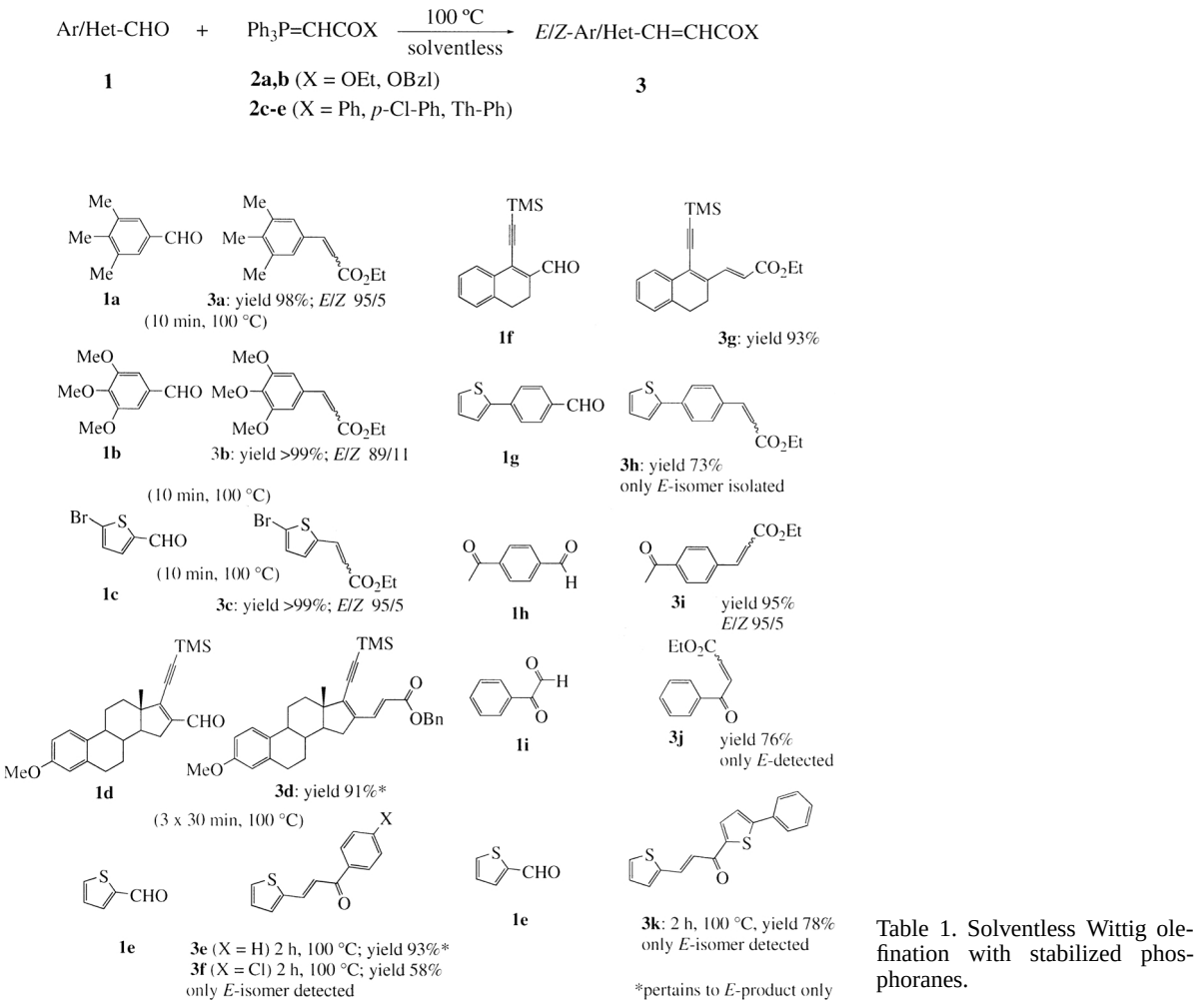


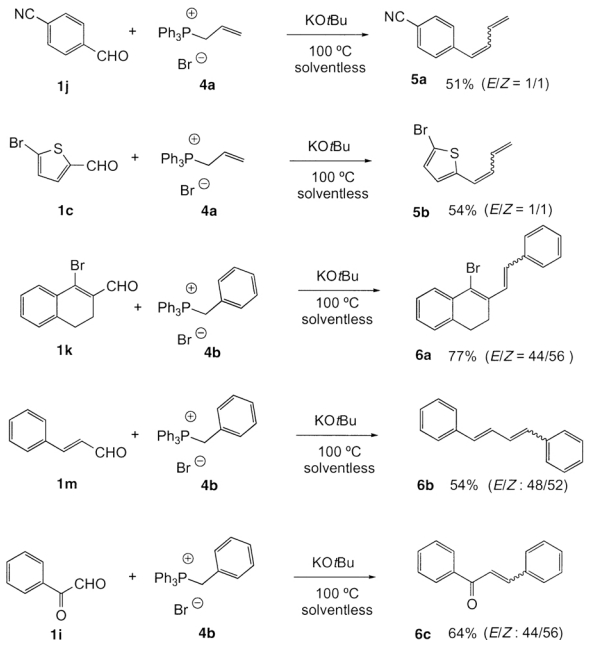
Table 1. Solventless Wittig olefination with stabilized phosphoranes.

carbaldehyde moiety of ketoarylcarbaldehydes such as in **1h** and **1i**. Under more forcing conditions such as under microwave irradiation the keto functionality also undergoes reaction.

Benzylidenetriphenylphosphorane also reacts selectively with carbaldehydes rather than with ketones in pure mixtures. This can be seen in the reaction of benzylidenetriphenylphosphorane with an equimolar amount of phenylglyoxal monohydrate (**1i**), where only the carbaldehyde function reacts to give a separable mixture of *E*-**6c** and *Z*-**6c** ($E/Z = 44/56$) (Scheme 1). Instead of benzylidenetriphenylphosphorane itself, the corresponding phosphonium bromide salt **4b** is used as starting material with addition of solid potassium *tert*-butanolate. Analogously, allyltriphenylphosphonium bromide **4a** can be used in solventless systems. These semi-stabilized phosphoranes, especially the allylmethylidenetriphenylphosphorane, derived from **4a**, give the olefins in poorer yields without significant E/Z-selectivity.

