Tetrahedron Letters No. 17, pp 1495 - 1499, 1973. Pergamon Press. Printed in Great Britain.

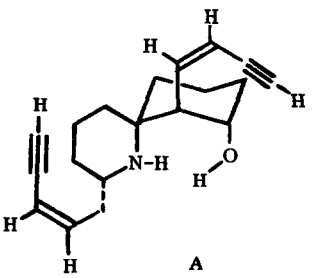
STEREOSELECTIVE METHODS FOR THE SYNTHESIS OF TERMINAL cis AND trans ENYNE UNITS

E. J. Corey and Ronald A. Ruden

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

(Received in USA 16 January 1973; received in UK for publication 19 March 1973)

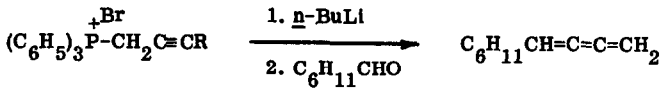
In connection with studies directed toward the total synthesis of the anticholinergic, spirocyclic alkaloid histrionicotoxin[1] (A), a method for the stereoselective introduction of a cis enyne grouping[2] was



A

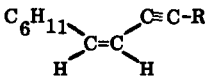
required. It was apparent from examination of the literature that existing methodology was totally inadequate.[3] This note reports a potential solution to this problem as well as our findings regarding the preparation of terminal enynes with particular reference to stereochemistry.

Wittig condensation of an aldehyde with propargylidenetriphenylphosphorane appeared to offer the most direct preparation of the desired enyne. When the requisite phosphonium salt[3] 1a in tetrahydrofuran (THF) was treated at 0° with 1 equivalent of n-butyllithium (n-BuLi), a red color appeared. Treatment of this solution with cyclohexane carboxaldehyde afforded in low yield the highly unstable cumulene 4 [i.r. 4.75 and 11.92 μ, p.m.r. three olefinic protons 5.08 (terminal CH_2 doublet, which in turn is finely split) and 5.55 p.p.m. (vinyl H, quartet, again finely split) in a ratio of 2:1]. The cumulene 4 might be formed as a consequence of isomerization of propargylidenetriphenylphosphorane to the allenylphosphorane 5 prior to Wittig condensation. This highly interesting observation awaits further investigation.

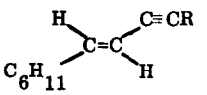


1a, R = H

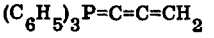
1b, R = trimethylsilyl



2



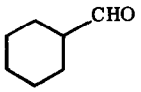
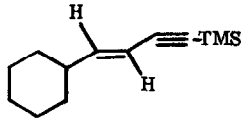
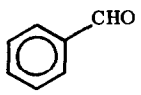
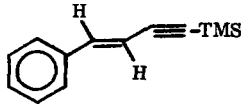
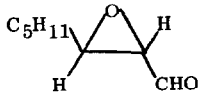
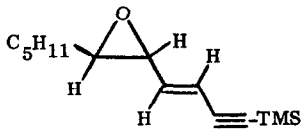
3



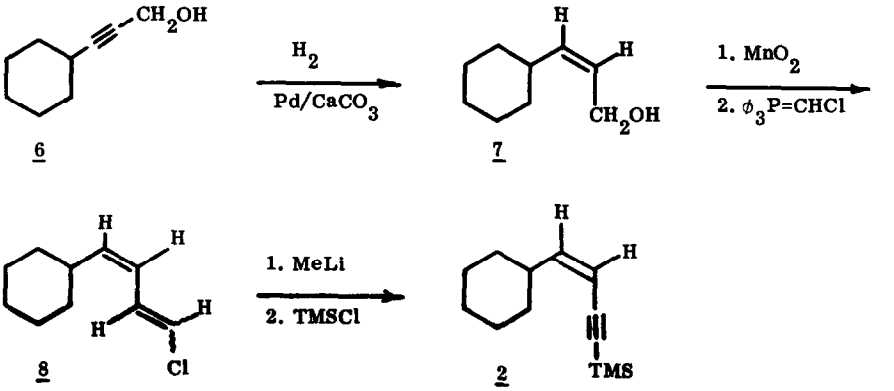
5

In the hope of obviating cumulene formation, the terminal trimethylsilyl (TMS) propargylic phosphonium salt 1b was prepared and converted to the phosphorane with 1 equivalent of n-BuLi. Subsequent condensation with three representative aldehydes afforded the expected protected enynes in good yield (Table I). However, this process was stereoselective for the trans, rather than the cis enyne unit. The trans-enyne 3 was characterized by a strong infrared absorption at 9.60 μ (C=C, out of plane bending) and by the coupling constant between the vicinal olefinic hydrogens (J_{AB} = 16.0 Hz.), observed in the n.m.r. spectrum. Quantitative removal of the TMS protecting group could be effected by treatment of a THF solution of silyl trans-enyne with an excess of $(n\text{-Bu})_4\overset{+}{N}F^{-}$ or $KF \cdot 2H_2O$ in dimethylformamide solution.

