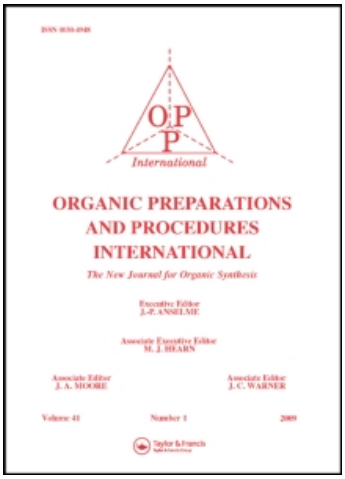

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article McCague, Raymond , Potter, Gerard A. and Jarman, Michael(1994) 'AN EFFICIENT, LARGE-SCALE SYNTHESIS OF IDOXIFENE {(E)-1-[4-[2-(*N*-PYRROLIDINO)ETHOXY]PHENYL]-1-(4-IODOPHENYL)-2-PHENYL-1-BUTENE}', Organic Preparations and Procedures International, 26: 3, 343 — 346
To link to this Article: DOI: 10.1080/00304949409458432
URL: http://dx.doi.org/10.1080/00304949409458432

ORGANIC PREPARATIONS AND PROCEDURES INT., 26 (3), 343-346 (1994)

AN EFFICIENT, LARGE-SCALE SYNTHESIS OF IDOXIFENE {(*E*)-1-[4-[2-(*N*-PYRROLIDINO)ETHOXY]PHENYL]-1-(4-IODOPHENYL)-2-PHENYL-1-BUTENE}

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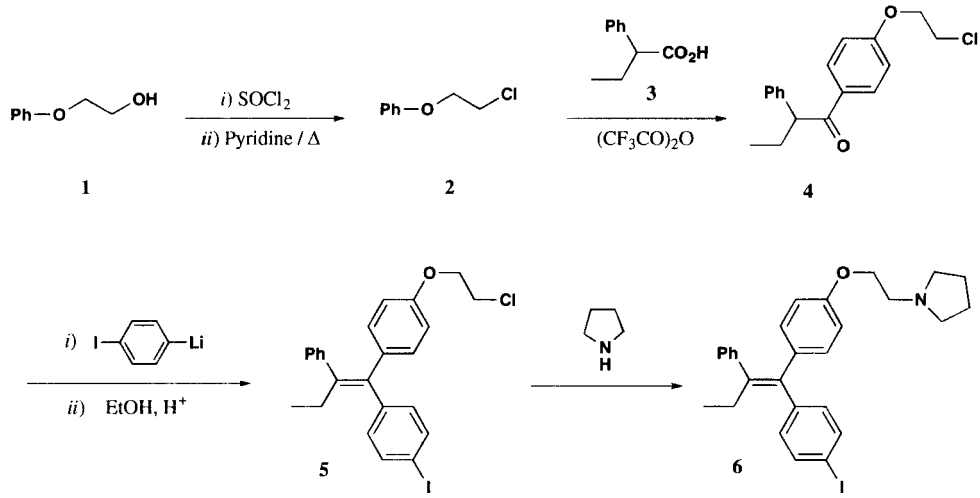
(E)-1-[4-[2-(*N*-Pyrrolidino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene (idoxifene, **6**)[1] is an analogue of the well-known anticancer drug tamoxifen, and is currently undergoing clinical trial to evaluate its efficacy in the treatment of hormone-dependent breast cancer. Enhanced binding affinity for the target estrogen receptor,[2] improved antagonism of calmodulin-dependent processes,[3] enhanced antitumour activity, reduced residual estrogenicity in rats,[4] and an improved metabolic profile[5], are all experimental advantages of idoxifene over tamoxifen which have prompted the selection of idoxifene for clinical evaluation. For this purpose, a large-scale (0.5 kg) synthesis, which could be amenable to even further scale-up was required.



Our previous, briefly described small-scale route to **6** involved Friedel-Crafts acylation of 2-chloroethoxybenzene[6] **2** by 2-phenylbutyric acid **3**, followed by reaction of the resulting ketone **4** with 4-iodophenyllithium, prepared by monolithiation of 1,4-diiodobenzene.[2] Dehydration of the intermediate tertiary alcohol produced the triphenylbutene **5**, as a mixture of *E* and *Z* isomers from which the

desired *E*-isomer was separated by crystallization. Elaboration of the chloroethoxy side-chain provided the required product **6**. This route has proved amenable to scale-up, but the products from each stage had to be isolable without chromatography, and in particular conditions for the efficient separation of the required *E*-isomer on a large-scale also needed to be established. Furthermore careful adjustment of the experimental conditions was necessary in order to avoid exothermic and potentially hazardous side-reactions encountered in the lithiation process on a large scale. An alternative method for preparing large quantities of the starting 2-chloroethoxybenzene **2** was also required.

