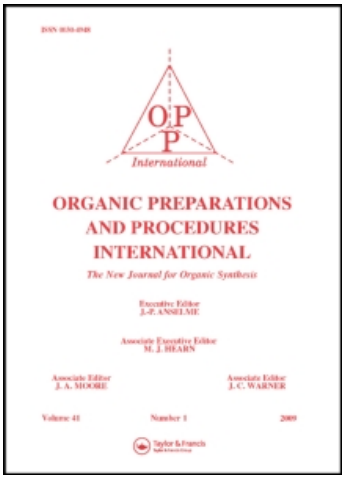

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APPLICATION OF POTASSIUM *t*-BUTOXIDE IN TOLUENE AS A BASE IN THE WITTIG REACTION IN LARGE-SCALE PHEROMONE SYNTHESES†

Submitted by (07/19/90)

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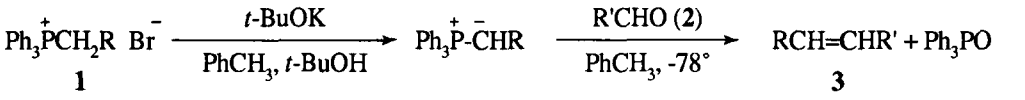
The stereoselective formation of a C-C double bond is the key step in the synthesis of unsaturated esters, which are the most important components of the pheromone mixtures used by Lepidopteran insects.[1] The Wittig condensation is one of the most useful reactions for the selective formation of C-C double bonds.[2] We have investigated the effects of reaction conditions on the stereoselectivity and yield of the Wittig reaction[3] in detail and found that potassium *tert*-butoxide (*t*-BuOK) in toluene gave the best results. This method is suitable for the preparation of unsaturated esters and other compounds on a large-scale.



Our first observation was that *t*-BuOK formed *in situ* before coupling gave the best results. The dissolution of powdered *t*-BuOK (purified by sublimation) posed some difficulties because it had only slight solubility in toluene. The proper concentration (0.075 g/ml) can be reached using *t*-BuOK prepared *in situ*. *tert*-Butanol was used in excess and after the dissolution of potassium, excess *t*-BuOH was distilled off with toluene. By dilution of the mixture with dry toluene to the starting volume, a clear solution of *t*-BuOK in toluene was obtained. When the phosphonium salt was added to the solution of the base, the color of the suspension became orange-red. The *tert*-butanol formed during the ylide generation should be distilled off immediately with toluene; otherwise, the alcohol will initiate side-reactions that consume the ylide.[4] These side-reactions are indicated by the change of the suspension from orange-red to light-yellow or white, indicating formation of phosphorus compounds, such as triphenylphosphine oxide and/or alkyl diphenylphosphine oxide from the ylide. After the *tert*-butanol generated from the ylide formation had been removed, the mixture was diluted to the starting volume with toluene. The aldehyde was then added at -78°, and the resulting mixture was stirred for 30 min at that temperature and then for 2 hrs at room temperature. The usual work-up

gave the olefin with (Z)-selectivity (95-98%; Table 1.).

High yields (60-80%) of olefin can be achieved if the alkyl chain of the phosphonium salt has no base-sensitive group. The toluene used should be alcohol free and dry. The final product were purified by semi-dry column chromatography (SDC) which is a modified version of dry column flash chromatography (DCFC).[5] In case of SDC, the column was never sucked completely dry and so the speed of purification was higher without decreasing its effectiveness. The SDC is a useful method for fast pre-purification or final purification of compounds in large amounts. The effectiveness of the method can be improved by gradient elution.

TABLE 1. Wittig Reaction Using *t*-BuOK as Base in Toluene

Cmpd	R	R´	Z/E[a]	Yield (%)
3a	$CH_3(CH_2)_3$-	$HO(CH_2)_4$-	98:2	60
3b	$CH_3(CH_2)_3$-	$MeO_2C(CH_2)_3$-	95:5	50
3c	$CH_3(CH_2)_3$-	$MeO_2C(CH_2)_7$-	98:2	60
3d	CH_3CH_2-	$MeO_2C(CH_2)_9$-	97:3	60

a)Ratio determined by GC.