TABLE I

Reactant	Product	Yield (%)	trans/cis
		56	>10 1
		54	2.7 ·1
		80	>10 1

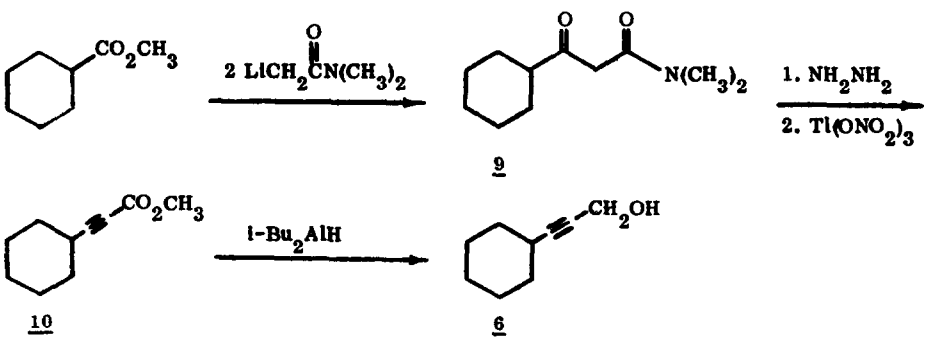
A third approach which led to a successful procedure for the synthesis of cis-enynes utilizes the well known conversion of chloroolefins to acetylenes as a key step (see Scheme I). The propargylic alcohol 6 was reduced with hydrogen using Pd-$CaCO_3$ as catalyst in benzene to afford the cis-allylic alcohol 7 (98% yield) Oxidation with activated manganese dioxide in methylene chloride gave the sensitive conjugated



SCHEME I

cis-aldehyde which was immediately treated with chloromethylenetriphenylphosphorane[5] in THF to afford the chlorodiene 8 as a mixture of Z and E isomers (83% overall). The chlorodiene 8 was next treated with methyllithium in THF at room temperature to effect dehydrohalogenation. After 12 hr., the reaction mixture was quenched with trimethylsilyl chloride, and the resulting silylated cis-enyne 2 (R = TMS) was isolated (70% yield). The cis-enyne 2 was characterized by strong infrared absorption at 13.10 μ and by a coupling constant between the vicinal olefinic hydrogens of 11.2 Hz observed in the n.m r spectrum

The requisite starting material, the propargylic alcohol 6, was prepared in good yield starting from methyl cyclohexane carboxylate as outlined below (Scheme II). The β-keto amide 9, obtained from the



SCHEME II

reaction of the reagent $LiCH_2\overset{O}{\overset{\|}{C}}NMe_2$ [6] (2 equiv. in THF) and methyl cyclohexane carboxylate, was treated sequentially with NH_2NH_2 (MeOH, 3 hr. reflux), then $Tl(ONO_2)_3$ [7] to afford the propriolic ester 10 (57% overall) Reduction of 10 with 3 equivalents of diisobutylaluminum hydride in hexane at 0° for 0.5 hr. proceeded smoothly and gave the propargylic alcohol 6 in greater than 80% yield. The applicability of this process to the synthesis of histrionicotoxin is under current investigation. [8]

The methods outlined above are further detailed by the following procedures for trans and cis-enyne synthesis.

A. trans-1-Cyclohexyl-2-trimethylsilylethynylethylene (3). To a cooled (-78°) suspension of phosphonium salt 1b (937 mg., 2.05 mmol.) in 10 ml. of THF was added 1.58 ml. of 1.29 M n-BuLi (2.05 mmol.). The solution was stirred at -40° for 0.5 hr. and cooled again to -78°. Cyclohexane carboxaldehyde (152 mg., 1.35 mmol.) was added, and the cooling bath was removed and replaced by ice water. After 1 hr., the product was isolated by extraction with pentane. Filtration through a short column of acidic alumina and purification of the product by preparative t.l.c. (pentane) afforded after evaporative distillation at 130° (bath) and 0.7 mm., 155 mg. (56%) of trans-enyne 3· i.r. $\lambda_{max.}^{film}$ 4.62, 6.91, 8.00, 9.60, and 11.80 μ, p.m.r. ($CDCl_3$) 6.02 (vinyl H, doublet of doublets, J_{AC} = 6.7 Hz., J_{AB} = 16.0 Hz.) and 5.25 p.p.m. (vinyl H, doublet, J_{AB} = 16.0 Hz.), molecular ion· calcd. for $C_{13}H_{22}Si$ 206.1490, found 206.1485.

