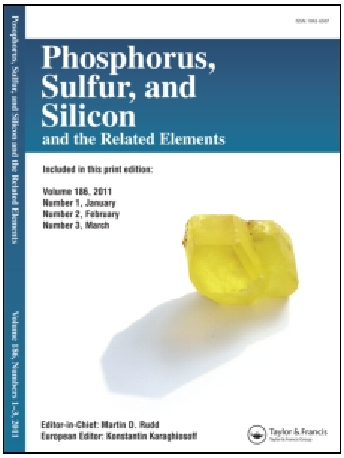

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New Synthetic Reactions Contributed by Sulfur

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NEW SYNTHETIC REACTIONS CONTRIBUTED BY SULFUR

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Abstract Eighteen kinds of new convenient synthetic reactions respectively contributed by divalent sulfur (7), sulfoxide (7) and sulfone (4) are shown.

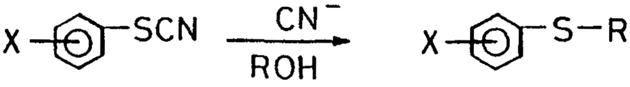
INTRODUCTION

Sulfur atoms appear in the structure of organic compounds as sulfide, polysulfide, sulfoxide, sulfone, sulfilimine etc. Divalent sulfur can stabilize both carbenium cations and carbanions adjacent to the sulfur atom, and the hypervalent sulfur groups can strongly stabilize adjacent carbanions. These sulfur groups characteristically undergo easily migration and/or elimination. By using these characteristics of sulfur functions, we can develop convenient synthetic reactions proceeding under mild conditions. The sulfur functions assure regio- and stereocontrol of these reactions to give the desired final products in which no sulfur atom is contained.

SULFIDE AND THIOL

1. Conversion of -SCN to -SR [1,2]

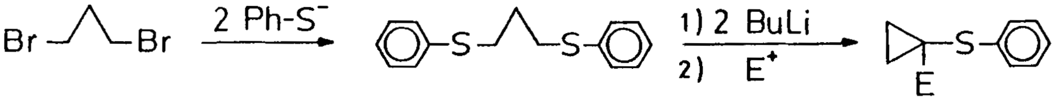
Aryl thiocyanates can be converted into aryl alkyl sulfides with alcohol in the presence of an equimolar amount of cyanide anion. 4-Nitrophenyl thiocyanate gave 4-nitrophenyl methyl sulfide in methanol (50^{o}C, 2 hr.). The yield was 70%.



eq. 1

2. New cyclopropane synthesis [3,4]

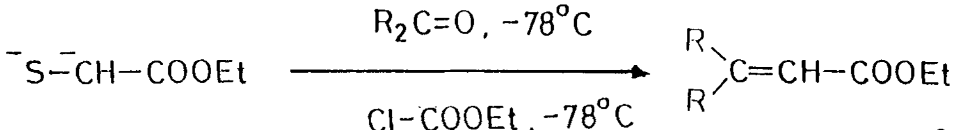
When 1,3-bis phenylthiopropane is treated with butyllithium at -78°C, cyclopropyl phenyl sulfide is formed with a yield of 88%. When equivalents of BuLi are used, an electrophile such as a ketone, an aldehyde or an epoxide can be introduced at α-position of the cyclopropyl sulfide.



eq. 2

3. Convenient synthesis of α,β-unsaturated carboxylates [5]

Certain α,β-unsaturated carboxylic acid esters can be obtained from alkyl thioglycolate by a one pot synthesis. The stable vicinal dianion (S - C -) can be generated by treating thioglycolic ester with two equivalents of lithium diisopropylamide (LDA) and a similar amount of tetramethylethylenediamine (TMEDA) in THF (-78°C, 1 hr). To the solution of the dianion an equimolar amount of a ketone or an aldehyde is added (-78°C, 2 hr) to give an alkoxide anion. Finally, ethyl chloroformate is added to the solution and it is kept at room temperature for 1 hr to give the desired α,β-unsaturated carboxylate in good yields.

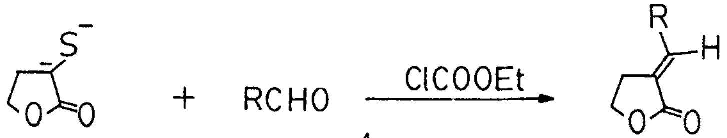


eq. 3

When acetophenone was taken as the ketone, ethyl α-methyl-cinnamate was isolated in 58% yield, the E isomer being predominant (E/Z = 97/3).

