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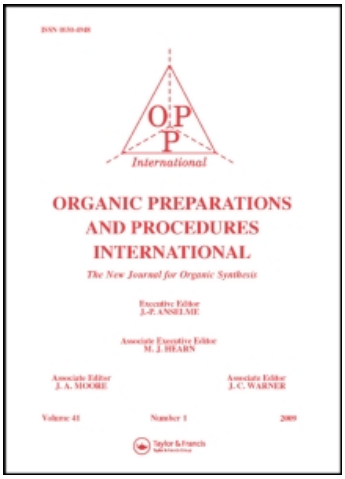


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# TRANSFORMATION OF SOME ARYL, BENZYL KETONES TO 2-ARYL-1,3-DICHLOROINDENES BY VILSMEIER REAGENT

I. W. Elliott[a]; S. L. Evans[b]; L. T. Kennedy[a]; A. E. Parrish[b]
[a] Department of Chemistry, Fisk University, Nashville, TN [b] Department of Pharmacology, Meharry Medical College, Nashville, TN

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# TRANSFORMATION OF SOME ARYL BENZYL KETONES TO 2-ARYL-1,3-DICHLOROINDENES BY VILSMEIER REAGENT


Submitted by (07/11/88) I. W. Elliott*†, S. L. Evans*††, L. T. Kennedy† and A. E. Parrish††

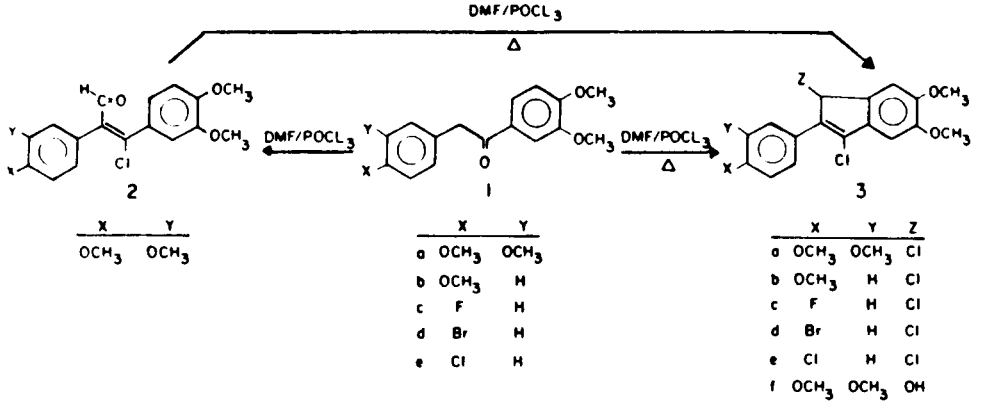
†Department of Chemistry, Fisk University Nashville, TN 37208

††Department of Pharmacology, Meharry Medical College, Nashville, TN 37208

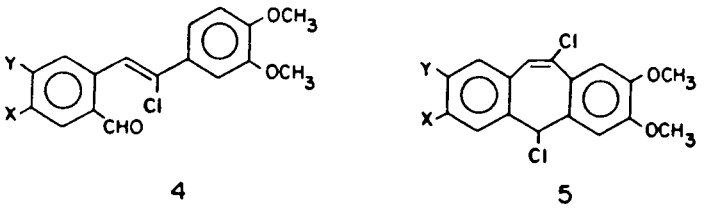

The prototypical Vilsmeier reagents, generated from dimethylformamide (DMF) and phosphorus oxychloride, is a weak, versatile electrophile which can formylate reactive aromatic rings[1] or transform ketones to β-chlorovinyl aldehydes.[2] We have found that desoxyveratroin (1a) is converted by DMF-$POCl_3$ to α-veratryl-β-chloro-3,4-dimethoxycinnamaldehyde (2) under mild conditions (0-60°) while 2-veratryl-1,3-dichloro-5,6-dimethoxyindene (3a) is obtained at elevated temperature (80-100°). Although Pulst et al.[2] prepared compounds analogous to 2, the tricyclic compound 3a is a new Vilsmeier reaction product from aryl benzyl ketones. Compound 2 can also be converted to 3a by hot DMF-$POCl_3$ solution. Cyclization to 3a appears to be facilitated by the p-methoxy group since aryl benzyl ketones (1b-e) with 3,4-dimethoxy substituents in the benzoyl ring readily gave indene derivatives 3b-e; in contrast, desoxybenzoin yields only the β-chlorovinyl aldehyde by our method or as reported by Weissenfels et al.[3]

