Crossed Coupling of Functionalised Ketones by Low Valent Titanium (The McMurry Reaction): A New Stereoselective Synthesis of Tamoxifen

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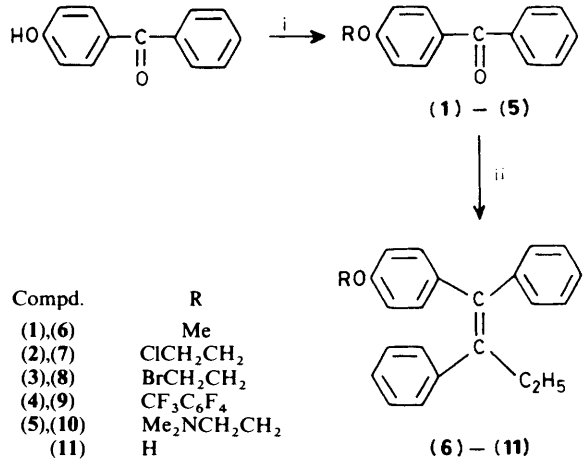
Low valent titanium-mediated crossed coupling of substituted benzophenones of the type 4-XPhCOPh, where X = MeO, $ClCH_2CH_2O$, $BrCH_2CH_2O$, $CF_3C_6H_4O$, HO and $Me_2NCH_2CH_2O$, with propiophenone affords the corresponding but-1-enes in high yield with a marked preponderance of the *Z*-isomer in most cases. Remarkably, when X = OH the *Z*:*E* ratio is 9:1. The value of this method is illustrated by simple syntheses of (*Z*)-1-{4-[2-(*N*,*N*-dimethylamino)ethoxy]phenyl}-1,2-diphenylbut-1-ene (Tamoxifen) a drug widely used in the treatment of oestrogen-dependent breast tumours.

As part of our study of derivatives of antitumour agents we have been preparing analogues of Tamoxifen [1-{4-[2-(*N*,*N*-dimethylamino)ethoxy]phenyl}-1,2-diphenylbut-1-ene (**10**)] first introduced by I.C.I. for the treatment of oestrogen-dependent breast tumours. Published syntheses of this butene[1] are usually long and at some stage, often near the end of the sequence, involve a separation of *E*- and *Z*-isomers. In seeking a simpler synthesis to these interesting compounds we looked for a method which would be flexible to allow the introduction of suitable functional groups using readily available reagents. Considerations of possible disconnections in the target molecule suggested the possibility of C=C formation as being a desirable step; three possibilities are, the Wittig reaction and its various modifications, the use of silicon-stabilised anions, and the McMurry reaction. Consideration of the availability of starting materials led us to consider the latter.

Low valent titanium-mediated coupling was first described by Mukaiyama[2] but greatly extended by McMurry.[3] There have been a number of reviews of the scope and limitations of the reaction by McMurry,[4] Yee-Hing Lai[5] and Finocchiaro *et al.*[6] The mechanism of the reaction has been studied particularly by Dams *et al.*[7] but without any precise conclusions being drawn. It has been concluded, however, by McMurry[4] that crossed coupling reactions may not be of significant synthetic value. Further, although some work has been done on the coupling of functionalised ketones[6] there appears to be no general view as to which groups will or will not interfere with the coupling. There are indications[4] that crossed coupling works best when one component is a diaryl ketone and we have been able to confirm this view. The stereochemistry of the resulting alkenes has by and large not been well studied, in most cases symmetrical ketones have been used and so the problem did not arise.

The ultimate object of our study was to find a simple route to substituted butenes leading to Tamoxifen analogues and it was reasoned that 4-substituted benzophenones and propiophenone were suitable partners for the coupling. There are several systems available for coupling and McMurry[4] has suggested that for aryl ketones the $TiCl_3$—Li system gives the best yields, and indeed benzophenone and acetophenone with this system give a good yield of the crossed product.

We first investigated the coupling reaction between 4-methoxybenzophenone and propiophenone, using $TiCl_3$–Li in dimethoxyethane under an argon atmosphere. A smooth reaction took place to afford a crystalline product in high (76%) isolated yield. Examination by h.p.l.c. indicated the presence of two components in the ratio 8:3. ^1H N.m.r. spectroscopy showed the expected resonances for a ethyl, methoxy and aryl protons, and confirmed from the integral ratios the 8:3 isomer



Compd.	R
(1),(6)	Me
(2),(7)	$ClCH_2CH_2$
(3),(8)	$BrCH_2CH_2$
(4),(9)	$CF_3C_6F_4$
(5),(10)	$Me_2NCH_2CH_2$
(11)	H