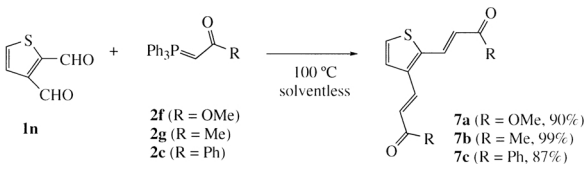
Double-Wittig olefinations are possible under solventless conditions as is witnessed by the transformation of 2,3-diformylthiophene (**2n**) with Wittig reagents **2c**, **2f**, and **2g** at 100 °C (Scheme 2). No side products are observed from a potential triene cyclization of the products at 100 °C. In fact, in contrast to other known dialkyl hexatriene-1,6-dicarboxylate derivatives, which undergo triene cyclization [6], **7a** has been found to be stable up to 155 °C (48 h, solution in diphenyl ether).

In certain cases, Wittig olefinations do not progress in solution, but proceed in solventless systems. In one such example, the Wittig olefination of 16-formylestra-1,3,5(10)-trien-17-one [7] does not work out in



Scheme 1. Solventless Wittig reaction with semi-stabilized phosphoranes prepared *in situ*.

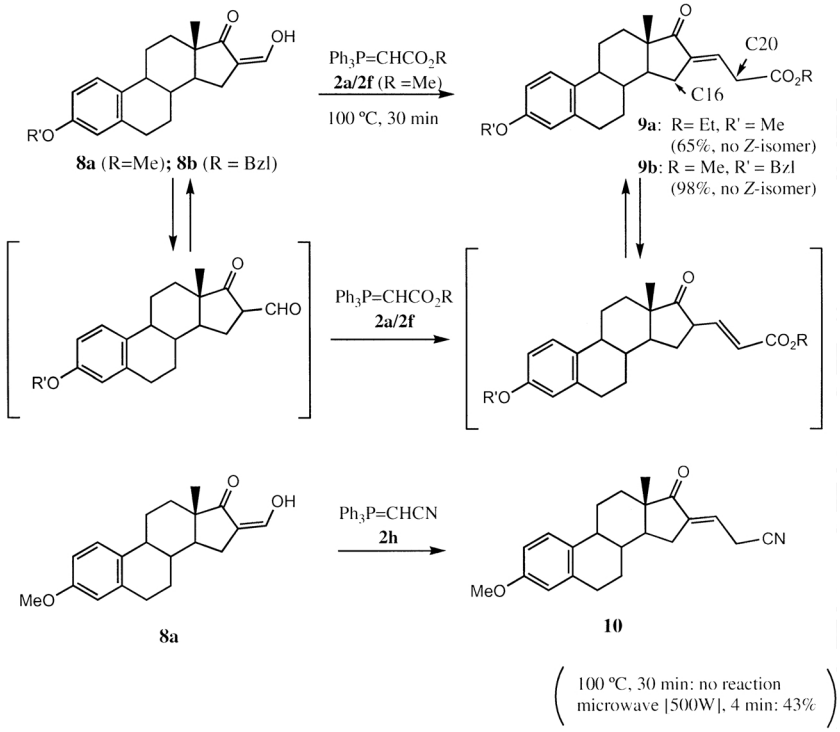
solution. Partly this is due to the poor solubility of the starting material. The reactivity of the 16-formyl group is much reduced because of hydrogen bonding



