Novel Synthesis of α-Methylene-γ-lactones

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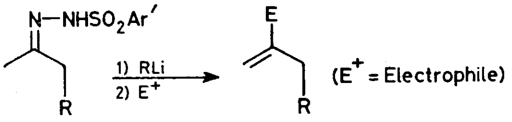
Summary α-Methylene-γ-lactones have been prepared from acetone 2,4,6-tri-isopropylphenylsulphonydrazone, an aliphatic ketone or aldehyde, and carbon dioxide in a 'one pot' good yield reaction.

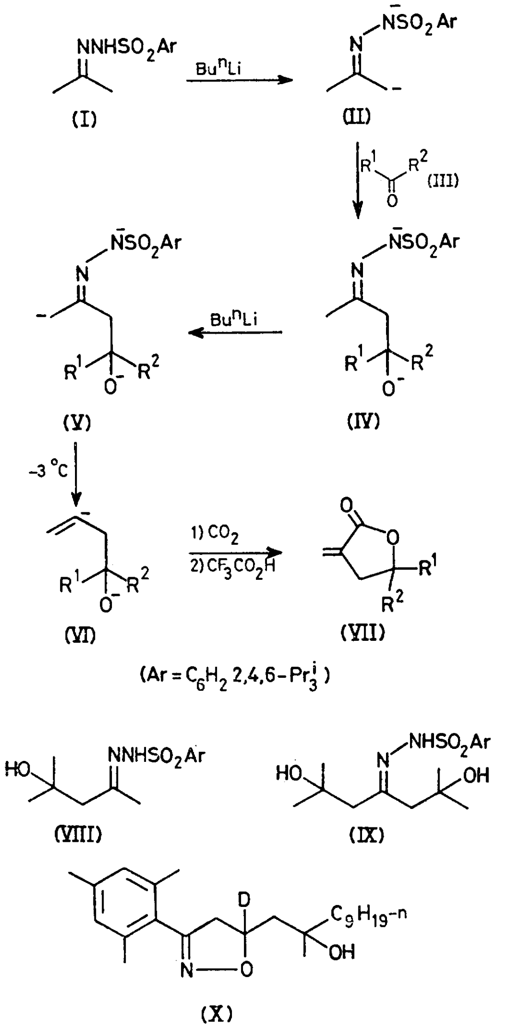
ON account of the cytotoxicity of numerous sesquiterpene lactones, several syntheses of α-methylene-γ-lactones have been developed. Outstanding total syntheses of vernolepin,[1] vernomenin,[1] *etc.* rely on α-methylenylation of preformed γ-lactones[2] or the oxidation of α-methyl-γ-lactones.[3] Alternative procedures exist,[4] some of which are synthetically less versatile on account of low yields and/or multistage reactions. Herein is described the preparation of α-methylene-γ-lactones from two ketones and carbon dioxide or a β-hydroxyketone and carbon dioxide.



Scheme 1

Ketone arylsulphonylhydrazones are useful intermediates in the generation of alkene derivatives by the Shapiro reaction (Scheme 1).[5] The recently described preparation of homoallylic alcohols from ketones[6] prompts us to describe the application of acetone 2,4,6-tri-isopropylphenylsulphonylhydrazone (I) in the preparation of α-methylene-γ-lactones (VII). Typically, n-butyl-lithium (2.2 equiv.), the ketone or aldehyde (III) (1·2 equiv.), and n-butyl-lithium (1·2 equiv.) were added in sequence to acetone 2,4,6-tri-isopropylphenylsulphonylhydrazone (I)† (1 mmol) in 1,2-dimethoxyethane (DME) at −70 °C. After warming to −3 °C and recooling to −70 °C the mixture was quenched with carbon dioxide. Work up, acidification, and chromatography gave the α-methylene-γ-lactones (VII) (Scheme 2), in the following yields: $R^1 = Me$, $R^2 =$ hexyl, 61; $R^1 = Me$, $R^2 = Bu^t$, 66; $R^1 = R^2 = Me$, 57; $R^1 = Me$, $R^2 = Et$, 61; $R^1 = H$, $R^2 = Pr^n$, 62; $R^1 = H$, $R^2 = Et$, 45; R^1, $R^2 = -[CH_2]_5-$, 40%. Alternatively, the lactone (VII, $R^1 = R^2 = Me$) (74%) was prepared from hydrazone (VIII),‡ n-butyl-lithium, and carbon dioxide. The yields of the lactones (VII) are good and the reaction is carried out in one vessel, with each step self-indicating [(II) golden, (IV) colourless, (V) orange-yellow, (VI) pale yellow].