4. A new way for the synthesis of α-alkylidene-γ-butyrolactones [6,7]

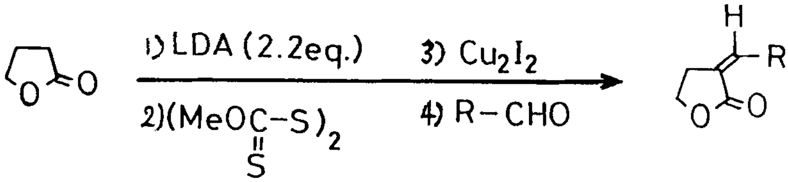
Since γ-butenyrolactones (butenolides) and α-alkylidene-γ-butyrolactones have strong biopotential activities, many efforts have been made for their synthesis. Applying the method mentioned in 3. according to eq. 4, we can get α-alkylidene-γ-butyrolactones easily in good yield. In this case, the E isomer is predominant (95-100%).



eq. 4

5. Stereo-controled synthesis of Z-α-alkylidene-γ-butyrolactones [8]

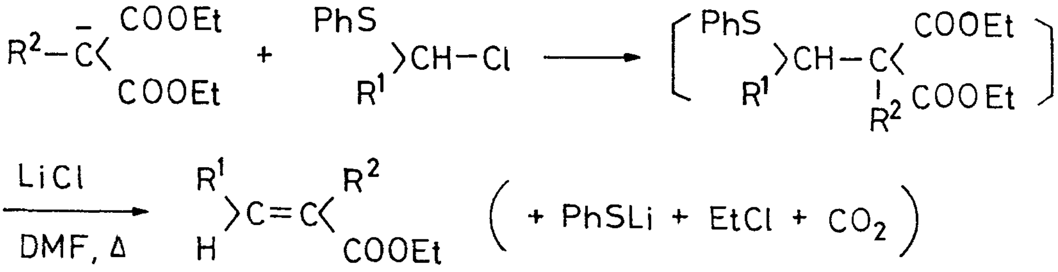
Contrary to the method mentioned in 4., Z-Alkylidenebutyrolactones can be obtained by using metal cations according to eq. 5. When butanal was used as the aldehyde, the lactone was formed in 56% yield (Z/E = 93/7).



eq. 5

6. Synthesis of α-alkyl-α,β-unsaturated carboxylates [8]

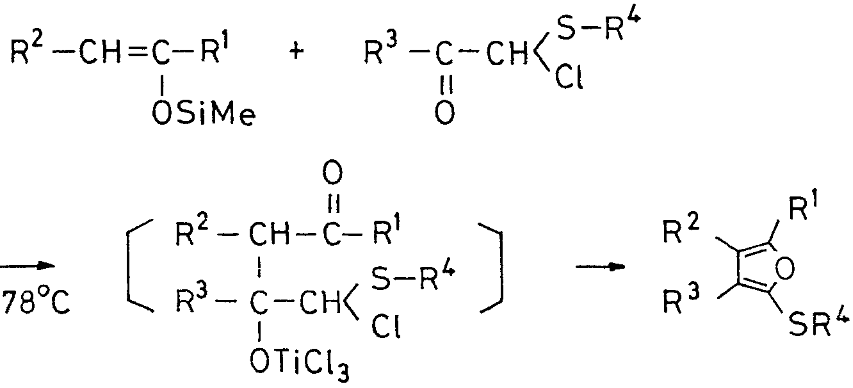
A new method for the synthesis of α-alkyl-α,β-unsaturated carboxylic acid esters is presented here, see eq. 6. In the case of R^1 = propyl, R^2 = butyl, the ester was obtained in 70% yield (E/Z = 90/10). For R^1 = phenyl, E/Z = 96/4 was found.



eq. 6

7. New synthesis of multi-substituted furanes [10]

Multi-substituted furanes can be easily synthesized by the use of $TiCl_4$ following eq. 7. When R^1, R^2, R^3, R^4 were Et, Me, Me, Ph, respectively, the yield of the furane was 88%.