Scheme 2. Double Wittig reaction under solventless conditions.

to the 17-keto group. In a pure mixture with ethoxycarbonylmethylidenetriphenylphosphorane (**2a**), however, the compound undergoes Wittig olefination at 100 °C (oven, 30 min) in acceptable yield, where the initial product undergoes a 1,3-proton shift to provide **9a** as a single isomer (Scheme 3). The double bond configuration of **9a** was established by DPFGSE-NOE-experiment (Double Pulsed Field Gradient Spin Echo NOE [8], irradiated at $\nu = 1924.7$ Hz [protons at C-20; 2.1% observed for H16α, H16β]. The analogous reaction with cyanomethylidenetriphenylphosphorane (**2h**) also proceeds, the analogous product **10** being formed in a little lower yield under the same conditions. Acetylmethylidenetriphenylphosphorane (**2g**) is not reactive enough to undergo a reaction in the pure mixture of starting materials at 100 °C.

The main drawback of all these reactions, however, lies in the work-up as it still necessitates the use of



Scheme 3. Derivatisation of estrane derivatives by solventless Wittig reaction.

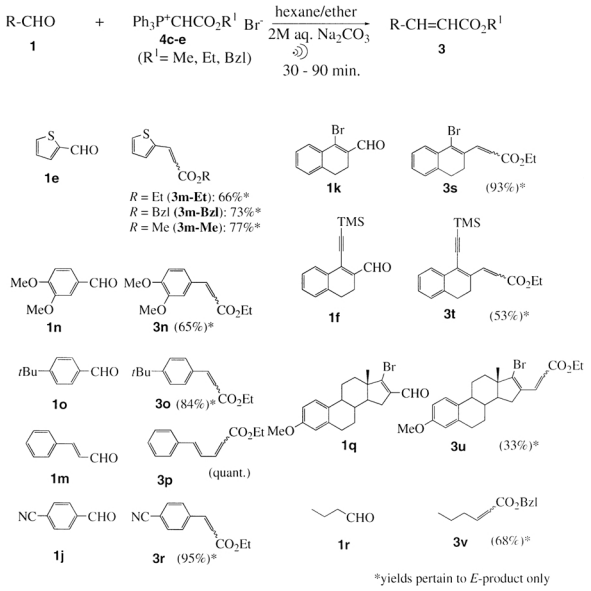
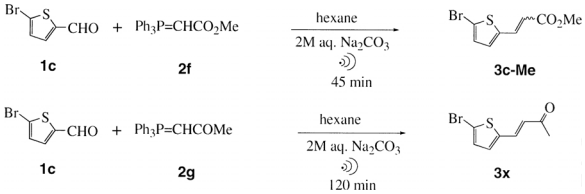


Table 2. Wittig olefination in a biphasic medium under ultrasonication.

solvents as eluents for short column chromatographic separations, mainly to separate triphenylphosphane oxide and small amounts of triphenylphosphane. On the other hand, olefins are also produced, albeit in slightly lower yields, when the carbaldehydes and phosphoranes are reacted at room temperature in an aqueous solvent or a mixture of hexane/ether (95/5 v/v) and water under ultrasound [9 – 11]. Reaction times are longer. The work-up, however, is minimal. In the case of solely using water as reaction medium, hexane can be added to the mixture near the completion of the reaction, where the product is extracted into the organic phase under ultrasound. Frequently, the product is sufficiently pure to be used in a subsequent reaction step without further purification. In other cases simple filtration over a pad with a thin layer of silica gel provides the pure product.