Intermediacy of the anion (IV, $R^1 = R^2 = Me$) has precedent[6] and was consistent with the fact that quenching with water gave the hydrazone (VIII)§ (95%). Addition of acetone and acetic acid in sequence to the trianion (V, $R^1 = R^2 = Me$) gave the hydrazone (IX) (31%). The stability of the vinyl anion (VI, $R^1 = Me$, $R^2 =$ nonyl) in DME at −3 °C was confirmed by quenching with D_2O and trapping of the olefin as the isoxazoline (X) with 2,4,6-trimethylbenzonitrile oxide (85%, *ca.* 100% D incorporation). The regioselective third deprotonation, (IV) to (V), has precedent.[6]



Scheme 2

Since both ketones (or aldehydes) and β-hydroxyketones are readily available versatile units, this reaction should find application in natural product synthesis.

(*Received*, *7th September* 1978; *Com.* 981.)

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† From acetone and 2,4,6-tri-isopropylphenylsulphonylhydrazine (92%). Structural assignments for all new compounds and all lactones were consistent with spectral data and microanalyses.

‡ Obtained (93%) as a mixture of isomers from 4-hydroxy-4-methylpentan-2-one and 2,4,6-tri-isopropylphenylsulphonylhydrazine.

§ Obtained as a single isomer, most plausibly *syn* (n.m.r.).

[1] S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Medicin. Chem.*, 1971, **14**, 1147.

[2] R. D. Clark and C. H. Heathcock, *Tetrahedron Letters*, 1974, **1713**; P. A. Grieco, Y. Ohfune, and G. Majetich, *J. Amer. Chem. Soc.*, 1977, **99**, **7393**; P. A. Grieco, M. Nishizawa, T. Oguri, S. D. Burke, and N. Marinovic, *ibid.*, p. 5773; S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *ibid.*, p. 6066; G. R. Kieczykowski and R. H. Schlessinger, *ibid.*, 1978, **100**, 1938; M. Isobe, H. Iio, T. Kawai, and T. Goto, *ibid.*, p. 1940; P. A. Grieco, J. A. Noguez, and Y. Masaki, *J. Org. Chem.*, 1977, **42**, 495.

[3] P. A. Grieco and M. Nishizawa, *J. Org. Chem.*, 1977, **42**, 1717; A. E. Greene, J-C. Muller, and G. Ourisson, *ibid.*, 1974, **39**, 186.

[4] P. A. Grieco, *Synthesis*, 1975, 67; N. Petragnani and H. M. C. Ferraz, *ibid.*, 1978, 476; A. Hassner, H. W. Pinnick, and J. M. Ansell, *J. Org. Chem.*, 1978, **43**, 1774; S. Torii, T. Okamoto, and T. Oida, *ibid.*, p. 2294; R. M. Carlson and A. R. Oyler, *ibid.*, 1976, **41**, 4065; J. R. Norton, K. E. Shenton, and J. Schwartz, *Tetrahedron Letters*, 1975, 51; R. M. Carlson, *ibid.*, 1978, **111**; T. F. Murray, V. Varma, and J. R. Norton, J.C.S. *Chem. Comm.*, 1976, 907; M. F. Semmelhack and E. S. C. Wu, *J. Amer. Chem. Soc.*, 1976, **98**, 3384; C. P. Casey and W. R. Brunsvold, *J. Organometallic Chem.*, 1975, **102**, 175.

[5] A. R. Chamberlin, J. E. Stemke, and F. T. Bond, *J. Org. Chem.*, 1978, **43**, 147, and references therein.

[6] M. P. Lipton and R. H. Shapiro, *J. Org. Chem.*, 1978, **43**, 1409.