Phase-transfer catalysed reaction of phenol with dichloroethane, used both as the reagent and solvent, proved a convenient route to 2-chloroethoxybenzene (**2**) on a sub-molar scale,[6] but requires a high dilution to avoid disubstitution of the dichloroethane. In order to minimize reaction volumes, and to avoid the chromatographic step required in that method, the method of choice on the large-scale was based on an earlier procedure[7] in which 2-phenoxyethanol (**1**) was treated with excess pyridine and thionyl chloride. Our modification uses pyridine only in catalytic amounts. Initial treatment of phenoxyethanol with thionyl chloride alone gave the crude intermediate chlorosulfinate to which pyridine (0.01 mol %) was then added and the mixture heated to afford the desired 2-chloroethoxybenzene (**2**) in 92% yield compared with 85% for both the literature method[7] and the phase-transfer procedure.[6] Ketone **4** was prepared essentially as previously described.[6] However, mono-lithiation of 1,4-diiodobenzene to prepare 4-iodophenyllithium, needed for subsequent introduction of the 4-iodophenyl substituent, required careful control of the reaction temperature on a large-scale. This is essential to prevent a nucleophilic substitution side-reaction between the by-product butyl iodide and the 4-iodophenyllithium. This reaction would exothermically generate 4-butyl-1-iodobenzene and any rise in temperature would promote further side-reaction with potentially hazardous consequences. Following addition of the ketone **4** to the 4-iodophenyllithium solution, the reaction was quenched with conc. HCl at -20° to prevent the intermediate lithium salt of the tertiary alcohol from dehydrochlorinating the side-chain.

In the synthesis of tamoxifen and its congeners, it is vital that the geometrical isomers of the end product, or its precursors, are separated because the desirable estrogen antagonist activity is generally exhibited only by one isomer. In the case of idoxifene, this is the *E*-isomer **6**, in which the unsubstituted phenyl and iodophenyl residues are in a *trans* relationship. Fortunately, repeated recrystallization of the mixture of isomers (*E* and *Z*) of the chloroethoxy precursor, obtained by dehydration of the tertiary alcohol, afforded the pure *E*-isomer (**5**). In the final step, the need to minimize solvent volumes required the use of a higher reaction temperature and a sealed vessel. This provided the product **6** in even higher yield (97%) than that obtained previously (92%).

EXPERIMENTAL SECTION

2-Phenoxyethanol, 2-phenylbutyric acid, and anhydrous grade tetrahydrofuran (THF) were obtained from Aldrich Chemical Co. Ltd. Except where otherwise stated, all products had ^{1}H-NMR spectra and melting points (determined as in ref. 2) identical to values for products obtained previously.[2,6] Thin layer chromatography (TLC) was performed using silica gel plates (Merck 5735)

with the developing solvent indicated. Elemental analysis was determined by CHN analysis Ltd, South Wigston, Leicester, UK.

2-Chloroethoxybenzene (2).- To thionyl chloride (2.5 L, 4080 g, 34.2 mol) in a 5 L three-necked flask, heated under reflux, was added 2-phenoxyethanol **1** (1630 g, 11.8 mol) over a 2.5 hrs period. The HCl evolved was absorbed into ice-water *via* an inverted funnel. The mixture was refluxed for a further 1 hr then thionyl chloride (in 300 mL portions) removed on a rotary evaporator (1997 g collected). The product was liberated from the crude intermediate [$PhOCH_2CH_2OS(=O)Cl$] as follows. It was placed in a 1 L flask and pyridine (0.1 mL) added and heated to ca. 105°. Sulfur dioxide was evolved and the mixture turned from orange-red to yellow. The mixture was heated to 160° to complete the reaction and allowed to cool to give crude **2** (1816 g). Distillation gave 1785.5 g (95%) of pure product, bp. 124°/34 mm Hg.

1-[4-(2-Chloroethoxy)phenyl]-2-phenyl-1-butanone (4).- 2-Phenylbutyric acid **3** (411 g, 2.50 mol), 2-chloroethoxybenzene **2** (431 g, 2.75 mol) and trifluoroacetic anhydride (371 mL) were placed in a 3 L flask and stirred. The solution changed from colorless to orange-red in a few minutes. Stirring was continued for 72 hrs. The solution was then poured into water (3 L) and the resultant oil was triturated with a glass rod until crystallization commenced. The crystalline product was collected (sintered funnel), washed with water (10 L) and dried *in vacuo* over P_2O_5, then recrystallized from light petroleum (bp. 80-100°, 3 L) to give 639.2 g (84%) of **4** as off-white crystals, mp. 69-70°, lit.[6] 69-70°.