In these experiments, the starting materials can be either the phosphorane or the phosphonium salt, which under the conditions is transformed to the phosphorane by the aqueous base. When an ultrasonic bath is used for the reaction, a semi-solid forms at the interphase of the aqueous and the organic phase (hexane/ether = 95/5). At the beginning the solid consists mostly of phosphorane, at the end of the reaction of residual phosphorane and triphenylphosphane oxide. During the sonication there is cavitation in the lower, aqueous phase which impinges on the bottom of the



Scheme 4. Wittig reaction of stabilized phosphoranes under ultrasonication.

interfacial layer. It is in this layer that the Wittig olefination takes place.

Benzyltriphenylphosphonium bromide (**4b**) also undergoes Wittig olefination under sonication in aqueous medium, *e.g.* with 5-methylthien-2-ylcarbaldehyde, to give (5-methylthien-2-yl)styrene (54%, E/Z = 1:1). Here, however, the advantage of an easy separation of the product by evaporation of the overlying hexane phase is not in evidence, as the reaction does not go to completion and product and starting aldehyde have to be separated over a short column.

In conclusion, we have shown that aryl- and hetarylcarbaldehydes undergo rapid Wittig olefination under solventless conditions with a number of stabilized and semi-stabilized phosphoranes. A chromatographic separation of the products is mandatory. Carbaldehydes can also be reacted in aqueous solution or in a mixture of non-polar organic solvents and water. In this case, the organic layer can be siphoned off and the product can be obtained by evaporation of the solvent, in a purity sufficient for subsequent transformations. Solventless Wittig olefination can be combined with an extraction of the solid/liquid product under ultrasonication. Here, however, the yields can be lower due to remaining product adsorbed to the solids formed.

Experimental Section

General remarks

Melting points were measured on a Yanaco microscopic hotstage and are uncorrected. Infrared spectra were measured with JASCO IR-700 and Nippon Denshi JIR-AQ2OM instruments. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL EX-270 spectrometer (^{1}H at 270 MHz, ^{13}C at 67.8 MHz) and a JEOL Lambda 400 FT-NMR spectrometer (^{1}H at 395.7 MHz, ^{13}C at 99.45 MHz). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). The DPFGSE-NOE experiment was carried out with a Lambda 600 spectrometer. Mass spectra were measured with a JMS-01-SG-2 spectrometer. Column chromatography was carried out on Wakogel 300. For the heating experiments, an electric oven, EYELA NDO-450N, preheated at

100 °C, was used. For the ultrasonication, a 35 KHz Elma Transsonic T-460 bath was used. The sonication experiments were carried out at 35 °C.

The phosphoranes **2a** [12a], **2b** [12a], **2c** [12b], **2d** [13], **2e** [13], **2f** [12a], **2g** [12b], **2h** [12c] and the phosphonium salts **4a** [12d], **4b** [12e], **4c – e** [12a] were prepared according to literature procedures. Estrane derivatives **8a/b** were synthesized analogous to a procedure by Tapolcsanyi et al. [7].

Typical procedures [14]

Wittig olefination under solventless conditions – Ethyl 2-[4-(trimethylsilylethynyl)-1,2-dihydronaphthalen-3-yl] acrylate (**3t**). – Aldehyde **1f** (1.27 g, 5.0 mmol) was reacted with phosphorane **2a** (2.61 g, 7.5 mmol) for 10 min at 100 °C. The melt was transferred to silica gel and chromatography (hexane/ether 5:1) gave **3t** (1.5 g, 93%) as yellow needles; m. p. 80 – 81 °C. – IR (neat): $\nu = 3068, 2958, 2892, 2136, 12708, 1613, 1302, 1169, 1042, 984$ cm^{-1}. – ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 0.32$ (s, 9H, $SiMe_3$), 1.34 (t, 3H, $^3J = 6.9$ Hz), 2.54 (t, 2H, $^3J = 7.6$ Hz), 2.84 (t, 2H, $^3J = 7.6$ Hz), 4.25 (q, 2H, $^3J = 6.9$ Hz), 6.10 (d, 1H, $^3J = 15.8$ Hz), 7.12 – 7.27 (m, 3H), 7.71 (d, 1H, $^3J = 5.3$ Hz), 8.25 (d, 1H, $^3J = 15.8$ Hz). – ^{13}C NMR (99.45 MHz, $CDCl_3$): $\delta = 0.04, 14.37, 23.45, 27.05, 60.48, 100.27, 105.86, 119.42, 125.94, 126.84, 126.92, 127.23, 128.80, 132.72, 140.10, 143.33, 167.22$. – MS (EI, 70 eV): m/z (%) = 324 (M^+, 100), 295 (21), 161 (59), 149 (38), 134 (100). – HRMS (found) 324.1549; calcd. for $C_{20}H_{24}O_2Si$: 324.1546. – $C_{20}H_{24}O_2Si$ (324.48): calcd. C 74.09, H 7.46; found C 74.03, H 7.45.