(6) – (11)

Scheme. *Reagents:* i, RX(X = F, Br, Cl, or I); ii, PhCOEt—$TiCl_3$—Li, or $TiCl_4$—Zn.

distribution. From a study by ourselves and others[8] we have noted that the distinctive pattern for protons constituting the A_2B_2 system of the 4-substituted aryl ring in the *Z*-isomer is well separated from the remaining aryl protons and usually lies in the region δ 6.1—6.8 whereas the corresponding aryl protons in the *E*-isomer coincide with remaining aryl protons at δ 6.8—7.4. Thus, we have a useful diagnostic tool for the determination of the *E*/*Z* isomer ratios. This effect is presumed to be due to the different shielding effects of the phenyl and the ethyl groups on the 4-substituted ring in the different isomers.

Although we have not found it possible to separate the *E*- and *Z*-isomers of the butene (**6**) the marked stereochemical preponderance of the *Z*-isomer was encouraging. It has been shown that separation of the *E*- and *Z*-isomers of 1-[4-(2-chloroethoxy)phenyl]-1,2-diphenylbut-1-ene (**7**) is possible by recrystallisation of the isomer mixture from propan-2-ol.[9] Thus, we next investigated the reaction between the corresponding benzophenone (**1**) (readily prepared by reaction of 4-hydroxybenzophenone and either 1,2-dichloroethane or 1-bromo-2-chloroethane under phase-transfer conditions), and propiophenone. There is some evidence that the titanium reagent reduces halogens but we found in fact that a smooth reaction occurred to give a crystalline solid shown by ^1H n.m.r. and h.p.l.c. to be a 7:1 mixture of the *Z*-and *E*-isomers of the desired but-1-ene (**7**). Recrystallisation of this mixture from propan-2-ol gave the pure *Z*-isomer. In a similar manner 4-(2-bromoethoxy)-

benzophenone and propiophenone afforded the corresponding but-1-ene (**8**) in a *Z*:*E* ratio of 4:1.

Recently there has been a report[10] that the use of heptafluorotolyl ethers allowed the separation of *E*- and *Z*-isomers of but-1-enes by simple recrystallisation and that the fluorocarbon group could readily be removed by reaction with methoxide ion. Thus, 4-[2,3,5,6-tetrafluoro-4-trifluoromethylphenoxy]benzophenone was prepared by reaction of 4-hydroxybenzophenone and perfluorotoluene. Coupling of this ketone with propiophenone gave a moderate (39%) yield of the corresponding butene (**9**). ^1H and ^{19}F N.m.r. spectroscopy indicated a 4:5 *Z*/*E* mixture which we could not completely separate by recrystallisation from light petroleum as suggested.

There are indications in the literature[6] that functional groups containing active hydrogens may interfere with the coupling reaction. We were thus somewhat surprised therefore to find that a reaction between 4-hydroxybenzophenone and propiophenone afforded the butene (**11**) in excellent (93%) yield. ^1H N.m.r. spectroscopy indicated a 9:1 *Z*:*E* ratio. In view of this result we attempted a similar reaction using 4-[2-(*N*,*N*-dimethylamino)ethoxy]benzophenone and propiophenone to produce the butene (**10**) (Tamoxifen) in one step. However, very little reaction occurred and no Tamoxifen was isolated. Although the latter reaction failed we now have obtained a simple route to Tamoxifen since the reaction of the butenes (**7**) and (**8**) with dimethyl-amine in ethanol yield pure Tamoxifen in high yield. A difficulty in this process has been the use of titanium(III)chloride and lithium both of which require careful handling in oxygen-free, dry systems, and in fact necessitate the use of a dry bag for manipulation. Such problems limit the usefulness of our reaction since it is difficult to scale up. Thus, an alternative method of preparing the titanium reagent was studied. In the original work by Mukaiyama, titanium(IV) chloride and zinc were used as the reagents. However, this mixture was not favoured by McMurry due to a tendency to pinacol* formation. This suggested to us that there may be incomplete reduction and so we investigated the use of a variation of the conditions to achieve a more favourable reaction. We found that addition of $TiCl_4$ to a suspension of zinc powder in THF or dimethoxyethane followed by a short reflux period yielded a more reactive metal system.