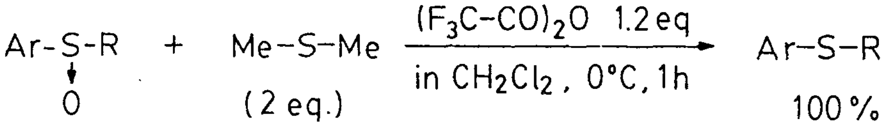


eq. 7

SULFOXIDE

8. Convenient reduction of sulfoxides to sulfides [11,12]

A sulfoxide can be converted to sulfide at $0^{O}C$ according to eq. 8. No other functional groups such as CO, CN, SO_2, halide and double bonds interfere in this reaction.

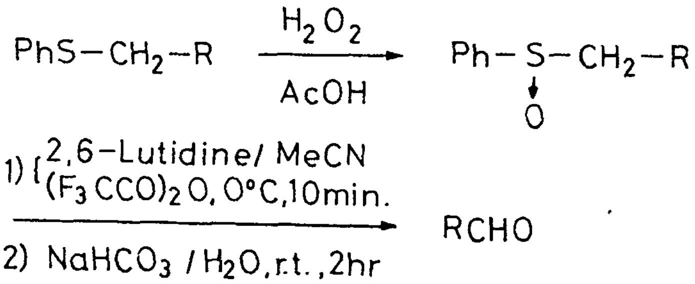


$$\text{Ar-}\underset{\overset{\downarrow}{O}}{S}\text{-R} + \underset{(2\ eq.)}{\text{Me-S-Me}} \xrightarrow[\text{in } CH_2Cl_2,\ 0^{\circ}C,\ 1h]{(F_3C\text{-}CO)_2O\ \ 1.2eq} \underset{100\%}{\text{Ar-S-R}}$$

eq. 8

9. New aldehyde synthesis [13]

Primary alkyl aryl sulfides give aldehydes at room temperature after oxidation by treatment with trifluoroacetic anhydride and 2,6-lutidine followed by the hydrolysis (eq. 9). In the case of octanal the yield was 86%.



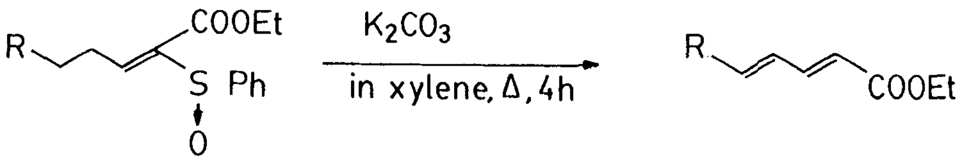
$$PhS\text{-}CH_2\text{-}R \xrightarrow[AcOH]{H_2O_2} Ph\text{-}\underset{\overset{\downarrow}{O}}{S}\text{-}CH_2\text{-}R$$

$$\xrightarrow[\text{2) } NaHCO_3\ /\ H_2O,\text{r.t.},2hr]{\text{1) } \left\{\begin{array}{l}\text{2,6-Lutidine/ MeCN}\\ (F_3CCO)_2O,\ 0^{\circ}C,10min.\end{array}\right.} RCHO$$

eq. 9

10. Synthesis of 2E, 4E-alkadienoic acid esters [14]

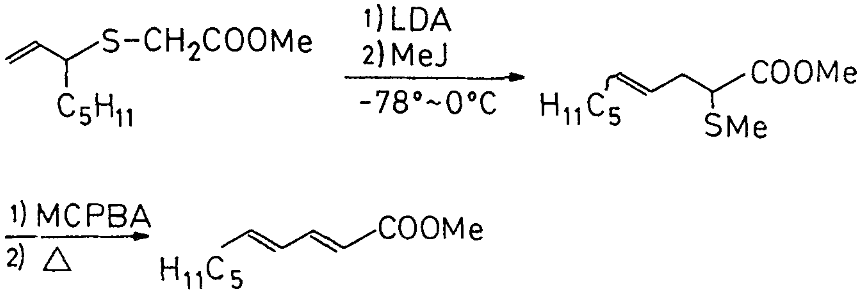
Pyrolysis of 2-phenylsulfinyl-2-alkenoates in boiling xylene gives 2E,4E-alkadienoates in good yield (eq. 10). The first example was given by Nokami et al. [Tetrahedron Lett. 21, 4455 (1980)]. Further examples and the reaction pathway were shown by the author. In the case of ethyl 2,4-decadienoate, the ratio of (2E, 4E)/other isomers was equal to 44/6.



