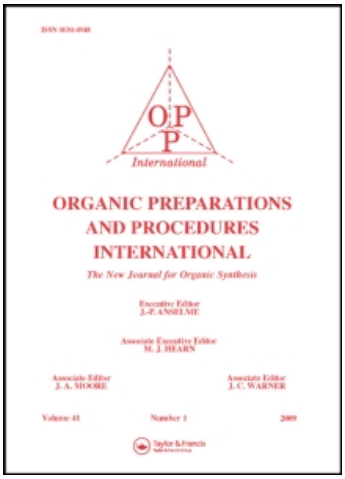
This article was downloaded by:
On: *27 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Organic Preparations and Procedures International

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

SYNTHESIS OF METHOXYTAMOXIFEN

Hoda A. El-Wakil[a]
[a] Department of Chemistry, Faculty of Science, Moharram Bay Alexandria University, Alexandria, EGYPT

To cite this Article El-Wakil, Hoda A.(1991) 'SYNTHESIS OF METHOXYTAMOXIFEN', Organic Preparations and Procedures International, 23: 6, 754 — 757
To link to this Article: DOI: 10.1080/00304949109458252
URL: http://dx.doi.org/10.1080/00304949109458252

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

(sept, 2H, 2 x -CH($C\underline{H}_3$)$_2$), 6.8 (s, 4H, aromatic).

The alkaline layer was acidified with conc. HCl and extracted with petroleum ether (3 x 60 ml). The organic layer was washed with water, brine, dried (Na_2SO_4). Removal of solvent and the distillation of the residue furnished a pale yellow oil (2.89, 63%) of O-isopropoxyphenol (**3**),[1] bp. 130°/4 mm, lit.[1] bp. 100-102°/11 mm. IR (neat) 3560, 3000, 1610, 1510, 1480, 1400, 1390, 1135, 790, 750 cm^{-1}. ^1H NMR (CCl_4): δ 1.23, 1.33 (d, 6H, J = 6 Hz, -CH($C\underline{H}_3$)$_2$), 4.46 (sept., 1H, -CH($C\underline{H}_3$)$_2$), 5.73 (s, 1H, OH), 6.6-6.9 (m, 4H, aromatic).

REFERENCES

† NCL Communication No. 5204.

1. A. J. Birch, *J. Chem. Soc.*, 102 (**1947**).
2. C. R. Worthing, "The Pesticides Manual", 7th Ed., P. 470; British Crop Protection Council, Croydon (1983).
3. K. Wedemeyer and W. Sutter, Ger offen. 1,962,091 (1971); C. A., **75**, 63403 (1971).
4. M. Paolo, M. Francescom and C. Mariano, Eur. 84/19,249 (1984); C. A., **104**, 19411x (1986); C. Mariano, M. Francesco and P. Pietro, Eur. 276,030 (1988); C.A., 109, 110018p (1988); W. Zhiguang, Z. Zhuhen and F. Zhuanli, Shenqing, Gongkai, Shuomingshu, CN. **104**, 306 (1988); C. A., **110**, 212350d (1989).
5. N. Barrota, G. Chuchani and J. Zabicky, *J. Org. Chem.*, **31**, 2330 (1966).

Downloaded At: 09:50 27 January 2011

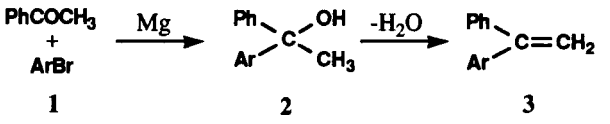
****

SYNTHESIS OF METHOXYTAMOXIFEN

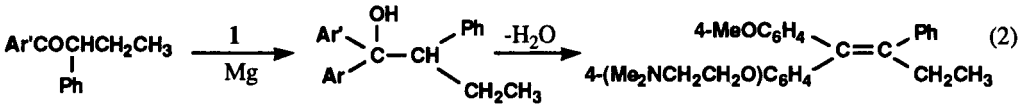
Submitted by (04/30/91) Hoda A. El-Wakil

Department of Chemistry
Faculty of Science, Moharram Bay
Alexandria University, Alexandria, EGYPT

In continuation of our earlier utilization of the heteroatom-facilitated lithiation of aromatic compounds[1] for the preparation of radiolabelled estrogens[2] and antiestrogens,[3] we needed to prepare methoxytamoxifen (**6**) and its radiolabelled derivatives. The key step in the synthesis of these antiestrogens is a Grignard reaction (Eq. 2). Since compounds having ether, hydroxy, amino and other similar groups are known to form the Grignard reagents in low yields, perhaps because of their



1 2 3 (1)



4 5 6 (2)

Ar = 4-($Me_2NCH_2CH_2O$)C_6H_4 Ar' = 4-$MeOC_6H_4$

ability to form associated polymeric Grignard reagents,[4] the success of the reaction depends on the choice of an appropriate phenol-protecting group and of the reaction conditions. It was then decided to determine the ideal reaction conditions using acetophenone as a model compound.