(*E*)-1-[4-(2-Chloroethoxy)phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene (5).- A 10 L flanged flask was charged with 1,4-diiodobenzene (692.3 g, 2.10 mmol) and fitted with an overhead mechanical stirrer, low temperature thermometer, gas outlet and rubber septum sealed inlet. The flask was purged with nitrogen then anhydrous THF (6 L) introduced. The solution was cooled by an acetone-cardice (Dry Ice) bath to ca. -65° (some diiodobenzene precipitates). *n*-Butyllithium (2.5 M; 839 mL, 2.10 mol) was then added during 1.5 hr by a double-ended transfer needle from a septum-sealed 250 mL measuring cylinder. During the addition extra cardice was continually added to the cooling bath to ensure the reaction temperature was maintained below -55°. A solution of the ketone **4** (571.7 g, 1.89 mol) in anhydrous THF (1.5 L) was then added during 45 min, the temperature being kept below -50°. The cooling bath was removed, the mixture allowed to reach ca. -20° and then conc. HCl (250 mL) was added. The resulting orange-red solution was concentrated on a rotary evaporator to provide the intermediate tertiary alcohol, an oil which solidified on standing. The course of the entire reaction was monitored by TLC (dichloromethane) and only the intermediate tertiary alcohol gave an orange color on the developed plate when sprayed with conc. H_2SO_4. To a solution of this intermediate in warm 95% ethanol (2.5 L), was added conc. HCl (30 mL) and the mixture was heated to reflux whereupon dehydration was complete. The cooled reaction mixture was seeded with the authentic *E*(*trans*) product,[2] whereupon crystalline material separated and was recovered by filtration. The solid was recrystallized from ethanol and the product was shown by NMR spectroscopy[2] to be a 2:1 mixture of the desired *E*(*trans*)-isomer (**5**) together with the *cis* counterpart. A further recrystallization from ethanol gave 626.9 g (68% yield) of product of variable *trans:cis* composition (depending on which

portion of the crystalline mass was sampled the *trans:cis* ratio varied from 3:1 to 24:1). Recrystallization of this from light petroleum (bp. 80-100°) gave 336.3 g (36%) of the pure *E*(trans)-isomer **5**, mp. 96-97°, lit.[7] 96-97°.

(*E*)-1-[4-[2-(*N*-Pyrrolidino)ethoxy]phenyl]-1-(4-iodophenyl)-2-phenyl-1-butene (Idoxifene, 6).- The chloroethoxy derivative **5** (110 g, 0.25 mol) was placed in a 600 mL bomb (Parr Scientific) together with ethanol (200 mL) and pyrrolidine (200 mL). The sealed bomb was then heated (with stirring of contents) at 100° (20 psi) for 1 hr, then for a further 3 hrs without stirring and allowed to cool. The product was deposited as white crystals which were collected on a sinter, washed with diethyl ether, drained and dried overnight in a vacuum dessicator to yield 99.6 g (85%). A further 14.4 g was obtained after concentration of the mother liquors. The total yield of **6** was therefore 114 g (97%). The product and starting material could be distinguished by TLC (light petroleum-diethyl ether-triethylamine, 8:1:1). The foregoing reaction was repeated 4 more times thus using a total of 550 g of chloroethoxy derivative. The first crop of crystals from the above experiments were combined (total 498 g) and recrystallized twice from ethanol to give white crystals (433 g), mp. 108.5-109°, lit.[2] mp. 108-109°.

Anal. Calcd for $C_{28}H_{30}NIO$: C, 64.25; H, 5.78; I, 24.24; N, 2.68
Found: C, 64.24; H, 5.84; I, 24.23; N, 2.69.

Acknowledgements.- This work was supported by grants from the Cancer Research Campaign, Medical Research Council, and British Technology Group.

REFERENCES

† Present address: Chiros Limited, Cambridge Science Park, Milton Road, Cambridge, CB4 4WE, UK.

1. R. McCague. British Patent Application No. 8621908 (1986).

2. R. McCague, G. Leclercq, N. Legros, J. Goodman, G. M. Blackburn, M. Jarman and A.B. Foster, *J. Med. Chem.*, **32**, 2527 (1989).

3. M. G. Rowlands, I. B. Parr, R. McCague, M. Jarman and P. M. Goddard, *Biochem. Pharmacol.*, **40**, 283 (1990).

4. S. K. Chander, R. McCague, Y. Luqmani, C. Newton, M. Dowsett, M. Jarman and R. C. Coombes, *Cancer Res.*, **51**, 5851 (1991).

5. B. P. Haynes, I. B. Parr, L. J. Griggs and M. Jarman, *Breast Cancer Res. Treat.*, **19**, 174 (1991).

6. R. McCague, *J. Chem. Res.* (*S*), 58; (*M*), 771 (1986).

7. R. A. Ellison and F. N. Kotsonis, *J. Org. Chem.*, **38**, 4192 (1973).

(Received October 23, 1993; in revised form December 20, 1993)