Selected data for further compounds obtained by solventless Wittig olefination:

Dimethyl thienyl-2,3-(*E*,*E*)-diacrylate (**7a**), colorless needles, m. p. 128 °C. – IR (KBr): $\nu = 1721, 1622, 1281, 1173, 1034, 963, 851, 751, 707$ cm^{-1}. – ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 3.82$ (s, 6H, 2 $COOCH_3$), 6.29 (d, 1H, $^3J = 15.9$ Hz), 6.34 (d, 1H, $^3J = 15.9$ Hz), 7.87 (d, 1H, $^3J = 15.9$ Hz), 8.02 (d, 1H, $^3J = 15.9$ Hz). – ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 51.88, 118.71, 119.96, 126.37, 127.83, 133.78, 134.71, 138.22, 139.80, 166.70, 167.19$. – MS (EI, 70 eV): m/z (%) = 252 (M^+, 45), 193 (64), 161 (59), 149 (38), 134 (100). – HRMS (found) 252.0453; calcd. for $C_{12}H_{12}O_4S$: 252.0456. – $C_{12}H_{12}O_4S$ (252.29): calcd. C 57.13, H 4.79; found C 57.10, H 4.81.

2,3-(*E*,*E*)-Bis(acetylethenyl)thiophene (**7b**), yellow needles, m. p. 144 °C. – IR (KBr): $\nu = 3082, 1645, 1604, 1361, 1257, 954, 768$ cm^{-1}. – ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 2.58$ (s, 3H, $COCH_3$), 2.65 (s, 3H, $COCH_3$), 6.33 (d, 2H, $^3J = 15.4$ Hz), 7.29 (d, 1H, $^3J = 5.7$ Hz), 7.37 (d, 1H, $^3J = 5.7$ Hz), 7.79 (d, 1H, $^3J = 15.4$ Hz), 7.93 (d, 1H, $^3J = 15.4$ Hz). – ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 28.06, 28.42, 126.56, 127.22, 128.15, 128.71, 131.60, 132.67, 139.00, 140.57, 197.14, 198.04$. – MS (EI, 70 eV): m/z (%) = 220 (M^+, 15), 177 (100), 163 (46), 134 (26). – HRMS (found) 220.0558; calcd. for $C_{12}H_{12}O_2S$: 220.0558.

2,3-(*E*,*E*)-Bis(benzoylethenyl)thiophene (**7c**), yellow needles, m. p. 167 °C. – IR (KBr): $\nu = 3070, 1655, 1576, 1335, 1314, 1274, 1248, 1215, 1019, 970, 776, 700, 573$ cm^{-1}. – ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.38 - 7.63$ (m, 10H), 7.99 – 8.08 (m, 5H), 8.23 (d, 1H, $^3J = 15.1$ Hz). – ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 122.82, 124.21, 126.76, 127.94, 128.47$ (4C), 128.69 (4C), 132.99 (2C), 133.56, 134.54, 137.83, 137.94, 139.81, 141.54, 189.27, 190.20. – MS (EI, 70 eV): m/z (%) = 344 (M^+, 6), 239 (100), 105 (55). – HRMS (found) 344.0874; calcd. for $C_{22}H_{16}O_2S$: 344.0871. – $C_{22}H_{16}O_2S$ (344.09): calcd. C 76.72, H 4.68; found C 76.54, H 4.72.