EXPERIMENTAL SECTION

tert-Butanol was distilled from sodium before use. Toluene was dried over calcium chloride and then distilled from sodium. The Z/E ratios of **3** were measured by GC on Perkin-Elmer F22 instrument with FID detector. The columns employed were: CPSIL 5CB capillary column (50 m x 0.22 mm i. d., df = 0.15 m/u; A) and CPWAX 57CB capillary column (25 m x 0.22 mm i. d., df = 0.15 m/u; B). The temperature of the injector and the detector was 200°.

General Procedure.- Potassium (1.1 equiv.) was dissolved in a mixture of *tert*-butanol (4.4 equiv.) and toluene (3 ml/ml *t*-BuOH) with heating at reflux. After dissolution of potassium, the excess of *tert*-butanol was distilled off with toluene. When the temperature of the mixture reached 110°, the solution was diluted with toluene to the initial volume. The phosphonium salt[3,7] (1.1 equiv.) was then added to the mixture at 25° and the *tert*-butanol formed was distilled off with toluene *immediately*! Distillation was continued until the vapor temperature was 110°. The dark-red suspension was diluted to the original volume with toluene, and the solution was cooled to -78°. The aldehyde (1.0 equiv.) in toluene (one ml/ml of R´CHO) was added to the mixture at -78° with stirring and the resulting suspension was stirred for 30 min at -78°, and then for 2 hrs at 25°. The reaction mixture was evaporated *in vacuo* and the residue was suspended in hexane (3 ml/g residue). The suspension was filtered, the precipitate was washed with hexane (max. 0.5 ml/g residue), and the combined filtrate was concentrated *in vacuo*. The residue was purified by SDC.

Semi-Dry Column Chromatography (SDC)

Preparation of Column.- The column used for SDC is a glass filter (fritted glass funnel; porosity: 15-6.4 micron) packed with a 1:1 mixture of silica gel 60 (0.063-0.200 mm; 70-230 mesh, MERCK) and silica gel HF (MERCK) used for thin layer chromatography. The height of the silica gel bed is 5-8 cm. Higher packing does not result in significantly better separation. For larger samples, the glass filter with a larger diameter gives better results. Some practical data for SDC are given in Table 2.

The mixture of silica gel was wetted with the eluent and filled into the glass filter. The eluent was sucked until the eluent flow became very slow (1 drop/1-2 sec). An alternate method is to fill the glass filter with a wet mixture of silica gels, suck it dry, reload 40 vol % of the resulting filtrate and suck it into the bed.

Separation .- The sample is dissolved or diluted with eluent (one ml/ml) and loaded on the top of column containing the wet packing. The solution is then drawn into the silica gel bed. The height of solution on the top of column should not be greater than 5 mm. If the volume of the solution is large, it should be divided to portions. *The next portion can be loaded on the top of the column after sucking the previous one.* After the entire sample is sucked into the column, elution is initiated using the same procedure. Each portion of eluent (see Table 2) is loaded on the top of column and sucked through the packing until the flow is 1 drop/1-2 sec.

TABLE 2. Practical Data for Semi-Dry Column Chromatography (SDC)

	I	II	III	IV	V
Diameter of glass filter (mm)	200	120	90	65	40
Packing:					
Kieselgel 60 (g) (0.063-0.200 mm)	500	200	100	30	10
Kieselgel HF (g)[a]	500	200	100	30	10
Volume (ml) of one fraction	160	80	60	30	8
Amount (g) of sample[b]	30-50	10-30	1-10	1-5	0.1-1

a) Utilized for preparation of thin layer chromatography; b) Highly dependent on the number of components in the mixture and their R_f-values.

5(Z)-Decen-1-ol (**3a**).- From pentyltriphenylphosphonium bromide and 5-hydroxypentanal[6] to yield **3a** (60%).

IR (film): 1650, 3030 (C=C), 3400, 1100 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 0.85 (t, J = 7Hz, 3H, $-CH_3$), 2.00 (m, 4H, $CH_2C{=}CCH_2$), 3.60 (m, 2H, CH_2O), 5.40 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$): δ 62.8 (C^1), 27.2 (C^4 + C^7), 129.2 + 130.3 (C^5 + C^6), 14.0 (C^{10}). GC: Column: A, T_{Column}: 90°, t_{ret}: 81.3 min (Z isomer of **3a**), 82.1 min (E isomer of **3a**).

Methyl 5(Z)-decenoate (**3b**).- From pentyltriphenylphosphonium bromide and methyl 4-formylbutanoate to yield **3b** (50%).