B. cis-1-Cyclohexyl-2-trimethylsilylethynylethylene (2). A solution of cis-allylic alcohol 7 (177 mg., 1.27 mmol.), CH_2Cl_2 (20 ml.), and 2.0 g of activated MnO_2 was stirred at room temperature for 14 hr. The solution was filtered, and the solvent was removed on a rotary evaporator to afford 167 mg. (95%) of cis-aldehyde i r. λ_{max}^{film} 5 97, 8.67, 10 51, and 11.16 μ, p m r. ($CDCl_3$) 10 13 (CHO, doublet, J = 8.0 Hz.), 6.52 (vinylic H, doublet of doublets, J_{AB} = 11.0 Hz., J_{AC} = 10.5 Hz.) and 5.93 p.p.m. (vinylic H, doublet of doublets, J_{AB} = 11.0 Hz., J_{AD} = 8.0 Hz.).

To a cooled (-78°) suspension of chloromethyltriphenylphosphonium chloride (1.30 g., 3.78 mmol.) in 10 ml. of THF was added n-BuLi (3.70 mmol.) in hexane. After 0.75 hr. at -78°, the cis-aldehyde (167 mg., 1.21 mmol) was added in 1 ml of THF. The cooling bath was removed and replaced by ice water. After 3 hr. the product was isolated by pentane extraction. Filtration through a short column of acidic alumina and evaporative distillation (b.p. 100° (bath) and 0.7 mm.) afforded 173 mg. (83% overall) of the chlorodiene 8: i.r. $\lambda_{max.}^{film}$ 6.32, 10.71, 11.18, and 14.00 μ, p.m.r. ($CDCl_3$) 7.00-5.20 p.p.m. (vinylic H's, complex), molecular ion calcd. for $C_{10}H_{15}Cl$ 170.0863, found 170.0864.

To a cooled (0°) solution of chlorodiene 8 (60 mg., 0.35 mmol.) in 10 ml. of dry THF was added 3 ml of 1.6 M methyllithium. The cooling bath was removed, and the solution was stirred at room temperature for 12 hr. Addition of trimethylsilyl chloride (0.5 ml) and isolation of the product by pentane extraction afforded after evaporative distillation (130° (bath) at 0.7 mm.) 53 mg. (70%) of the desired cis-enyne 2·

ı r. $\lambda_{max.}^{film}$ 4.62, 8.00, 11.75, and 13.10 μ, p.m.r. ($CDCl_3$) 5.58 (vinylic H, doublet of doublets, J_{AB} = 11.2 Hz., J_{AC} = 8.1 Hz) and 5.15 p.p.m. (vinylic H, doublet, J_{AB} = 11.2 Hz.), molecular ion calcd. for $C_{13}H_{22}Si$ 206.1490, found 206.1485.

References

1. J. W. Daly, I. Karle, C. W. Meyers, T. Tokuyama, J. A. Waters, and B. Witkop, Proc. Nat. Acad. Sci., 68, 1870 (1971). See also B. Witkop, Experientia, 27, 1121 (1970).
2. For other methods of preparation of cis-enynes by non-selective reduction of 1,3-diynes, see G. Zweifel and N. Polston, J. Amer. Chem. Soc., 92, 4068 (1970), and B. G. Shakhovski, M. D. Stadnichuck, and A. A. Petrov, J. Gen. Chem. USSR, 34, 2646 (1960).
3. K. Eiter and H. Oediger, Ann., 682, 62 (1965). These workers noted that under their reaction conditions only conjugated aldehydes were suitable substrates for Wittig condensation with propargylidenetriphenylphosphorane.
4. For fluoride-ion promoted cleavage of TMS ethers, see E. J. Corey and B. B. Snider, J. Amer. Chem Soc., 94, 2549 (1972).
5. D. Seyferth, S. O. Gum, and T O. Read, J. Amer. Chem. Soc., 82, 1570 (1960).
6. D. Seebach and D. N Crouse, Chem. Ber., 101, 3113 (1968).
7. E. C. Taylor, R. L. Robey, and A. McKillop, Angew. Chem. Intern. Ed. Engl., 11, 48 (1972).

8. This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation.