Elimination–Addition. Part XXII.[1] Addition of Enolates to Allenic Sulphonium Salts; a New General Furan Synthesis †

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Furans are produced by reactions of β-keto-esters, β-diketones, and β-keto-sulphones with allenic sulphonium salts. Procedures are simple and yields are high. 2,3,4-Trisubstituted furans are typically produced by this method, which thus complements synthesis of 2,3,5-trisubstituted furans from prop-2-ynyl halides and β-keto-esters. Mechanistic aspects of the synthesis are briefly discussed.

A REMARKABLY limited number of general syntheses of furans are available;[2] these commonly involve cyclisation of 1,4-diketones either directly or *via* such precursive reactions as alkylation of β-keto-esters with α-halogeno-ketones (Feist) or the addition of enolates to nitroalkenes. We now report a new, simple, general synthesis of furans in which the products typically have a vacant 5-position, an alkyl group at position 4 and a carbanion-stabilising group at position 3.

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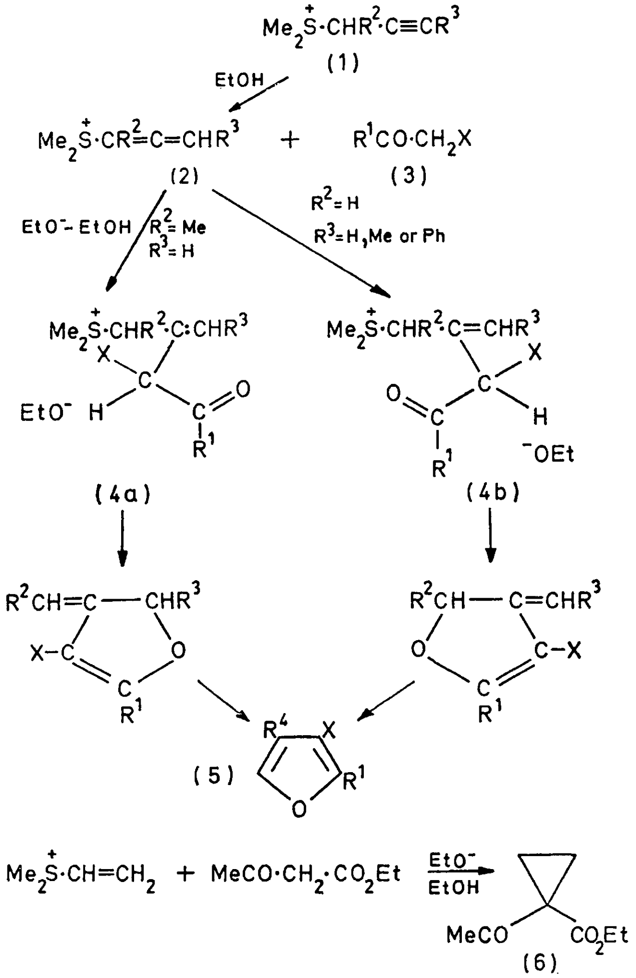
† Preliminary communication, J. W. Batty, P. D. Howes, and C. J. M. Stirling, *Chem. Comm.*, 1971, 534.

[1] Part XXI, J. W. Batty, P. D. Howes, and C. J. M. Stirling, preceding paper.

[2] P. Bosshard and C. H. Eugster, *Adv. Heterocyclic Chem.*, 1966, **7**, 378.

The basis of the method is addition of a stabilised α-carbonyl carbanion to the electrophilic allene system produced by prototropic isomerisation of a prop-2-ynyl-sulphonium salt [1,3] (Scheme). The presumed intermediates are not isolated and furans are obtained directly from reaction mixtures.



Br^- counter-ion throughout

SCHEME

This synthesis depends upon three special features of the reactivity of allenic sulphonium salts: (i) the sulphonium group renders the 1,2-carbon–carbon double bond of the allene extremely susceptible to nucleophilic addition; (ii) a carbon–carbon double bond remains after the addition of the first nucleophilic species, and (iii) the sulphonium group is itself readily displaced by nucleophilic attack at the adjacent carbon atom.

Addition of enolate ions to electrophilic alkenes and alkynes is a familiar and widely used reaction,[4] but examples of reactions with alkynes in which the acceptor bears a *displaceable* polarising substituent have not been previously investigated.

Operation of the synthesis is simple; a primary or secondary prop-2-ynyl halide, most simply obtained by addition of an acetylenic organometallic compound to an aldehyde and treatment of the resulting alcohol with phosphorous tribromide, is treated with *e.g.* dimethyl sulphide in acetonitrile. The resulting sulphonium salt is subsequently treated with the ketone (3) in ethanolic sodium ethoxide, giving the furan directly.

The scope of the reaction is indicated in the Table. In systems so far investigated, group X in the ketone (3) may be acyl (β-diketone), alkoxycarbonyl (β-ketoester), or arylsulphonyl. In reactions with diethyl malonate, alkyl transfer from the sulphonium group is the preferred reaction; [5] this type of reaction will be discussed in a later paper. When the unsymmetrical benzoylacetone was used, roughly equimolecular amounts of the two possible isomers were obtained (Table).

A study of structural variation in the sulphonium salt reveals that cyclisation of the initial adduct (4b) may occur by an attack on C-1 by the carbonyl oxygen atom when C-1 is unsubstituted and there is a substituent at C-3. Attack at C-3 (reaction 2 in the Table) occurs when C-1 of the salt bears a substituent. Thus reaction of the salt (2; $R^2 = Me$, $R^3 = H$) with ethyl acetoacetate gave the furan (5; $R^1 = Me$, $X = CO_2Et$, $R^4 = Et$) by intramolecular S_N' displacement of the sulphonium group (4a). Aromatisation of the intermediates formed from (4a) and (4b) occurs extremely readily under the basic conditions used and is undoubtedly promoted by the presence of a carbanion-stabilising group. No further evidence on the mechanism of this process is available at present.

An aspect of this new synthesis that makes for simplicity is that isolation of the sulphonium salt is not required. In one experiment, successive addition of prop-2-ynyl bromide, acetylacetone, and ethanolic sodium ethoxide to a solution of dimethyl sulphide in acetonitrile gave the furan (5; $R^1 = Me$, $X = Ac$, $R^4 = Me$) in 71% yield.

A fruitless attempt was made to isolate the primary adduct (4) from the reaction of the sulphonium salt (1; $R^2 = R^3 = H$) and ethyl acetoacetate. When one tenth of the stoicheiometric amount of base was used, the yield of furan was simply reduced to 10%. This observation indicates that cyclisation of the intermediate (4) is rapid by comparison with its formation.

The new synthesis makes an interesting and valuable complement to a recently described furan synthesis [6] in which a β-keto-ester reacts diredtly under basic conditions with a prop-2-ynyl halide. This reaction leads to 2,3,5-trisubstituted furans.

The sulphonium salt synthesis is not applicable to dihydrofurans under the mild conditions used. Addition of ethyl acetoacetate to dimethyl(vinyl)sulphonium

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[3] G. D. Appleyard and C. J. M. Stirling, *J. Chem. Soc.* (*C*), 1969, 1904.

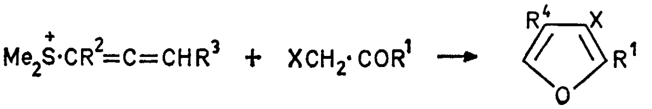
[4] E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, 1959, **10**, 179.

[5] J. W. Batty, P. D. Howes, and C. J. M. Stirling, Abstracts Fourth International Symposium on Organic Sulphur, Venice, 1970.

[6] K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm.*, 1962, **295**, 627.

TABLE

Furan syntheses



(2) (3) (5)

	(2)	(3)	(5)	Yield (%)
1.	$R^2 = H$ $R^3 = H$	$X = CO_2Et$ $R^1 = Me$	$R^1 = Me$ $X = CO_2Et$ $R^4 = Me$	86 *
2.	$R^2 = Me$ $R^3 = H$	$X = CO_2Et$ $R^1 = Me$	$R^1 = Me$ $X = CO_2Et$ $R^4 = Et$	49
3.	$R^2 = H$ $R^3 = Ph$	$X = CO_2Et$ $R^1 = Me$	$R^1 = Me$ $X = CO_2Et$ $R^4 = PhCH_2$	63
4.	$R^2 = H$ $R^3 = H$	$X = Ac$ $R^1 = Me$	$R^1 = Me$ $X = Ac$ $R^4 = Me$	89 †
5.	$R^2 = H$ $R^3 = H$	$X = Bz$ $R^1 = Ph$	$R^1 = Ph$ $X = Bz$ $R^4 = Me$	72
6.	$R^2 = H$ $R^3 = H$	$X = p$-MeC_6H_4-SO_2 $R^1 = Me$	$R^1 = Me$ $X = p$-MeC_6H_4-SO_2 $R^4 = Me$	78
7.	$R^2 = H$ $R^3 = H$	$X = Bz$ $R^1 = Me$	$R^1 = Ph$ $X = Ac$ $R^4 = Me$ $R^1 = Me$ $X = Bz$ $R^4 = Me$	83

* Alkaline hydrolysis gave 2,4-dimethyl-3-furoic acid, m.p. and mixed m.p. 120° [lit., 122° (E. R. Alexander and S. Baldwin, *J. Amer. Chem. Soc.*, **1951**, **73**, 355)]. † One-pot reaction, yield 71%.

Properties of the furans (5)

^1H N.m.r. data (τ values)

1. 2·7 (1H, s), 5·5 (2H, q, *J* 7 Hz), 7·35 (3H, s), 7·75 (3H, s), 8·6 (3H, t, *J* 7 Hz)
2. 2·7 (1H, s), 6·55 (2H, q, *J* 7 Hz), 7·4 (5H, m), 8·6 (6H, m)
3. 2·5 (5H, m), 2·95 (1H, s), 5·6 (2H, q, *J* 7 Hz), 5·95 (2H, s), 7·4 (3H, s), 8·7 (3H, t, *J* 7 Hz)
4. 2·7 (1H, s), 7·4 (3H, s), 7·55 (3H, s), 7·75 (3H, s)
5. 1·75—2·6 (11H, m), 7·95 (3H, s)
6. 2·0—2·6 (4H, q), 2·85 (1H, s), 7·5 (3H, s), 7·7 (3H, s), 8·1 (3H, s)
7. 1·8—2·4 (5H, m), 2·65 (1H), 7·8 (3H, m), 8·0 (3H, m)

	Refr. index	B.p. (°C/Torr)	Found (%)		Reqd. (%)
1.	n_D^{16} 1·4704	85/15	(Lit.,* n_D^{20} 1·4680)		
2.	n_D^{17} 1·4674	91/12	C, 66·1; H, 7·85	$C_{10}H_{11}O_3$	C, 65·9; H, 7·7
3.	n_D^{18} 1·5364	112/0·15	C, 73·4; H, 6·6	$C_{15}H_{16}O_3$	C, 73·7; H, 6·6
4.	n_D^{20} 1·4935	83/11	C, 69·4; H, 7·3	$C_8H_{10}O_2$	C, 69·5; H, 7·3
5.	n_D^{22} 1·6247	142/0·35	C, 82·1; H, 5·4	$C_{18}H_{14}O_2$	C, 82·4; H, 5·4
6.		(M.p. 109°)	C, 62·6; H, 5·8	$C_{13}H_{14}O_3S$	C, 62·4; H, 5·6
7.		83—90/0·25	C, 78·0; H, 6·15	$C_{13}H_{12}O_2$	C, 78·0; H, 6·0

* See footnote to first section of Table

bromide, generated[7] *in situ* from dimethyl-(2-phenoxyethyl)sulphonium bromide, gave ethyl 1-acetylcyclopropanecarboxylate (6). 1,3-Cyclisation is preferred over 1,5-cyclisation in accordance with conjugative control of three-membered ring formation.[8] Formation of cyclopropanes by addition of carbanions to αβ-unsaturated sulphonium salts has previously been described by Gosselck and his collaborators.[9] Cyclopropyl ketones require rather severe conditions for conversion into dihydrofurans.[10] Dihydrofurans, however, can be obtained by a mechanistically closely related process. Addition of hydroxy-ketones to vinylphosphonium salts gives compounds of this type in variable yield.[11]

An attempt to widen the scope of the synthesis to addition of simple ketones was not successful. Treatment of the unsubstituted sulphonium salt with dibenzyl ketone under the conditions used for *e.g.* ethyl acetoacetate reactions gave no furan, and ketone was recovered in high yield. Further work to enlarge the scope of the synthesis by the use of ketones bearing β-substituents capable of carbanion stabilisation and the use of β-substituted aldehydes to give 3,4-disubstituted furans is in progress.

EXPERIMENTAL

Dimethyl(prop-2-ynyl)sulphonium bromide was prepared as previously described.[3]

Dimethyl-(3-*phenylprop-*2-*ynyl*)*sulphonium Bromide*.—3-Phenylprop-2-ynyl bromide (20 mmol) in acetonitrile (2 ml) was treated with dimethyl sulphide (20 mmol). The mixture was stirred in a darkened flask for 1 h and the white crystals produced were washed with anhydrous ether and dried to yield the *sulphonium salt* (80%) m.p. 119° [raised to 127° (from ethanol)] (Found: C, 51·6; H, 5·1. $C_{11}H_{13}BrS$ requires C, 51·4; H, 5·1%), τ (D_2O) 2·0 (5H, m), 5·15 (2H, s), and 6·80 (6H, s).

Dimethyl-(1-*methylprop-*2-*ynyl*)*sulphonium Bromide*.—3-Bromobut-1-yne[12] (60 mmol) in acetonitrile (10 ml) was treated with dimethyl sulphide (60 mmol) in acetonitrile (10 ml). After 48 h addition of a large volume of anhydrous ether gave an oil which was separated and pumped free of solvent. The crude salt, which did not crystallise, was used without further purification.

Typical Procedure for Furan Synthesis.—Dimethyl(prop-2-ynyl)sulphonium bromide (10 mmol) in ethanol (110 ml) was treated with acetylacetone (20 mmol) and sodium ethoxide (10 mmol) in ethanol (100 ml). (Double quantity of nucleophile was only used in the first instance when it was thought that 2 mol. equiv. of nucleophile might be necessary. When this was found not to be the case equimolar amounts of nucleophile and sulphonium salt were used. Thus a *typical* procedure would use 10 mmol of acetylacetone and not 20 mmol as stated.) The mixture was boiled under reflux for 4 h, ethanol was distilled off, and ether was added to the residue. Filtration and distillation of the filtrate gave 3-*acetyl-*2,4-*dimethylfuran* (89%), b.p. 82—85° at 11 Torr.

Unchanged acetylacetone (92%) was detected by g.l.c.

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[7] J. Crosby and C. J. M. Stirling, *J. Chem. Soc.* (*B*), 1970, 671.

[8] A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc.* (*B*), 1968, 67.

[9] G. Schmidt and J. Gosselck, *Tetrahedron Letters*, **1969**, 2623.

[10] E. E. Schweizer and C. M. Kopay, *Chem. Comm.*, **1970**, 677.

[11] E. E. Schweizer and J. G. Liehr, *J. Org. Chem.*, **1968**, **33**, 583.

[12] M. Gaudemar, *Ann. Chim.* (*France*), **1956**, **1**, 161.

analysis (SE30 column at 150°) in the solvent removed from the reaction mixture. During the reaction a slow stream of nitrogen was passed through the mixture and then into methanolic methyl iodide. Trimethylsulphonium iodide (15%) was obtained, m.p. and mixed m.p. 202°.

A ' one-pot ' reaction was carried out by addition of 3-bromopropyne (10 mmol) to dimethyl sulphide (10 mmol) in acetonitrile (10 ml). After 10 h, acetylacetone (10 mmol) and sodium ethoxide (10 mmol), in ethanol (25 ml), were added and the mixture was boiled under reflux for 3 h. Work-up as before gave 3-acetyl-2,4-dimethylfuran (71%).

Reaction of Dimethyl-(2-phenoxyethyl)sulphonium Iodide with Ethyl Acetoacetate.—The sulphonium salt (10 mmol) in ethanol (100 ml) was treated with ethyl acetoacetate (10 mmol) and sodium ethoxide (10 mmol) in ethanol (100 ml). The mixture was boiled under reflux for 5 h, ethanol was distilled off, the residue was treated with ether (250 ml), and the mixture was filtered. The filtrate was washed with aqueous 0·1M-sodium hydroxide (2 × 50 ml) and then with water (100 ml), and dried ($MgSO_4$). Evaporation of the ethereal solution and distillation of the residue gave *ethyl 1-acetylcyclopropanecarboxylate* (61%), b.p. 72—75° at 12 Torr, n_D^{20} 1·4420 (Found: C, 61·4; H, 8·1. $C_8H_{12}O_3$ requires C, 61·5; H, 7·7%), $\nu_{C=O}$ 1740 cm^{-1}, τ (CCl_4) 5·6 (2H, q, *J* 7·5 Hz), 7·5 (3H, s), and 8·6 (7H, m).

Attempted Preparation of a Furan from Dibenzyl Ketone.—Dimethyl(prop-2-ynyl)sulphonium bromide (2 g) and dibenzyl ketone (2·33 g) were added to ethanolic 0·5M-sodium ethoxide (22 ml). The mixture was kept at 20° for 16 h; half of the solution was then boiled under reflux for 3·5 h. The reaction mixtures, treated separately, were diluted with water, adjusted to pH 7, and extracted with dichloromethane. The residue from evaporation of the extracts from each reaction was unchanged dibenzyl ketone (1·9 g, 81% in all), identical (i.r. spectrum and t.l.c.) with an authentic specimen.

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