The infrared spectrum of the product of the reaction of acetophenone with the Grignard reagent prepared from *p*-[β-(N,N-dimethylamino)ethoxy]phenyl bromide (**1**), using known methods of activation[4] such as magnesium and 1,2-dibromoethane system or iodine activated magnesium, showed no hydroxylic stretching absorption; TLC analysis showed one spot (R_f = 0.22, 20:1 acetone-triethylamine) and its mass spectra (m/e 328) suggested it to be 4,4'-bis[(β-dimethylamino)ethoxy]biphenyl. However, the use of finely powered activated magnesium (to increase the surface are of magnesium) in an inert atmosphere gave 1-phenyl-1-[*p*-(β-N,N-dimethylamino)ethoxy]phenylethanol (**2**), dehydration of which gave 1-phenyl-1-[*p*-(β-N,N-dimethylamino)ethoxyphenylethylene (**3**); compounds **2** and **3** were identified spectroscopically and by their elemental analysis. Under the same conditions, 2-phenyl-1-(*p*-methoxyphenyl]-1-butanone (**4**)[5] gave methoxytamoxifen (**6**) in 52% yield.

EXPERIMENTAL SECTION

Finely powdered activated magnesium metal was prepared by the reduction of an anhydrous magnesium(II) halide with sodium.[4,6] ^1H NMR spectra were recorded on 100 MHz instrument in $CDCl_3$ containing 1% TMS as an internal standard. Flash chromatography was performed according to the procedure of Still,[7] (silica gel 60, 230-400 mesh). Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

1-Phenyl-1-[*p*-(β-N,N-dimethylamino)ethoxy]phenylethanol (2).- To a refluxing suspension of finely powered magnesium (0.159 g, 6.15 mmol)[6,8] in 20 ml of tetrahydrofuran, in a 3-necked round-bottomed flask was added dropwise *p*-[β-(N,N-dimethylamino)ethoxy]phenyl bromide (1.59 g, 6.15 mmol). The reaction mixture was stirred for 4 hrs at 30° and cooled to 0°; then acetophenone (0.616 g, 5.13 mmol) in tetrahydrofuran was added dropwise through a dropping funnel. The mixture was refluxed overnight under nitrogen, cooled, quenched with a saturated solution of ammonium chloride

Downloaded At: 09:50 27 January 2011

and then extracted with ether. The extracts were dried (anhydrous sodium sulfate) and evaporated to afford an oily product, which was purified by flash chromatography on silica gel using $CHCl_3$-MeOH (95:5) as an eluent. Recrystallization from hexane-ethyl acetate gave 0.95 g (65%) of white crystals, mp. 70-72°, identified as **2**. ^1H NMR (60 MHz, $CDCl_3$): δ 1.83 (3H, s), 2.23 (6H, s), 2.65 (2H, t, J = 6 Hz), 3.1 (1H, br) 3.99 (2H, t, J = 6 Hz), 6.6-7.4 (9H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.97, 45.78, 58.18, 65.34, 75.79, 113.95, 125.71, 126.92, 127.07, 127.98.

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.98. Found: C, 75.72; H, 8.05; N, 4.95

1-Phenyl-1-[*p*-(β-N,N-dimethylamino)ethoxy]phenylethylene (3).- A solution of 1.85 g of **2** in methanol, and 2 mL of HCl was refluxed overnight; it was then cooled to 0°, neutralized with 6 N sodium hydroxide and extracted with ethyl acetate. After drying over anhydrous sodium sulfate; the solvent was evaporated and flash chromatography of the crude product on silica gel using $CHCl_3$-MeOH (92:8) as an eluent gave 1.55 g (89%) of **3** (R_f = 0.34) as a yellow solid. ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.90, 58.31, 65.58, 112.35, 114.44, 126.62, 127.54, 128.30, 129.27.

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.94; N, 5.24. Found: C, 80.81; H, 7.98; N, 5.25

1-[4-Methoxyphenyl]-1-[*p*-(β-N,N-dimethylamino)ethoxy]phenyl-2-phenyl-1-butanol (5).- To a refluxing suspension of finely powdered magnesium[6] (0.312 g, 13 mmol) in 40 mL of tetrahydrofuran in a 3-necked round-bottomed flask, was added dropwise 3.0 g (12.3 mmol) of **1**. The reaction mixture was stirred for 4 hrs at 30° and cooled to 0°. Then 2-(phenyl)-1-(4-methoxyphenyl)-1-butanone (2.84 g, 11 mmol)[8] in tetrahydrofuran was added dropwise through a dropping funnel. The mixture was refluxed overnight under nitrogen, cooled, quenched with a saturated solution of ammonium chloride. The mixture was then extracted with ether and the extract was dried over anhydrous sodium sulfate. Evaporation of the solvent afforded an oil, which was purified by flask chromatography to give 2.51 g (53%) of a yellow oil identified as **5**. ^1H NMR (100 MHz, $CDCl_3$): δ 12.66, 23.44, 44.78, 55.06, 56.55, 58.21, 65.71, 80.38, 112.35, 113.39, 126.23, 127.07, 127.52, 129.34, 130.18, 138.43, 139.01, 139.23, 157.26, 157.65.