The preparation of the chlorocinnamaldehyde 2 was carried out in tetrahydrofuran; when

1a, DMF and $POCl_3$ were used without solvent, the crude product was a difficulty separable mix-




ture of 2 and 2-veratryl-3-chloro-5,6 dimethoxy-1H-inden-1-ol (3f). The structures of 2 and 3a were based on elemental analysis and spectral data. Other possible structures such as 4 and 5 were considered. However, the choice of 3a for $C_{19}H_{18}Cl_2O_4$ was made on the basis of the 300 MHz $^1$H-NMR spectrum which showed a pattern of ortho and meta couplings in the aromatic region that could occur in structure 3a but not in structure 5; this also established structure 2 for the intermediate compound $C_{19}H_{18}ClO_5$. Spectra of compounds 3b-d were comparable to that of 3a.




4 5

## EXPERIMENTAL SECTION

Mps. were taken on a Mel-temp apparatus and are uncorrected. IR spectra were recorded as paraffin oil mulls on a Perkin-Elmer 727 spectrophotometer. Routine $^1$H NMR spectra were obtained on a Varian EM390 spectrometer. Microanalyses were carried out by Desert Analytics, Tuscon, Arizona.

α-Veratryl-β-chloro-3,4-dimethoxycinnamaldehyde (2).- Desoxyveratroin (2.5 g, 0.0079 moles) was dissolved in an ice-cooled solution of tetrahydrofuran (20 mL); dimethylformamide (12 mL) and phosphorus oxychloride (7 mL) was added over a period of 20 min. After 2 hrs at room temperature, the reddish solution upon scratching gave orange crystals. After 4 hrs, the slurry was poured into water (200 mL) and stirred overnight. The crude product (2.9 g, mp. 162-166°) was crystallized from methanol-benzene to afford 1.7 g (59%) of needles, mp. 183-184°. IR (mull): 1665, 1589 $cm^{-1}$; $^1$H-NMR ($CDCl_3$): δ 3.93 (s, 12H), 7.0 (m, 6H), 9.8 (s, 1H); mass spectrum: $M^+$ 364 (100%).



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Anal Calcd for $C_{19}H_{19}ClO_5$: C, 62.89; H, 5.28; Cl, 9.77. Found: C, 63.09; H, 5.22; Cl, 9.60

1,3-Dichloro-2-veratryl-5,6-dimethoxyindene (3a).(a) From Desoxyveratroin.- To an ice-cooled solution of DMF (20 mL)-$POCl_3$ (10 mL) was added desoxyveratroin (2.5 g, 0.0079 mole), and the slurry was heated at 85-95° for 4 hrs. The cooled brown solution was added to cold water (150 mL), and the suspension was stirred overnight. The crude product was collected and recrystallized from a minimum of methanol-benzene. The product was collected in two crops as golden crystals, 1.3 g (35%), mp. 167-168°. IR (mull): 1600, 1250 $cm^{-1}$; $^1$H-NMR ($CDCl_3$): δ 3.88 and 3.96 (12H), 5.65 (s, 1H), 6.96 (d, J = 6Hz, 1H), 6.97 (s, 1H), 7.14 (s, 1H), 7.27 (dd, J = 2 Hz, J = 6 Hz, 1H), 7.43 (d, J = 2 Hz, 1H); mass spectrum: 382, 381, 380 ($M^+$ for $^{35}Cl_2$), 347, 346, 345 (base peak).

Anal. Calcd for $C_{19}H_{18}Cl_2O_4$: C, 59.86; H, 4.76; Cl, 18.60

Found: C, 60.17; H, 4.79; Cl, 18.44

(b) From Compound 2.- To a solution of DMF (15 mL)-$POCl_3$ (7 mL) was added compound 2 (2.0 g). The mixture was heated to about 90° for 8 min. The cooled reaction was added to ice water (150 mL) and the precipitated solid was collected and recrystallized from ethanol containing a small amount of toluene to afford crystals, 1.2 g (57%), identical to compound 3a by mp. and IR comparisons.

The following products were obtained as described above for 3a.

1,3-Dichloro-2-(4-methoxyphenyl)-5,6-dimethoxyindene (3b), obtained as yellow needles in 37% yield, mp. 147-148° (from ethanol). IR (mull): 1620, 1320 $cm^{-1}$; $^1$H-NMR ($CDCl_3$): δ 3.80 (s, 3H), 3.92 (s, 6H), 5.59 (s, 1H), 7.35 (m, 6H); mass spectrum: 354, 352, 350 ($M^+$ for $^{35}Cl_2$),325 (base peak, loss of Cl).

Anal. Calcd for $C_{18}H_{16}Cl_2O_3$: C, 61.55; H, 4.59; Cl, 20.19

Found: C, 61.27; H, 4.66; Cl, 19.93

1,3-Dichloro-2-(4-fluorophenyl)-5,6-dimethoxyindene (3c), obtained as yellow needles in 24% yield, mp. 166.5-167° (from ethanol). IR (mull): 1620, 1320 $cm^{-1}$, $^1$H-NMR ($CDCl_3$): δ 3.98 (s, 6H), 5.62 (s, 1H), 7.52 (m, 6H); mass spectrum: 340, 338 ($M^+$ for $^{35}Cl_2$), 303 (base peak, loss of Cl).

Anal. Calcd for $C_{17}H_{13}Cl_2FO_2$ : C, 60.20; H, 3.86; Cl, 20.90; F, 5.60

Found: C, 60.09; H, 3.85; Cl, 21.10; F, 5.68

1,3-Dichloro-2-(4-bromophenyl)-5,6-dimethoxyindene (3d), obtained as yellow needles in 22% yield, mp. 165.5-166.5° (from ethanol). IR (mull): 1620, 1330 $cm^{-1}$; $^1$H-NMR ($CDCl_3$): δ 3.95 (s, 6H), 5.60 (s, 1H) 7.30 (m, 6H); mass spectrum: 402, 400, 398 ($M^+$ for $^{79}Br$ and $^{35}Cl_2$) 365 (base peak, loss of Cl).

Anal. Calcd or $C_{17}H_{13}BrCl_2O_2$ : C, 51.03; H, 3.28; Cl, 17.72; Br, 19.97

Found : C, 51.07; H, 3.22; Cl, 18.06; Br, 19.63

1,3-Dichloro-2-(4-chlorophenyl)5,6-dimethoxyindene (3e), obtained as yellow needles in 20% yield, mp. 154-155° (from ethanol). IR (mull): 1620; $^1$H-NMR ($CDCl_3$): δ 3.94 (s, 6H), 5.60



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(s, 1H), 7.30 (m, 6H); mass spectrum: 360, 358, 354 ($M^+$ for $^{35}Cl_3$), 319 (base peak, loss of Cl).

Anal. Calcd for $C_{17}H_{13}Cl_3O_2$: C, 57.41; H, 3.69; Cl, 29.91
Found: C, 57.34; H, 3.64; Cl, 29.89

2-Veratryl-3-chloro-5,6-dimethoxy-1H-inden-1-ol (3f).- The title compound was obtained in 3% purified yield by fractional recrystallization of the reaction product from a room temperature reaction of 1a with DMF-$POCl_3$ as colorless solid: mp. 189-190°. IR (mull): 3200-3400 $cm^{-1}$, $^1$H-NMR ($CDCl_3$): δ 1.95 (d, J = 9 Hz, 1H), 3.88 (s, 12H), 5.40 (d, J = 9 Hz), 6.82-7.50 (m, 5H).

Anal. Calcd for $C_{19}H_{19}ClO_5$: C, 62.89; H, 5.28; Cl, 9.77
Found : C, 63.03; H, 5.24; Cl, 9.61

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## AN IMPROVED SYNTHESIS OF (S)-3-METHYL-γ-BUTYROLACTONE

Submitted by (05/27/88) Patrizia Ferraboschi†, Paride Grisenti, Alberto Fiecchi and Enzo Santaniello*

Dipartmento di Chimica e Biochimica Medica
Universita di Milano, ITALY

(S)-(-)-3-Methyl-γ-butyrolactone (1), a useful chiron for the synthesis of natural products[1] and of some intermediates for the construction of steroid side chains,[2] has been obtained by baker's yeast biohydrogenation of the unsaturated ethyl ester 2a.[3] Ethyl (S)-3-methyl 4-hydroxybutanoate and the (E)-unsaturated ester 3a are the initial products of the above biohydrogenation; the lactone 1 can be obtained by distillation from the cyclization reaction carried out subsequently on the crude fermentation products.