Thus, we found that using our system, we could obtain pure (*Z*)-1-[4-(2-chloroethoxy)phenyl]-1,2-diphenylbut-1-ene (**7**) in 55% isolated yield; the yield of crude product was greater than 90% and the isomer ratio *Z*:*E* was between 7:1 and 9:1. The reaction was repeated with 4-hydroxybenzophenone and propiophenone and we obtained a 98% yield of the desired 4-hydroxybutene (**11**) with an isomer ratio of 7:1 (*Z*:*E*), thus confirming our earlier result using titanium(III) chloride. More surprisingly, it was found that using this system we were able to prepare Tamoxifen (**10**) directly from 4-[2-(*N*,*N*-dimethylamino)ethoxy]benzophenone and propiophenone in 88% yield with an isomer ratio *Z*:*E* of 3:1, as indicated by ^1H n.m.r. spectroscopy and h.p.l.c. analysis.

A sample of Tamoxifen was then prepared from the 4-hydroxybutene (**11**) from the titanium(IV) chloride experiment with an isomer ratio *Z*:*E* 7:1 without purification of the latter, by reaction with 2-chloro-1-(*N*,*N*-dimethylamino)ethane to see if it was possible to purify the mixture at the final step. We obtained a very high yield of Tamoxifen isomers from which we were only able to crystallise a relatively small amount (*ca.* a third of the product) in a 7—8:1 *Z*:*E* mixture. The residue was a *ca.* 3:2 mixture of *Z*:*E* isomers. This result indicates that in the process some isomerisation of the 4-hydroxy derivative has taken place.

The mechanism of the reaction is still not clear from our results. Whether the reaction proceeds *via* a radical anion as favoured by McMurry[4] and Dams *et al*[7] we cannot tell. Further, there is a puzzle regarding the high stereoselectivity observed. A possible explanation for this result could be a preferred orientation of the two ketones, one of which may be bound to the metal surface brought about by a weak interaction between the substituted phenyl group of the benzophenone and the phenyl group of the propiophenone. We believe that whatever the mechanism of the reaction, the benzophenone reacts first with the metal, since we have in some reactions found traces of the self-coupled products of propiophenone but not of the benzophenones. We feel that we have demonstrated that cross coupling of ketones can, under the right conditions, be a very useful synthetic process. We believe that the two-step process *via* the 2-chloroethoxybutene (**7**) followed by reaction with dimethylamine is the best route to the pure *Z*-isomer of Tamoxifen and is a route of considerable commercial potential.

Since this work was filed as a Patent application, a European Patent[11] has appeared which uses the McMurry reaction to prepare Tamoxifen directly but in poorer yield and with less stereospecificity than the method we describe.

Experimental

4-(2-*Chloroethoxy*)*benzophenone* (**2**).—4-Hydroxybenzophenone (19.8 g, 0.1 mol), benzyltributylammonium bromide (3.6 g, 0.01 mol), sodium hydroxide (8.0 g, 0.2 mol), water (75 cm^3), and 1,2-dichloroethane (75 cm^3) were stirred together (Vibromixer) at reflux for 18 h. The mixture was cooled, the upper aqueous layer removed, and the organic layer dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded a red oil which crystallised from ethanol–water to yield 4-(2-*chloroethoxy*)*benzophenone* (22.8 g) (88%), m.p. 77—78 °C (lit.,[12] 78 °C).

4-(2-*Bromoethoxy*)*benzophenone* (**3**).—In a similar manner but using 1,2-dibromoethane, 4-(2-bromoethoxy)benzophenone m.p. 62 °C was prepared in 78% yield.

4-(2,3,5,6-*Tetrafluoro*-4-*trifluoromethylphenoxy*)*benzophenone* (**4**).—Perfluorotoluene (2.4 g), and 4-hydroxybenzophenone (1.98 g) in dichloromethane were stirred with sodium hydroxide (1M; 30 cm^3) and tetrabutylammonium hydrogen sulphate (1.7 g) as a phase-transfer agent at 18 °C for 2 h. Separation of the dichloromethane, extraction of the aqueous layer with dichloromethane (3 × 20 cm^3), and evaporation of the combined dried ($CaCl_2$) organic layers afforded, after recrystallisation from ethanol 4-(2,3,5,6-*tetrafluoro*-4-*trifluoromethylphenoxy*)*benzophenone* (4.0 g, 94%), m.p. 125 °C. (Found: C, 58.2; H, 1.9. $C_{20}H_9F_7O_2$ requires C, 58.0; H, 2.15%); δ_H 6.95—7.95 (9 H, m, ArH); δ_F ($CFCl_3$) 53.6 (3 F, t, CF_3), 139.5 [2 F, m, *m*-ArF (relative to CF_3)], and 151.5 [2 F, m, *o*-ArF (relative to CF_3)] p.p.m.; $\nu_{max.}$ 1 650 cm^{-1} (C=O).

