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PREPARATION OF β-METHYLATED α,β-UNSATURATED KETONES VIA DICHLOROCARBENE ADDUCTS OF ENOL ETHERS. SYNTHESIS OF dl-MUSCONE FROM CYCLOTETRADECANONE

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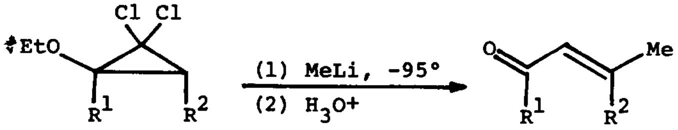
Although there have been several methods for one-carbon ring expansion by use of dichlorocyclopropanes,[1] the known procedures are synthetically not satisfactory as they require several further steps for the introduction of a useful functional group.[2] We wish to disclose in this communication a new one-carbon homologation method to prepare β-methylsubstituted α,β-unsaturated ketone in a single procedure.[3]



I II

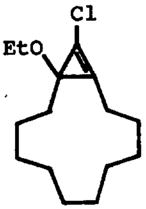
a: $R^1,R^2 = -(CH_2)_{10}-$ b: $R^1,R^2 = -(CH_2)_{12}-$

c: $R^1 = H$, $R^2 = n\text{-}C_5H_9$ d: $R^1 = n\text{-}C_4H_9$, $R^2 = n\text{-}C_3H_7$

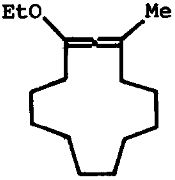
Dichlorocarbene addition to 1-ethoxycyclododecene gave a dichloroethoxycyclopropane Ia[4] in 71% yield. The cyclopropane was subsequently treated with methyllithium (two mol ratio) at -95° in tetrahydrofuran (THF). The reaction mixture was warmed up to room temperature and acidified with 2% sulphuric acid. Preparative tlc gave 3-methyl-2-cyclotridecenone (IIa, 47% yield, E/Z = 3:1).[4] The yield of IIa was improved by adding N,N,N',N'-tetramethylethylenediamine (two mol ratio) up to 58%. Further improvement (75%) with the same

E/Z ratio was attained by the reaction in THF-hexamethylphosphoric triamide (HMPA) (5:1). Quantitative hydrogenation of IIa was achieved with Raney Ni at an atmospheric pressure of hydrogen.

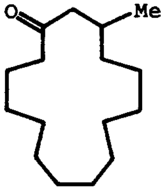
The mechanism of the reaction can be explained in terms of the elimination of hydrochloric acid[5] by one equivalent of methyllithium and the subsequent addition[6] of another equivalent of methyllithium to induce the ring-enlargement of the resulting carbenoid which gives an ethoxy allene. Hydrolysis[7] of the allene affords an E/Z mixture of β-methyl enone. Actually the unstable intermediates, chlorocyclopropene III[8] and ethoxy allene IV,[9] were identified spectrometrically, and the treatment of III with equimolar methyllithium, followed by the acidic work-up, afforded IIa.



III



IV



V

The sequence was applied to dl-muscone synthesis.[10] 1-Ethoxycyclotetradecene[11] was subjected to dichlorocarbene addition to give an adduct Ib (63%),[4] which was then treated with two molar methyllithium in THF-HMPA (5:1). 3-Methyl-2-cyclopentadecenone (IIb)[4] obtained in 69% yield was subjected to hydrogenation which gave dl-muscone (V) in a quantitative yield. R_f value on tlc and all the spectral data were identical with the authentic sample.[10a]

The reaction sequence was extended to open chain enol ethers with less satisfactory results. When the procedure was applied to Ic, metal-halogen exchange reaction predominated over elimination to give trans-2-octenal (49%)[12] and cis-3-nonen-2-one (14%).[13] Reaction without HMPA resulted in the increase of the cis-nonenone (27%) at the expense of trans-2-octenal (37%). Similar reaction of Id in the presence of HMPA afforded cis-6-decen-5-one (26%) along with IId (25%), while in the absence of HMPA the product was only IId (42%, E/Z = 3:2).[14]

A typical experiment is exemplified by the preparation of IIa. Dichlorocarbene addition to 1-ethoxycyclododecene was performed as described earlier,[15] affording Ia (71%).[4] Mp(n-hexane) 51.0-51.5°; ir: 1058, 856, 844 cm^{-1}; ms: m/e 292 (M^+), 256 (M^+-HCl). The adduct Ia (292 mg, 1 mmol) was dissolved in a mixture of THF (4 ml) and HMPA (0.8 ml), and cooled at -95°. To this solution 2 mmol of methyllithium in ether was added under a nitrogen atmosphere, and the mixture was stirred for an hour at -95°. The colour turned pale brown. Then the reaction mixture was stirred for an additional hour at room temperature and aqueous sulphuric acid (2%, 6 ml) was added. After stirring overnight the organic phase was separated and the aqueous one was extracted with dichloromethane. The combined extracts were washed with saturated sodium chloride, dried over sodium sulphate and concentrated *in vacuo*. Preparative tlc of the residue (silica gel, benzene/n-hexane 4:1, R_f 0.5) gave the desired enone IIa (155 mg, 75%); bp 121°/0.12 mm; ir: 1681, 1609 cm^{-1}; ms: m/e 208 (M^+).