Ethyl 3-(4'-bromo-1',2'-dihydronaphthalen-3'-yl)-acrylate (**3s**), colorless needles; m. p. 89 °C. – IR (KBr): $\nu = 1700, 1614, 1475, 1453, 1364, 1299, 1269, 1234, 1173, 1037, 971, 943, 854, 762$ cm^{-1}. – ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.34$ (t, 3H, $^3J = 7.3$ Hz), 2.58 (dd, 2H, $^3J = 8.6$ Hz, $^3J = 5.9$ Hz), 2.88 (dd, 2H, $^3J = 8.6$ Hz, $^3J = 5.9$ Hz), 4.26 (q, 2H, $^3J = 7.3$ Hz), 6.12 (d, 1H, $^3J = 15.7$ Hz), 7.13 – 7.31 (m, 3H), 7.77 (m, 1H), 8.11 (d, 1H, $^3J = 15.7$ Hz). – ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 14.35, 25.91, 27.49, 60.58, 120.46, 126.98, 128.61, 129.27, 133.19, 133.98, 137.14, 144.02, 167.03$. – MS (EI, 70 eV): m/z (%) = 308 ([^{81}Br]M^+, 9), 306 ([^{79}Br]M^+, 9), 227 (71), 199 (100), 181 (21). – HRMS (found) 306.0259; calcd. for $C_{15}H_{15}O_2{}^{79}Br$: 306.0255. $C_{15}H_{15}O_2Br$ (307.18): calcd. C 58.65, H 4.92; found C 58.66, H 4.92.

Wittig olefination under ultrasonication – Methyl 2-(thien-2-yl)acrylate (**3m-Me**). A suspension of thiophene-2-carbaldehyde (**1e**) (348 mg, 3.1 mmol) and methoxycarbonylmethyltriphenylphosphonium bromide (**4c**) (1.93 g, 4.6 mmol) in a mixture of a 2 M aq. Na_2CO_3 solution (10 ml) and hexane/ether (5 ml, 95/5 v/v) was sonoirradiated for 3×30 min, where the temperature of the mixture was kept at 35 °C. Therafter, the upper organic layer was separated, and the remaining mixture was extracted under ultrasonication with hexane/ether (95/5 v/v, 2×30 ml). The combined organic phase was evaporated *in vacuo* to give **3m-Me** (0.4 g, 77%) with triphenylphosphine oxide as an impurity (5%). Further purification by filtration over a pad of silica gel can be carried out to give analytically pure **3m-Me**.

16-(2'-(*E*)-Ethoxycarbonylethylidene-3-methoxyestra-1,3,5(10)-trien-17-one (**9a**). – 16-Formyl-3-methoxyestrone (**8a**) (312 mg, 1.0 mmol) was mixed with ethyl (triphenylphosphoranylidene)acetate (**2a**) (523 mg, 1.5 mmol). The mixture was heated in an electric oven at 100 °C for 30 min. The reaction mixture was then subjected directly to column chromatography on silica gel (toluene : ethyl acetate = 5 / 1) to give **9a** (250 mg, 65%) as a colorless solid; m. p. 93 – 103 °C. – IR(KBr): $\nu = 3438, 2936, 1731, 1653, 1611, 1576, 1497, 1451, 1394, 1375, 1305, 1280, 1259,$

1182, 1101, 1084, 1052, 1036, 869, 843, 818, 783 cm^{-1}. – ^1H NMR (270 MHz, $CDCl_3$): $\delta = 0.92$ (s, 3H, CH_3), 1.28 (t, 3H, $^3J = 7.4$ Hz, CH_3), 1.44 – 2.92 (m, 13H), 3.21 (d, 2H, $^3J = 7.5$ Hz), 3.78 (s, 3H, OCH_3), 4.18 (q, 2H, $^3J = 7.4$ Hz, OCH_2), 6.65 (d, 1H, $^4J = 2.7$ Hz, C-1), 6.73 – 6.77 (m, 2H, C-2 and olefinic proton), 7.21 (d, 1H, $^3J = 8.7$ Hz, C-1). – MS (70 eV): m/z (%) = 383 (MH^+, 27%), 382 (M^+, 100%). – HRMS (found): 382.2144; calcd. for $C_{24}H_{30}O_4$: 382.2146. – $C_{24}H_{30}O_4$+0.05H_2O (383.39): calcd. C 75.19, H 7.91; found C 74.92, H 7.86.