4-[2-(N,N-*Dimethylamino*)*ethoxy*]*benzophenone* (**5**).—The sodium salt from 4-hydroxybenzophenone (10 g) prepared as above, 2-chloro-1-dimethylaminoethane [from the hydrochloride (25.5 g) in toluene (100 cm^3)] were heated under reflux for 24 h. Filtration and evaporation of the solvent afforded a brown oil which on distillation under reduced pressure afforded 4-(2-dimethylaminoethoxy)benzophenone (9.7 g), b.p. 174—179 °C/0.3 mmHg (lit.,[13] 176—180 °C/0.3 mmHg).

(E/Z)-1-(4-*Methoxyphenyl*)-1,2-*diphenylbut*-1-*ene* (**6**).—Lithium pieces (0.45 g, 65 mmol) were added to a slurry of titanium(III) chloride (2.87 g, 18.6 mmol) in dry dimethoxyethane (30 cm^3) under argon and when the addition was complete, the mixture was heated under reflux for 1 h. The black mixture was cooled to 18 °C and a solution of 4-methoxybenzophenone (**1**)

* 2,3-Dimethylbutane-2,3-diol

(0.49 g) and propiophenone (0.31 g) in dimethoxyethane (15 cm^3) was added. The reaction mixture was stirred at 18 °C for 2 h. and then at reflux for 20 h. To the cooled black suspension light petroleum (b.p. 60—80 °C) (50 cm^3) was added. The organic layer was separated and the solvent evaporated to leave a brown oil (0.77 g). Purification by chromatography on a silica gel column with hexane–ethyl acetate (9.1; v/v) afforded (*E*/*Z*)-(4-methoxyphenyl)-1,2-diphenylbut-1-ene (0.55 g), m.p. 109—111 °C (lit.,[12] 120—122 °C, pure *Z* isomer) (Found: C, 87.8; H, 7.3. Calc. for $C_{23}H_{22}O$: C, 87.9; H, 7.0%) ^{1}H n.m.r. spectroscopy was consistent with the structure, the integral ratio of the peaks indicated an 8:3 *Z*:*E* ratio of isomers.

1-[4-(2-*Chloroethoxy*)*phenyl*]-1,2-*diphenylbut*-1-*ene* (**7**).—(*a*) In a similar manner to that described for 4-methoxybenzophenone, 4-(2-chloroethoxy)benzophenone (0.54 g), and propiophenone (0.31 g) afforded a crude oil (0.77 g). Chromatography yielded a colourless oil (0.51 g) shown by ^{1}H n.m.r. to have a *Z*:*E* isomer ratio of 4:1. Recrystallisation from propan-2-ol (20 cm^3) afforded pure (Z)-1-[4-(2-*chloroethoxy*)*phenyl*]-1,2-*diphenylbut*-1-*ene* (**7**) (0.3 g), m.p. 63—65 °C (Found: C, 79.7; H, 6.3. $C_{24}H_{23}ClO$ requires C, 79.6; H, 6.4%); δ_H 0.88 (3 H, t, CH_2*Me*), 2.34 (2 H, q, *C*H_2Me), 3.65 (2 H, t, OCH_2CH_2Cl), 4.06 (2 H, t, OCH_2CH_2Cl), 6.34—6.85 (4 H, A_2B_2, ArH), 7.07 (5 H, s, Ph), and 7.21 (5 H, s, Ph); $\nu_{max.}$ (Nujol) 1 610 (C=O) and 1 510 cm^{-1} (Ar).

(*b*) Titanium tetrachloride (3.44 g, 18 mmol) was added dropwise to a stirred suspension of zinc powder (2.3 g, 36 mmol) in tetrahydrofuran (30 cm^3) at −10 °C under dry argon. The resulting dark mixture was heated under reflux for 1 h. The suspension was cooled to 18 °C and a mixture of 4-(2-chloroethoxy)benzophenone (1.59 g) and propiophenone (0.80 g) in THF (20 cm^3) was added. The mixture was refluxed and stirred for 2 h., cooled, and poured into 10% aqueous potassium carbonate (22 cm^3). The aqueous layer was extracted with ether (3 × 100 cm^3) and the combined organic extracts were dried and evaporated to give a yellow oil. Recrystallisation from propan-2-ol as above gave (*Z*)-1-[4-(2-chloroethoxy)phenyl]-1,2-diphenylbut-1-ene (1.2 g), m.p. 64—68 °C.