1. R. Barlet and Y. Vo Quang, *Bull. Soc. Chim. Fr.*, 3729 (1969); J. T. Grouves and K. W. Ma, *Tetrahedron Lett.*, 909 (1974); D. Seebach and H. Neumann, *Chem. Ber.*, **107**, 847 (1974).
2. C. W. Jefford, U. Burger, and F. Delay, *Helv. Chim. Acta*, **56**, 1083 (1973); W. E. Parham, R. W. Soeder, J. R. Throckmorton, K. Kuncl, and R. M. Dodson, *J. Amer. Chem. Soc.*, **87**, 321 (1965); A. J. Birch, J. M. H. Graves, and F. Stansfield, *Proc. Chem. Soc.*, **282** (1962); G. M. Iskander and F. Stansfield, *J. Chem. Soc.*, 1390 (1965).
3. L. Skattebøl, *J. Org. Chem.*, **31**, 1554 (1966); M. Santelli, *C. R. Acad. Sci. Paris Ser. C*, **261**, 3150 (1965).
4. The new compounds gave satisfactory elemental analyses and spectral data.
5. Similar reaction mode of butyllithium is observed in K. G. Taylor, W. E. Hobbs, M. S. Clark, and J. Chaney, *J. Org. Chem.*, **37**, 2436 (1972). In our experiment n-butyllithium (two equivalents) reacted with Ia (-40°), giving 3-butyl-2-cyclotridecenone in only a 29% yield. Supposedly association of the lithium reagent influences the reactivity.

6. D. E. Applequist and E. G. Saurborn, *J. Org. Chem.*, **37**, 1676 (1972); R. M. Magid, T. C. Clarke and C. D. Duncan, *ibid.*, **36**, 1320 (1971).

7. E. J. Corey and S. Terashima, *Tetrahedron Lett.*, 1815 (1972); I. D. Jonge and W. Drenth, *Rec. Trav. Chim. Pays-Bas*, **92**, 420 (1973).

8. Use of one molar methyllithium, quenching at low temperature and basic work-up gave III, ms: m/e 256 (M^+), 258 ($M^+ + 2$); ir: no characteristic absorptions except methylenes and methyl.

9. Use of two molar methyllithium and a mild work-up (nonacidic, no heat) gave an oil which showed ms: m/e 236 (M^+); ir: 1950 cm^{-1}.

10. dl-Muscone synthesis: (a) H. Nozaki, H. Yamamoto, and T. Mori, *Can. J. Chem.* **47**, 1107 (1969). (b) B. D. Mookherjee, R. W. Trenkle, and R. R. Patel, *J. Org. Chem.*, **36**, 3266 (1971). (c) R. Baker, B. N. Blackett, and R. C. Cookson, *J. Chem. Soc. Chem. Commun.*, 802 (1972). (d) G. Ohloff, J. Becker and K. H. Schulte-Elte, *Helv. Chim. Acta*, **50**, 705 (1967). (e) A. Eschenmoser, D. Felix, and G. Ohloff, *ibid.*, **50**, 708 (1967). (f) D. Felix, J. Schreiber, G. Ohloff, and A. Eschenmoser, *ibid.*, **54**, 2896 (1971).

11. The compound was prepared as follows: 2-hydroxycyclotetradecanone [T. Mori, T. Nakahara, and H. Nozaki, *Can. J. Chem.*, **47**, 3266 (1969)] → (zinc powder, hydrochloric acid, acetic acid, 71%) → cyclotetradecanone → (ethyl orthoformate, p-toluenesulfonic acid, 80%) → 1-ethoxycyclotetradecene.

12. E. J. Corey, B. W. Erickson, and R. Noyori, *J. Amer. Chem. Soc.*, **93**, 1724 (1971).

13. The methine proton on the ethoxy substituted carbon was eliminated regioselectively, leading to this product.

14. The reason of this solvent effect is not clear. Polymethylene chain which always solvates the reaction site intramolecularly probably facilitates the elimination of hydrochloric acid in THF-HMPA media, while the solvent system favours lithium-chlorine exchange in acyclic system.

15. G. C. Joshi, N. Singh, and L. M. Pande, *Tetrahedron Lett.*, 1461 (1972); T. Hiyama, M. Tsukanaka, and H. Nozaki, *J. Amer. Chem. Soc.*, in press.