16-(2'-(*E*)-Methoxycarbonylethylidene-3-benzyloxyestra-1,3,5(10)-trien-17-one (**9b**). – **8b** (388 mg, 1.0 mmol) and **2f** (401 mg, 1.2 mmol) were reacted to give after separation by column chromatography on silica gel (hexane : ether : CH_2Cl_2 = 4 / 1 / 1) to give **9b** (437 mg, 98%) as a colorless prisms. m. p. 118 °C. – IR (KBr): $\nu = 3032$, 3931, 2857, 1735, 1654, 1605, 1574, 1498, 1454, 1436, 1377, 1340, 1304, 1280, 1256, 1230, 1199, 1173, 1119, 1100, 1084, 1050, 1017, 985, 949, 905, 888, 844, 819, 788, 733, 696, 646, 575 cm^{-1}. – ^1H NMR (270 MHz, $CDCl_3$) $\delta = 0.92$ (s, 3H, CH_3, C-18), 1.43 – 2.43 (m, 10H), 2.62 – 2.69 (m, 1H), 2.88 – 2.91 (m, 2H), 3.22 (d, 2H, $^3J = 6.4$ Hz), 3.72 (s, 3H, OCH_3), 5.04 (s, 2H, OCH_2Ph), 6.70 – 6.76 (m, 2H, C-1 and olefin), 6.79 (d, 1H, $^3J = 8.6$ Hz, C-2), 7.20 (d, 1H, $^3J = 8.6$ Hz), 7.26 – 7.44 (m, 5H). – $C_{29}H_{32}O_4$ (444.56): calcd. C 78.35, H 7.26; found C 78.10, H 7.27.

[1] Part 1: T. Thiemann, M. Watanabe, Y. Tanaka, S. Mataka, New J. Chem. **28**, 578 (2004).

[2] For typical examples, see: a) E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson, S. Hammerström, J. Am. Chem. Soc. **102**, 1436 (1980) (for DME); b) S. Fliszàr, R. F. Hudson, G. Salvadori, Helv. Chim. Acta **47**, 159 (1964) (for chloroform); c) D. Spitzner, H. Swoboda, Tetrahedron Lett. **27**, 1281 (1986) (for benzene); d) T. Thiemann, D. Ohira, Y. Q. Li, T. Sawada, S. Mataka, K. Rauch, A. de Meijere, J. Chem. Soc., Perkin Trans. 1 2968 (2000) (for benzene); e) J.-P. Surivet, J.-N. Volle, J. M. Vatéle, Tetrahedron: Asymmetry **7**, 3305 (1996) (for toluene).

[3] a) C. Rüchardt, P. Panse, S. Eichler, Chem. Ber. **100**, 1144 (1967); b) D. P. Mariott, S. R. Bantick, Tetrahedron Lett. **22**, 3657 (1981).

[4] H. Moison, F. Texier-Boullet, A. Foucaud, Tetrahedron **43**, 537 (1987).

[5] a) F. Toda, H. Akai, J. Org. Chem. **55**, 3446 (1990); b) W. Liu, Q. Xu, Y. Ma, Y. Liang, N. Dong, D. Guan, J. Organomet. Chem. **625**, 128 (2001); c) C. Xu, G. Chen, X. Huang, Org. Prep. Proceed. Int. **27**, 559 (1995); d) A. Spinella, T. Fortunati, A. Sorienti, Synlett 93 (1997); e) V. P. Balema, J. M. Wiench, M. Pruski, V. K. Pecharsky, J. Am. Chem. Soc. **124**, 6244 (2002); f) H. Valizadeh, A. Shockravi, M. M. Heravi, H. A. Ghadmin, J. Chem. Res. 718 (2003).

[6] a) K. Voigt, P. von Zezschwitz, K. Rosauer, A. Lansky, A. de Meijere, Eur. J. Org. Chem. 1521 (1998); b) P. von Zezschwitz, F. Petry, A. de Meijere, Chem. Eur. J. **7**, 4035 (2001).

[7] P. Tapolcsanyi, J. Woelfling, G. Falkay, A. Marki, R. Minorics, G. Schneider, Steroids **67**, 371 (2002).

[8] a) K. Scott, J. Stonehouse, J. Keeler, T.-L. Hwang, A. J. Shaka, J. Am. Chem. Soc. **117**, 4199 (1995); b) S. Berger, S. Braun, 200 and more NMR experiments, p. 492, Wiley-VCH, Weinheim (2004).