IR (film): 1645, 3020 (C=C), 1740 (C=O), 1250 cm^{-1} (C-O-C_{ester}); ^1H NMR ($CDCl_3$): δ 0.90 (t, J = 7Hz, 3H, -CH_3), 2.05 (m, 4H, $CH_2C{=}CCH_2$), 2.25 (m, 2H, $CH_2C{=}O$), 3.65(s, 3H, OCH_3), 5.38 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$): δ 174.2 (C^1), 29.5 (C^2), 27.1 +27.2(C^4 + C^7), 129.9 + 130.2 (C^5 + C^6), 13.9 (C^{10}), 51.1 (C_{OCH}). GC: Column: A, T_{Column}: 90°, t_{ret}: 51.2 min (Z isomer of **3b**), 51.9 min (E isomer of **3b**).

Methyl 9(Z)-tetradecenoate (**3c**).- From pentyltriphenylphosphonium bromide and methyl 8-formyl-octanoate to yield **3c** (60%).

IR (film): 1650, 3030 (C=C), 1750 (C=O), 1240 cm^{-1} (C-O-C_{ester}); ^1H NMR ($CDCl_3$): δ 0.85 (t, J = 7Hz, 3H, -CH_3), 2.00 (m, 4H, $CH_2C{=}CCH_2$), 2.30 (m, 2H, $CH_2C{=}O$), 3.61 (s, 3H, OCH_3), 5.40 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$): δ 174.1 (C^1), 29.4 (C_2), 27.3 (C^8 + C^{11}), 131.1 (C^9 + C^{10}), 14.0 (C^{14}), 51.2 (C_{OCH_3}). GC: Column: B, T_{Column}: 140°, t_{ret}: 18.6 min (Z isomer of **3c**), 18.4 min (E isomer of **3c**).

Methyl 11(Z)-tetradecenoate (**3d**).- From *n*-propyltriphenylphosphonium bromide and methyl 10-formyl decanoate to yield **3d** (60%).

IR (film): 1640, 3030 (C=C), 1740 (C=O), 1250 cm^{-1} (C-O-C_{ester}); ^1H NMR ($CDCl_3$): δ 0.90 (t, J = 7Hz, 3H, -CH_3), 2.05 (m, 4H, $CH_2C{=}CCH_2$), 2.20 (m, 2H, $CH_2C{=}O$), 3.64 (s, 3H, OCH_3), 5.30 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$): δ 174.3 (C^1), 29.4 (C^2), 27.2 + 27.3 (C^9 + C^{12}), 131.4 (C^{10} + C^{11}), 14.0 (C^{14}), 51.2 (C_{OCH_3}). GC: Column: B, T_{Column}: 160 °, t_{ret}: 5.9 min (Z isomer of **3d**), 5.7 min (E isomer of **3d**).

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A CONVENIENT SYNTHESIS OF 2,5-DIAMINO-1,4-BENZENEDIOL

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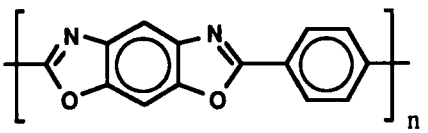
Recently, there has been considerable interest in the area of high strength liquid crystalline polymers such as poly[p-phenylenebenzobis(oxazole)] (PBO).[1] We wanted to evaluate the *trans*-isomer (**2**) for comparison and needed multi-gram quantities of 2,5-diamino-1,4-benzenediol (**5**), the precursor of **2**. The synthetic route [2,3] for compound **5** involves four steps starting from



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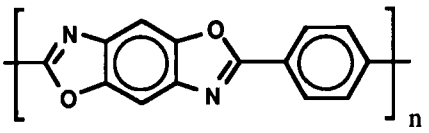

2

hydroquinone with a low overall yield of 18%. We report herein a novel and high-yield process for the synthesis of **5** from commercially available starting materials.

It is known[4,5] that *p*-chloranil, on treatment with ammonium hydroxide, undergoes selective displacement of two chlorine atoms to afford 2,5-diamino-3,6-dichlorobenzoquinone (**3**) in quantitative yield. It was reasoned that simultaneous reduction of the quinone moiety to hydroquinone as well as hydrogenolysis of the halogens in **3** should provide the desired compound **5**.