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OXIDATIVE COUPLING OF ENONES AND DIENONES WITH BROMINE; A ROUTE TO HIGHLY CONJUGATED COMPOUNDS

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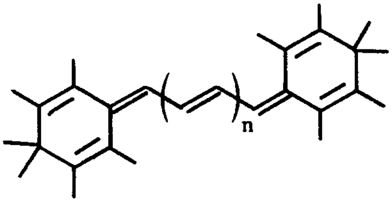
Hünig and Schilling[1] recently described an interesting series of polyenes with cross-conjugated end groups having the general structure 1 (n = 1,2,3). These compounds were synthesized by linking the two rings via the Wittig reaction. However attempts to synthesize the parent member of this series (n = 0) by this method failed.[1] We wish to describe here a simple, high yield synthesis of 1 (n = 0). The method, which is capable of extension to the synthesis of a variety of highly conjugated compounds, begins with the novel oxidative coupling of an enolate with bromine.



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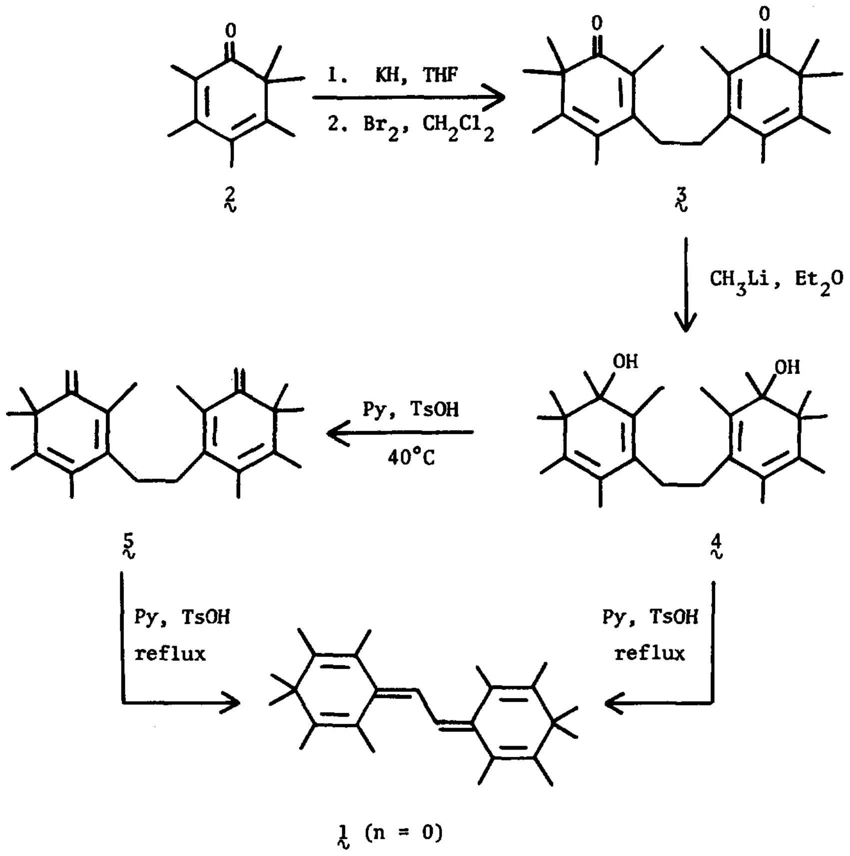
Hexamethyl-2,4-cyclohexadienone (2; 30 mmol)[2] was treated with a 10% excess of potassium hydride in THF at room temperature for 30 min, resulting in complete conversion to the enolate.[3] Treatment of the enolate at 0°C with 15 mmol of bromine in methylene chloride for 2 min, followed by dilution with hexanes and workup gave a 90% yield of the oxidative coupling product 3 as pale yellow crystals, mp 139-140°C (ethyl acetate).[4,5] Treatment of 3 with methyllithium (3.4 equiv. in ether, 30 min, 25°C) gave after workup (NH_4Cl, H_2O) a quantitative yield of the bis-tertiary alcohol 4 as a white solid, mp 158-160°C (hexane - ethyl acetate).[5]

Alcohol 4 could be converted to either the 1,2- or 1,4-dehydration product, depending on reaction conditions. A solution of 4 (1.0 g, 2.6 mmol) in 10 ml of pyridine to which a few crystals of p-toluenesulfonic acid monohydrate were added was kept at 40°C for 10 min, then diluted with pentane, washed with water and dried. Evaporation of the solvent gave a 95% yield of 5[5] as pale yellow needles (methanol), mp 83-84°C. When the dehydration was carried out at reflux



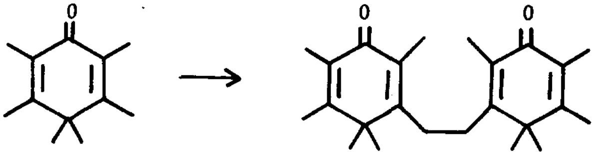
(all other conditions the same) the product was the desired 1, obtained as a pale yellow solid, mp 130-131°C (ethyl acetate) in 90% yield.[4,5]

The structure of 1 (n = 0) was clear from its spectral properties. The proton NMR spectrum of 1 (n = 0) showed peaks at δ1.07 (s, 12H), 1.77 (br s, 12H), 1.90 (br s, 6H), 2.10 (br s, 6H) and 6.23 (s, 2H). The peaks at δ1.90 and 2.10 are due to the two different sets of methyls adjacent to the butadiene moiety which joins the two rings.[6] In contrast, the proton NMR spectrum of 5 had peaks at δ1.10 (s, 12H), 1.75 (q, 6H, *J* = 0.8Hz), 1.85 (q, 6H, *J* = 0.8Hz), 1.98 (s, 6H), 2.33 (s, 4H), 4.98 (s, 4H). The peaks at δ1.75 and 1.85 are due to adjacent, homoallylically coupled vinyl methyls, whereas the peak at δ1.98 is due to the isolated vinyl methyls (apparently not appreciably coupled to the adjacent methylenes).