[9] For reports on Wittig Horner reactions under ultrasound, see: a) H. El Faikh, F. Pautet, D. Peters, H. Fillion, M. Soufiaoui, J. L. Luche, J. Prakt. Chem. **339**, 176 (1997); b) H. El Faikh, F. Pautet, H. Fillion, J. L. Luche, Tetrahedron Lett. **33**, 4909 (1992); c) H. Fillion, B. Refouvelet, M. H. Pera, V. Dufaud, J. L. Luche, Synth. Commun. **19**, 3343 (1989); see also ref. [10].

[10] a) A. Fuentes, J. M. Marinas, J. V. Sinisterra, Tetrahedron Lett. **28**, 2951 (1987); b) J. V. Sinisterra, A. Fuentes, J. M. Marinas, J. Org. Chem. **52**, 3875 (1987).

[11] For reports on the effect of ultrasound on Wittig reactions in toluene and other organic solvents, see: a) C. Yang, D. T. C. Yang, R. G. Harvey, Synlett 799 (1992); b) S. Ring, G. Teichmueller, G. Weber, S. Schwarz, B. Erhart, B. Undeutsch, H. Raethe, P. Moellmann, C. Pfeiffer, H.-J. Palme, Eur. Pat. Appl. EP 643070, 1995; Chem. Abstr. **123**, 33509 (1995).

[12] a) O. Isler, H. Gutmann, M. Montavon, R. Ruegg, G. Ryser, P. Zeller, Helv. Chim. Acta **40**, 1242 (1957); b) F. Ramirez, S. Dershowitz, J. Org. Chem. **22**, 41 (1957); c) S. Trippett, D. M. Walker, J. Chem. Soc. C 3874 (1959); d) G. Wittig, U. Schoellkopf, Chem. Ber. Rec. **87**, 1318 (1954); e) Autorenkollektiv, Organikum, p. 203, VEB Deutscher Verlag der Wissenschaften, Berlin (1988).

[13] a) T. Thiemann, K. Umeno, D. Ohira, E. Inohae, T. Sawada, S. Mataka, New J. Chem. **23**, 1067 (1999); b) T. Thiemann, K. Umeno, J. Wang, K. Arima, M. Watanabe, Y. Tabuchi, Y. Tanaka, H. Gorohmaru, S. Mataka, J. Chem. Soc., Perkin Trans. **1**, 2090 (2002).

[14] All compounds gave satisfactory ^1H NMR, ^{13}C NMR, IR, MS and HRMS data. The following compounds have been reported before: **3b**: S. Frattini, M. Quai, E. Cereda, Tetrahedron Lett. **42**, 6827 (2001); **3c**: P. Berthelot, C. Vaccher, N. Flouquet, M. Debaert, M. Luyckx, C. Brunet, J. Med. Chem. **34**, 2557 (1991); **3e**: J. P. Yadav, K. Anuradha, B. V. S. Reddy, B. Eeschwaraiah, Tetrahedron Lett. **44**, 8959 (2003); **3f**: G. Dannhardt, W. Kiefer, G. Kramer, S. Maehrlein, V. Nowe, B. Fiebich, Eur. J. Med. Chem. **35**, 499

(2000); **3i**: M. Moreno-Manas, M. Perez, R. Pleixats, Tetrahedron Lett. **37**, 7449 (1996); **3j**: M. Knollmuller, M. Ferencic, P. Gartner, U. Girreser, M. Klinge, L. Gaishin, K. Mereiter, C. R. Noe, Monatsh. Chem. **130**, 769 (1999); **3k**: A. E. Lipkin, N. I. Putokhin, S. I. Borisov, Khim. Geterotsk. Soedin. 476 (1966); for **3m-Me**, **3m-Et**, **3n**, **3o**, and **3p**: see ref. 1; **3m-Bzl** and **3v**: A. Katritzky, P. Zhang, A. Soares, M. Wang, ARKIVOC 54 (2001); **3r**: Y. Z. Jin, N. Yasuda, J. Inanaga, Green Chem. **4**, 498 (2002); **3u**: T. Thiemann, C. Thiemann, S. Sasaki, V. Vill, S. Mataka, M. Tashiro, J. Chem. Res. (S) 248 (1997); **5a**: Q. Wang, M. El Khoury, M. Schlosser, Chemistry **6**, 420 (2000); **6b**: B. B. Corson, Org. Synth. **16**, 28 (1936).

Druck: AZ Druck und Datentechnik GmbH, Kempten