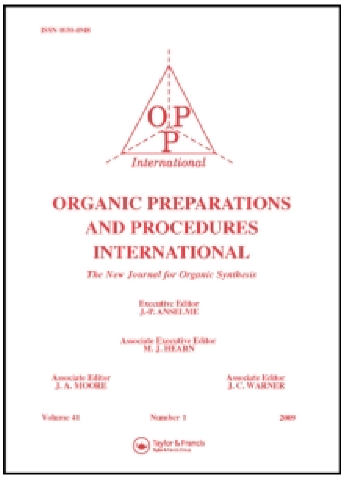


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

ETHYL 3-CHLORO-2-ETHOXY-5-FORMYL-6-HYDROXY-4-METHYLBENZOATE

Kau-Ming Chen[a]; Madeleine M. Joullié[a]
[a] Department of Chemistry, University of Pennsylvania, Philadelphia, PA

To cite this Article Chen, Kau-Ming and Joullié, Madeleine M.(1986) 'ETHYL 3-CHLORO-2-ETHOXY-5-FORMYL-6-HYDROXY-4-METHYLBENZOATE', Organic Preparations and Procedures International, 18: 2, 109 — 112

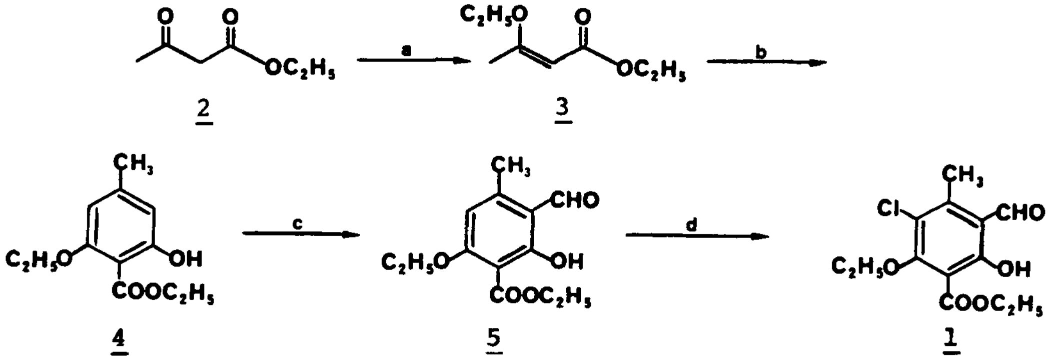
To link to this Article: DOI: 10.1080/00304948609356830

URL: http://dx.doi.org/10.1080/00304948609356830

ETHYL 3-CHLORO-2-ETHOXY-5-FORMYL-6-HYDROXY-4-METHYLBENZOATE

Submitted by Kau-Ming Chen and Madeleine M. Joullié*
(06/03/85)
Department of Chemistry
University of Pennsylvania, Philadelphia, PA 19104

The synthesis of hexasubstituted aromatic rings with appropriate substituents and manipulable functionality is of interest because these compounds serve as precursors in the synthesis of fungal metabolites such as colletochlorin D,[1] ascofuranone,[2] and ascochlorin.[3] In connection with our studies dealing with these natural products,[4,5] we have achieved the synthesis of a highly substituted aromatic compound (1) *via* the self-condensation of ethyl β-ethoxy-*cis*-crotonate[6] (3) which in turn, was obtained from ethyl acetoacetate (2) in 89% yield. A detailed procedure for the conversion of 3 to 4[7] using titanium tetrachloride has been devised. Formylation of 4 by a modified Gatterman reaction,[8] using zinc cyanide, aluminum chloride and anhydrous hydrogen chloride, gave 5 in 55% yield. Compound 1 was obtained in 75% yield by chlorination of 5 with sulfuryl chloride in ether.



[a]$CH(OEt)_3$, H_2SO_4; [b]$TiCl_4$, CH_2Cl_2; [c]$Zn(CN)_2$, $AlCl_3$, HCl (g); [d]SO_2Cl_2, Et_2O.

EXPERIMENTAL SECTION

General Methods.- ^{1}H NMR spectra were obtained in $CDCl_3$ on a Bruker WM (250 MHz) Fourier transform spectrometer. High-resolution mass spectra were obtained on a Hitachi-Perkin Elmer RMH-2 high resolution, double focusing, electron impact spectrometer or a vacuum Generator's V.G. 707H spectrometer interfaced with a Kratos DS-50-S data system. Infrared spectra (IR) were obtained on Perkin-Elmer infrared spectrophotometers, models 137, 281, or 781, in potassium bromide disks, or as solution in carbon tetrachloride in sodium chloride cells. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (250 μm) with a fluorescent indicator, supplied by E. Merck. Visualization was effected with ultraviolet light (UV), or 7% w/v ethanolic 12-phosphomolybdic acid (PMA). Preparative thin layer chromatography (PTLC) was performed on precoated silica gel plates (1000 μm) with a fluorescent indicator, supplied by Analtech, Inc. Flash column chromatography was performed on Merck SG-60 (230-400 mesh) silica gel. All solvents used were reagent grade. Anhydrous benzene, ether, and tetrahydrofuran (THF) were distilled from sodium and benzophenone; methylene chloride was distilled from calcium hydride.

Ethyl 2-ethoxy-6-hydroxy-4-methylbenzoate (4).- In a 250 ml three-necked, round-bottomed flask charged with ethyl β-ethoxy-(2Z)-crotonate (3) (35.95 g, 0.226 mol) and 70 ml of anhydrous methylene chloride was added dropwise titanium tetrachloride (42.92 g, 0.226 mol) by means of an addition funnel at 0° over a period of 1.5 hr. The color of the reaction mixture turned from red to orange and the mixture was stirred at room temperature for 24 hrs; crushed ice was then added to effect hydrolysis. The aqueous layer was extracted with 3 x 35 ml of methylene chloride. The combined organic layers were washed first with 3 x 35 ml of 2% $NaHCO_3$ solution, and then several times with water. After drying the organic layer ($MgSO_4$), the solvent was evaporated to give the crude product which was recrystallized from methylene chloride to give 4 (8.99 g, 35%) as a white solid, mp. 77-78°, lit.[7] mp. 79°; IR (CCl_4): 2929, 1670, 1625, 1570, 1380, 1310, 1268, 1226, 1130, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.4 (dt, 6H, J = 7 Hz), 2.28 (s, 3H), 4.03 (q, 2H, J = 7 Hz), 4.4 (q, 2H, J = 7 Hz), 6.4 (s, 1H), 6.2 (s, 1H), 11.6 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.76, 14.11, 22.1, 61.1, 64.78, 104.8, 106.4, 110.4, 146.2, 160.5, 163.6, 171.34.

Ethyl 2-ethoxy-5-formyl-6-hydroxy-4-methylbenzoate (5).- A 50 ml three-necked round-bottomed flask was fitted with a magnetic stirrer, an adapter provided with a reflux condenser, a gas inlet tube extending nearly to the bottom of the flask and an exit tube leading to an aqueous sodium hydroxide trap. The flask was charged with 4 (0.5 g, 2.23 mmol) in 15 ml of anhydrous benzene and ether (9:1 ratio) and powdered dry aluminum chloride (0.909 g, 6.9 mmol) was introduced; the solution became cloudy within 10 min. Zinc cyanide (0.413 g, 4.2 mol) was then added to the solution (use a good hood) and hydrogen chloride was passed into the stirred mixture at 40-45° for 5 hrs. Water (8.3 ml) was then added and the mixture was heated on a steam bath for 1.5 hr (temperature 80-90°). The solution was diluted with 30 ml benzene and the aqueous layer was extracted with 30 ml of benzene. The combined organic layers were dried (Na_2SO_4), the drying agent removed and the solvent was evaporated to give a crude mixture which was purified by flash column chromatography using 12% ethyl acetate in hexane to afford 5 (0.31 g, 55% yield), mp. 83-84° as a white solid. IR (KBr): 2920, 2800, 1730, 1640, 1560 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.4 (dt, 6H, J = 6.9 Hz), 2.58 (s, 3H), 4.15 (q, 2H, J = 6.9 Hz), 4.4 (q, 2H, J = 6.9 Hz), 6.27 (s, 1H), 10.17 (s, 1H), 12.55 (s, 1H), ^{13}C NMR (62.6 MHz, $CDCl_3$): 14.5, 14.3, 19.3, 61.03, 64.86, 106.4, 109.2, 114, 146.87, 162.9, 163.4, 165.8, 192.5; high resolution mass spectrum: M^+ Calcd for $C_{13}H_{16}O_5$ m/e 252.0997; found m/e: 252.1008.

Ethyl 3-chloro-2-ethoxy-5-formyl-6-hydroxy-4-methylbenzoate (1).- In a 25 ml one-necked round-bottomed flask charged with 5 (168 mg, 0.67 mmol) in anhydrous ether (12 ml) was added sulfuryl chloride (0.126 ml, 1.57 mmol) dropwise at 0°. After the addition was completed, the reaction mixture was stirred at room temperature for 24 hrs and then was diluted with 50 ml ether. The organic layer was washed with 3 x 5 ml 2% aqueous $NaHCO_3$

solution and 3 x 9 ml of water until it became neutral. The ethereal layer was dried ($MgSO_4$), the drying agent removed and the solvent evaporated under reduced pressure to give the crude product which was purified by flash column chromatography using 16% ethyl acetate in hexane as eluent to afford product 1 as a white solid (144 mg, 75% yield, mp. 73.5-75°). IR (KBr): 2900, 1720, 1642, 1620, 1300, 1200, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.42 (m, 6H), 2.67 (s, 3H), 4.19 (q, 2H, J = 6.9 Hz), 4.4 (q, 2H, J = 7.3 Hz), 10.28 (s, 1H), 12.53 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.2, 15.2, 15.37, 62.95, 70.8, 116.3, 116.4, 120.5, 143.02, 159.52, 161.23, 164.43, 193.48; high resolution mass spectrum: M^+ Calcd for $C_{13}H_{15}O_5Cl$ m/e 286.0608; found: m/e 286.0620.

Acknowledgements.- We gratefully acknowledge the Chemistry Department of the University of Pennsylvania for financial support of this work and for two fellowships (University and Karcher) to K.-M. Chen.

REFERENCES

1. Y. Kosuge, A. Suzuki and S. Tamura, Agr. Biol. Chem., 38, 1553 (1974).
2. H. Sasaki, T. Okutomi, T. Hosokawa, Y. Nawata and K. Ando, Tetrahedron Lett., 2541 (1972).
3. G. A. Ellestad, R. H. Evans, Jr. and M. P. Kunstmann, Tetrahedron, 25, 1323 (1969).
4. K. M. Chen and M. M. Joullie, Tetrahedron Lett., 23, 4567 (1982).
5. K. M. Chen and M. M. Joullie, ibid., 25, 3795 (1984).
6. E. E. Smissmann and A. N. Voldeng, J. Org. Chem., 29, 3161 (1964).
7. G. Declercq, G. Moutardier and P. Mastagli, Compt. Rend., 28(C), 279 (1975).
8. W. E. Truce, "Organic Reactions", Vol. IX, R. Adams, ed., John Wiley & Sons, 1957, p. 37.