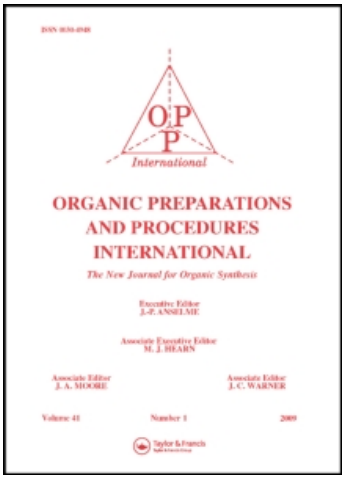


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A SUPERIOR METHACYCLINE SYNTHESIS BY PHOSPHINE OR PHOSPHITE DEHALOGENATION

H. Faubl[a]
[a] Central Research, Pfizer Inc., Groton, Connecticut

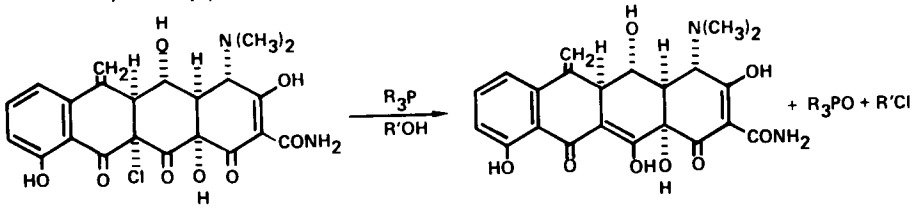
To cite this Article Faubl, H.(1976) 'A SUPERIOR METHACYCLINE SYNTHESIS BY PHOSPHINE OR PHOSPHITE DEHALOGENATION', Organic Preparations and Procedures International, 8: 4, 155 — 158
To link to this Article: DOI: 10.1080/00304947609355614
URL: http://dx.doi.org/10.1080/00304947609355614

ORGANIC PREPARATIONS AND PROCEDURES INT. 8(4), 155-158 (1976)

A SUPERIOR METHACYCLINE SYNTHESIS BY PHOSPHINE OR PHOSPHITE DEHALOGENATION

H. Faubl
Central Research, Pfizer Inc.
Groton, Connecticut 06340

As part of another project, we discovered that tertiary phosphines and phosphites are useful reagents for dechlorination of I,[1] affording II (methacycline, a clinically important tetracycline derivative[2]) in near quantitative yields without over-reduction or formation of other tetracycline by-products.



I II

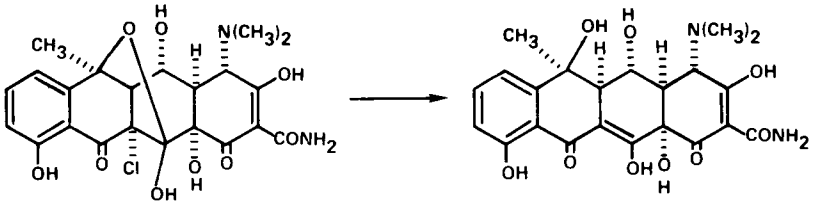
Treatment of the p-toluenesulfonic acid salt of I with a 2% molar excess of Ph_3P in 9:1 MeOH-H_2O at room temperature afforded a quantitative conversion of I to II in less than 20 minutes. Addition of an aqueous solution of 5-sulfosalicylic acid (SSA)[1] precipitated II in the form of its SSA salt in 97% yield.

The hydrochloride salt of I works as well as the p-toluenesulfonic acid salt. The reaction can be carried out in lower alcohols or ketones either alone or in combination with water, and in dimethylformamide alone or in combination with water or benzene. The presumed reaction course[3] requires a hydroxyl group source. In non-hydroxylic solvents the reactions required a longer reaction time to go to completion. The fact that in these solvents quantitative conversions to pure methacyclines were obtained, while surprising, is presumably related to the fact that the salts I used contained several percent water. Quantitative conversions were observed for all solvent/phosphine systems investigated. The yields of isolated II·SSA ranged from the high 80% to the high 90%. More methacycline as well as all the Ph_3PO could be detected in the filtrate.

In addition to Ph_3P, other effective phosphines include $(n\text{-}Bu)_3P$, $(p\text{-}C_6H_4OMe)_3P$, Me_2PPh and Ph_2PH.[4] The tertiary phosphines are transformed to the corresponding

phosphine oxides as shown by identification of isolated $(n\text{-}Bu)_3PO$ and Ph_3PO in several cases. The phosphine oxides and excess phosphines conveniently remain in solution when the salts of methacycline are isolated.

The scope of these reactions was investigated. Treatment of 11a-chloro-oxytetracycline (III) with Ph_3P in MeOH-H_2O at room temperature resulted in a rapid, clean conversion to oxytetracycline (IV). On the other hand, III gave decomposition products in addition to IV with $(EtO)_3P$ in refluxing EtOH. Finally, the 11a-fluorine analog of I upon treatment with either Ph_3P or $(n\text{-}Bu)_3P$ in MeOH-H_2O and EtOH-H_2O mixtures resulted in no apparent



III IV

formation of II even at reflux but only in a gradual buildup of decomposition products; similar results were obtained with excess $(EtO)_3P$ in refluxing EtOH.

The ability of phosphines to effect dehalogenation of α-haloketones is known[3-5] although low yields and mixtures of products are often observed because of the multitude of possible reaction pathways.[6] The use of triethyl phosphite for the conversion of the I to II was investigated since it is also capable of reductive dehalogenation of α-haloketones.[7] The mechanism presumably involves a Perkow reaction to form the enol phosphate followed by alcoholysis of this intermediate to the reduced ketone.[8] In contrast to the use of phosphines, $(EtO)_3P$ dehalogenations of I required a large excess of the phosphite, anhydrous methanol or ethanol as solvent and high temperatures. The requirement for excess reducing agent is presumably necessary because the water present in I decomposes some of the phosphite. Nevertheless, transformations of I to II proceeded cleanly and quantitatively.