1-(4-*Hydroxyphenyl*)-1,2-*diphenylbut*-1-*ene* (**11**).—(*a*) 4-Hydroxybenzophenone (0.46 g) and propiophenone (0.31 g) in dimethoxyethane (15 cm^3) were added to the titanium reagent [from lithium (0.45 g) and titanium(III) chloride (2.87 g) as above]. The mixture was heated under reflux for 12 h. cooled to 18 °C, and ethanol (50 cm^3) was added. The solvents were removed to yield a brown oil which was partitioned between chloroform (40 cm^3) and 10% hydrochloric acid (50 cm^3). The organic layer was separated and the aqueous layer extracted with chloroform (2 × 40 cm^3). Evaporation of the dried ($CaCl_2$) chloroform layer afforded a brown oil (0.63 g) with i.r. and n.m.r. spectral characteristics identical with those of an authentic sample.[11]

(*b*) Titanium(IV) chloride (7.5 cm^3) was added *via* a syringe and subaseal to a stirred suspension of zinc powder (9.0 g) in dry, freshly distilled dimethoxyethane at −10 °C in an inert atmosphere. When the addition was complete, the mixture was warmed to room temperature and then refluxed for 2 h. To the cooled suspension of the titanium reagent, 4-hydroxybenzophenone (4.5 g, 0.022 mol) and propiophenone (3.0 g, 0.022 mol) in dry dimethoxyethane (30 cm^3) were added. The mixture was refluxed for 4 h, cooled, and poured into 10% aqueous potassium carbonate (300 cm^3) and extracted with ether (3 × 100 cm^3). The combined ether extracts were dried ($MgSO_4$) and the solvent removed to give a light brown oil (6.5 g, 98%) which crystallised to give a 7:1 (n.m.r.) *Z*:*E* mixture of 1-(4-hydroxyphenyl)-1,2-diphenylbut-1-ene, m.p. 109—117 °C with ^{1}H n.m.r. and i.r. spectra consistent with those reported for *Z*:*E* mixtures.[12]

1-{4-[2-(*N*,*N*-*Dimethylamino*)*ethoxy*]*phenyl*}-1,2-*diphenylbut*-1-*ene* (**10**).—(*a*) *From* (Z)-1-[4-(2-*chloroethoxy*)*phenyl*]-1,2-*diphenylbut*-1-*ene*. (*Z*)-1-[4-(2-Chloroethoxy)phenyl]-1,2-diphenylbut-1-ene (100 mg) was heated with 30% (w/v) dimethylamine in ethanol (3 cm^3) for 3 days at 75 °C in a sealed vessel. The solvents were evaporated and the product purified by chromatography on silica gel using chloroform–methanol (9:1 v/v) as the eluant. Recrystallisation from chloroform–hexane yielded (*Z*)-1-[4-(2-dimethylaminoethoxy)phenyl]-1,2-diphenylbut-1-ene (85 mg), m.p. 94—95 °C (lit.,[12] 96—98 °C) (Found; C, 84.2; H, 8.1; N, 3.5. Calc. for $C_{26}H_{29}NO$: C, 84.1; H, 7.8; N, 3.8%), with a ^{1}H n.m.r. spectrum identical to that of an authentic sample.*

(*b*) *From* 4-[2-(N,N-*dimethylamino*)*ethoxy*]*benzophenone and propiophenone*. 4-[2-(N,N-Dimethylamino)ethoxy]benzophenone (1.55 g) and propiophenone (0.8 g) were allowed to react with the titanium reagent from $TiCl_4$—Zn as above. After work-up, a pale yellow oil (1.97, 88%) was obtained which was shown by ^{1}H n.m.r. spectroscopy to be a *Z*/*E* mixture of 1-{4-[2-(*N*,*N*-dimethylamino)ethoxy]phenyl}-1,2-diphenylbut-1-ene (Tamoxifen). The isomer ratio was 3:1.

(*c*) The sodium salt of 1-(4-hydroxyphenyl)-1,2-diphenylbut-1-ene [from the butene (1.00 g)] and 1-chloro-*N*,*N*-dimethylaminoethane [from its hydrochloride (1.44 g)] were heated under reflux in toluene for 12 h. The precipitated sodium chloride was filtered off and the solvent removed to give an oil. Recrystallisation from light petroleum (b.p. 60—80 °C) gave a *Z*/*E* mixture of {4-[2-(*N*,*N*-dimethylamino)ethoxy]phenyl}-1,2-diphenylbutene (Tamoxifen) (0.3 g) m.p. 77—83 °C. ^{1}H N.m.r. spectroscopy showed the *Z*:*E* ratio to be 7:1. Evaporation of the solvent afforded a further sample (0.7 g) m.p. 73—80 °C with a *Z*:*E* isomer ratio of 3:2.

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