1-[4-Methoxyphenyl]-1-[*p*-(β-N,N-dimethylamino)ethoxy]phenyl-2-phenyl-1-butene (6).- A solution of 250 g of **5** in methanol and 1.5 mL of 10N HCl was refluxed overnight; it was then cooled to 0°, neutralized with 6N sodium hydroxide and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil which was flash chromatographed on silica gel using $CHCl_3$:MeOH (91:9) to give a yellow oil **6** (2.30 g, 95%) which was shown to be a 1:1 mixture of the E and Z isomers of methoxytamoxifen.[9] ^1H NMR (100 MHz, $CDCl_3$): δ 0.95 (3H, t, J = 6 Hz, CH_2CH_3), 2.25 and 2.27 (6H, s, $N(CH_3)_2$, 2.60-2.90 (4H, m, CH_2CH_3 and OCH_2CH_2N), 3.67 and 3.78 (3H, s, OCH_3) 3.95-4.25 (2H, t, OCH_2CH_2N), 6.53, 6.57 (2H, t, two overlapped doublets, J = 9 Hz), 6.78 (2H, d, J = 9 Hz), 6.88-7.19 (9H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.79, 29.99, 45.97, 55.19, 78.37, 65.77, 112.60, 113.30, 125.39, 127.35, 129.73, 130.57, 131.94, 135.34, 136.24, 137.36, 140.96, 142.74, 156.72, 158.23.

Downloaded At: 09:50 27 January 2011

REFERENCES

1. a) H. A. El-Wakil and S. Abdel Baky, *Spectroscopy Lett.*, **23**, 497 (1990); b) R. Hanson and H. A. El-Wakil, *J. Org. Chem.*, **52**, 3687 (1987).

2. R. N. Hanson and H. A. El-Wakil and F. Murphy, *J. Labelled Comp. and Pharm.*, **27**, 615 (1989).

3. a) R. N. Hanson and H. A. El-Wakil, To be published; b) D. E. Seitz and H. A. El-Wakil and R. A. Millius, *Synth. Comm.*, **11**, 281 (1981).

4. Y. H. Lai, *Synthesis*, 585 (**1981**).

5. a) J. S. Buck and W. S. Ide, *J. Am. Chem. Soc.*, **54**, 3012 (1932); b) D. W. Robertson and J. A. Katzenellenbogen, *J. Org. Chem.*, **47**, 2387 (1982).

6. R. D. Reike and P. M. Hudnall, *J. Am. Chem. Soc.*, **94**, 7178 (1972).

7. W. C. Still, M. Kahn and A. Miltra, *J. Org. Chem.*, **43**, 2923 (1978).

8. J. W. Wilson, A. Burger, L. B. Turnbull, M. Peters and F. Milnes, ibid., **18**, 96 (1953).

9. The ^{1}H NMR spectrum was virtually indentical to the published spectrum of E and Z tamoxifen [G. R. Bedford and D. N. Richardson, Nature, **212**, 733 (1966)] with the obvious addition of the *O*-methyl peak.

Downloaded At: 09:50 27 January 2011

****

TWO IMPROVED SYNTHESES OF N,N'-*bis*(3 ,3-DIETHOXYPROPYL)SUCCINAMIDE

Submitted by (07/22/91) John T. Hortenstine* and John E. Mills

The R. W. Johnson Pharmaceutical Research Institute
Welsh and McKean Roads
Spring House, PA 19477-0776

The title compound (**1**) has been used as an intermediate in the four-step synthesis of spermine diacetal dinitrate (**2**),[1] an experimental immunosuppressive agent[2] of novel chemical structure. Interest in **2** led us to produce larger quantities of it. Succinamide **1** has previously been prepared in three steps by reaction of 3-chloropropionaldehyde diethyl acetal with potassium phthalimide to give N-(3,3-diethoxypropyl)phthalimide in 92% yield. The phthalimide was converted to 3,3-diethoxypropylamine (**3**), with hydrazine in 74% yield, and **3** was then reacted with succinyl chloride in methylene chloride at -50° to form **1** in 43% yield.[1] Unfortunately, upon scale-up