The uv spectra of 1 (n = 0) and 5 are also distinctive. In cyclohexane 5 has a broad maximum at 315 nm (ε11,300)[7] whereas 1 (n = 0) shows a series of shoulders and maxima at 382 nm (ε32,700), 365 (38,300), 346 (28,000) typical for the series 1 (n = 1-3).[1] The longest wavelength bands in 1 (n = 0-3) form a steady progression:

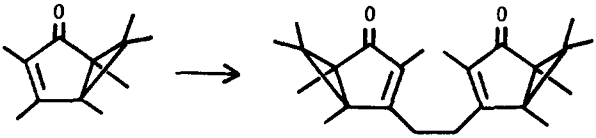
1, n=	CH_2Cl_2 λ_{max} (nm)	Δ	log ε
3	472		4.96
		23	
2	449		4.96
		28	
1 (E isomer)	421		4.82
		39	
0	382		4.51

We have explored briefly oxidative couplings similar to that used to prepare 3 from 2. Treatment of 6[8], 7[9] and 8[10] with KH in THF, followed by bromine, gave the corresponding coupling products 9, 10 and 11 in excellent yield.



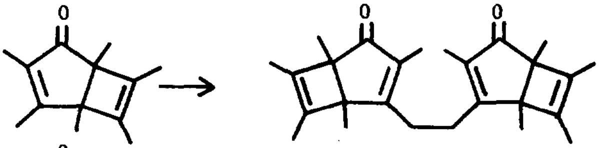
6 9

mp 239-240°C (96%)[4,5]



7 10

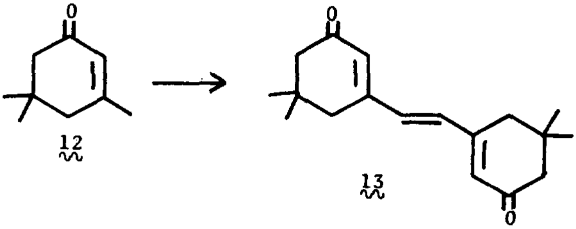
mp 136-138°C (70%)[4,5]



8 11

mp 195-198°C (70%)[4,5]

Under some circumstances the initial coupling product may be further oxidized. For example we isolated 13[4,5] (10% yield, not optimized) from analogous coupling of isophorone.



12 13

We do not yet know what the mechanism of these coupling reactions is. They may simply involve formation of the monobromo derivative of the enone which then undergoes displacement by enolate, or they may involve one of the many other known oxidative coupling mechanisms.[11,12]

We are not unmindful of the interesting chemistry which may ensue from the protonation, irradiation and other chemistry of the unique coupling products accessible via the routes described here, and are actively extending these studies.

Acknowledgement. We are indebted to the National Institutes of Health (GM 15997) for support of this research.

References and Notes

1. S. Hünig and P. Schilling, *Liebig's Ann. Chem.*, 1103 (1976).
2. H. Hart, R.M. Lange and P.M. Collins, *Organic Syntheses Coll. Vol. 5*, 598 (1973).
3. The enolate is formed from proton loss at the C3 (not C5) methyl; see H. Hart, G.M. Love and I.C. Wang, *Tetrahedron Lett.*, 1377 (1973).
4. The compound gave a correct elemental analysis.
5. Spectral properties (ir, nmr, uv, mass) were in accord with the assigned structure; details will be presented in a full account.
6. The methyls adjacent to the gem-dimethyl groups, which should also be differentiated into two types, appeared as a broadened singlet at δ1.77.
7. Calculated 318 nm via Woodward's Rules; compare with 303 nm observed for 5-methylene-1,3-cyclohexadiene by W.J. Bailey and R.A. Baylouny, *J. Org. Chem.*, **27**, 3476 (1962).
8. H. Hart and D.W. Swatton, *J. Am. Chem. Soc.*, **89**, 1874 (1967).
9. H. Hart, P.M. Collins and A.J. Waring, *J. Am. Chem. Soc.*, **88**, 1005 (1966).
10. H. Hart and M. Nitta, *Tetrahedron Lett.*, 2109 (1974).
11. For a review, see P.D. McDonald and G.A. Hamilton in "Oxidation in Organic Chemistry, Part B," edited by W.S. Trahanovsky, Academic Press, Inc., 1973, pp. 97-134.
12. Similar $CuCl_2$ catalyzed couplings of ketone enolates have recently been described (Y. Ito, T. Konoike, T. Harada and T. Saegusa, *J. Am. Chem. Soc.*, **99**, 1487 (1977)). We have applied this method to the oxidative coupling of **2** and find the yield comparable to that obtained with bromine.