EXPERIMENTAL

The Ph_3P was obtained from J.T. Baker, Ph_2PH from Ventron and $(n\text{-}Bu)_3P$, Me_2PPh and $(p\text{-}C_6H_4OMe)_3P$ from Strem Chemical Co. $(EtO)_3P$ was purchased from Aldrich Chemical Co. Authentic samples of all tetracyclines were available.[1,2] Their purities were determined by UV analysis (the only significant impurities were small amounts of water and methanol or isopropanol). The TLC system used for all cases consisted of silica gel plates buffered to pH 6, 95-5 THF-H_2O for development, and a UV lamp for visualization.

Methacycline (II) using Ph_3P. – To a stirred mixture of 90.2 g (0.139 mole, corrected for purity) of the p-toluenesulfonic acid salt of I[1] in 812 ml of MeOH and 90 ml of H_2O was

added 38.7 g (0.146 mole) of Ph_3P over 5 minutes. The temperature gradually rose from 26° to a maximum of 33° over 10 minutes and then slowly drifted down again. A TLC taken 20 minutes after the Ph_3P addition showed Ph_3PO and methacycline as the only tetracyclic component. Fifty minutes after the Ph_3P addition, 616 ml of 10% aqueous SSA was added at a uniform rate over a 2 hr.-period. The resulting slurry was stirred for 1.5 hr, then cooled to 10° over the next 1.5 hr. The precipitate was collected, washed with 100 ml of 1:1 MeOH-H_2O and dried to afford 95 g (97%) of pure methacycline·SSA identical to authentic material according to spectroscopic and chromatographic data.

Methacycline (II) using $(EtO)_3P$. – A mixture of triethyl phosphite (3.82 g, 23.0 mmole) and the p-toluenesulfonic acid salt of I[1] (3.21 g, 4.51 mmole, corrected) in 34 ml ethanol was heated at reflux for 1 hr. At this time TLC showed only II and no I. The reaction was cooled to 0°, filtered, treated with 20 ml of 10% aqueous SSA, and stirred at room temperature. The SSA salt of II was filtered, washed with cold MeOH and dried to afford 2.163 g (73%) of the yellow crystals of II·SSA. The filtrate contained more II according to TLC analysis.

Oxytetracycline (IV) using Ph_3P. – To 2.40 g (4.51 mmole) of III·HCl[1] in a solution of 30 ml MeOH and 4 ml H_2O was added 1.20 g (4.60 mmole) of Ph_3P. The mixture was stirred at room temperature and after 30 minutes the III to IV conversion was complete according to TLC. The reaction was diluted with 18 ml MeOH and then 20 ml of 10% aqueous SSA was added. The SSA salt of IV did not precipitate under these conditions and therefore the MeOH was removed under vacuum and the aqueous residue was extracted with EtOAc. Continued stirring of the residue resulted in the formation of crystals which were collected, affording a 62% yield of IV·SSA identical to authentic material.

Oxytetracycline (IV) using $(EtO)_3P$. – To 2.40 g (4.51 mmole) of III·HCl[1] in 34 ml of EtOH was added 0.71 g (4.60 mmole) of $(EtO)_3P$. The resulting slurry was heated to reflux for 1.5 hr. A TLC showed spots corresponding to III, IV and unknown materials. The reaction mixture was cooled and the precipitate collected, affording 0.40 g of yellow crystals of an unknown tetracycline-derived material. The filtrate from above was combined with 20 ml of 10% aqueous SSA and the new crystals that formed were collected, washed with cold MeOH and dried to afford 0.54 g (18%) of IV·SSA.

ACKNOWLEDGEMENT. – The excellent technical assistance of Mrs. A.M. Belton, Mr. C.F. Ebbinghaus and Ms. L.M. Smith is gratefully acknowledged, as is the guidance and encouragement provided by Dr. I.M. Goldman. GLC analyses for triphenylphosphine and triphenylphosphine oxide levels were kindly supplied by Dr. J. Dokladalova.

REFERENCES

1. *R.K. Blackwood, J.J. Beereboom, H.H. Rennhard, M. Schach von Wittenau, and C.R. Stephens, J. Am. Chem. Soc., 85, 3943 (1963).*
2. *R.K. Blackwood, in "Encyclopedia of Chemical Technology" 2nd Ed., Vol. 20, p. 1, A. Standen, Ed., John Wiley & Sons, Inc., New York, 1969.*
3. *I.J. Borowitz and L.I. Grossman, Tet. Letters, 471 (1962).*
4. *I.J. Borowitz, K.C. Kirby, Jr., P.E. Rusek, and E. Lord, J. Org. Chem., 34, 2687 (1969).*
5. *(a) R.D. Partos and A.J. Speziale, J. Am. Chem. Soc., 87, 5068 (1965);*
   (b) P.A. Chopard and R.F. Hudson, J. Chem. Soc. (B), 1089 (1966);
   (c) I.J. Borowitz, K.C. Kirby, Jr., P.E. Rusek, and R. Virkhaus, J. Org. Chem., 33, 3686 (1968).
6. *R.F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry", p. 146 ff, Academic Press, New York, 1965.*
7. *B.A. Arbuzov and N.P. Bogonostseva, Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk, 837 (1954); Chem. Abstr., 49, 13940 g (1955).*
8. *F.W. Lichtenthaler, Chem. Rev., 61, 607 (1961).*

(Received May 3, 1976; in revised form July 11, 1976)