eq. 1o

11. Synthesis of 2E,4E-alkadienoic acid esters II [15]

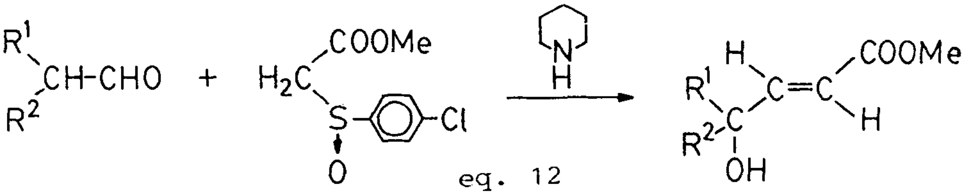
Methyl S-(1-vinylalkyl)thioglycolate undergoes [2,3]-sigmatropic migration by the action of base (LDA). Methylation of the resulting thiolate gives methyl 2-methyl thio-4-alkenoate (E/Z = 95/5) in high yield. Oxidation of the ester to the sulfoxide followed by Cope-elimination gives methyl 2,4-alkadienoate (2E,4E)/other isomers = 85/15).



eq. 11

12. Convenient synthesis of 4-hydroxy-2E-alkenoic acid esters [16]

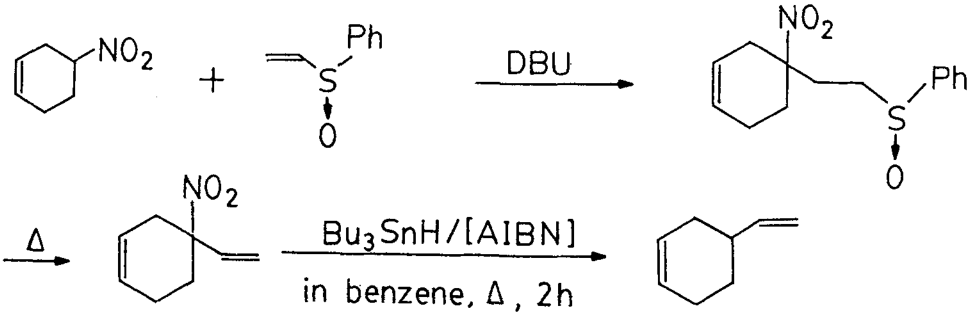
Aldehydes can react with methyl 4-chlorophenylsulfinyl acetate at room temperature in the presence of an equimolar amount of piperidine to give 4-hydroxy-2-alkenoates in which the E isomer is predominant (eq. 12) in most cases. For hexanal, the yield was 83%.



eq. 12

13. New route for the vinylation of alkanes [17]

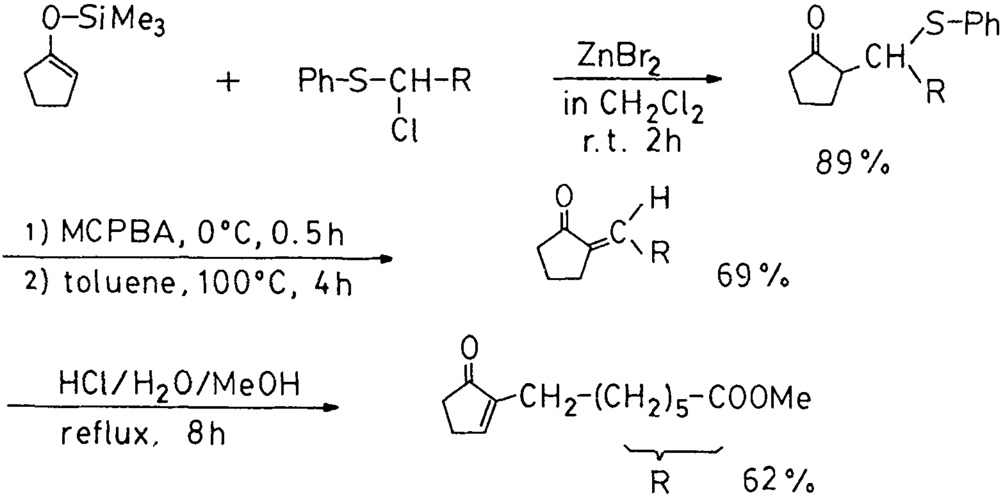
Nitro alkanes can undergo Michael addition to aryl vinyl sulfoxides in the presence of 1,8-diazabicyclo [5,4,0] undeca-7-ene (DBU) giving high yields. Thermal elimination of the resulting sulfoxide followed by the denitrohydrogenation reaction with Bu_3SnH gives the vinylalkane in good yields (eq. 13). Thus aryl vinyl sulfoxides can be a synthon for the vinyl cation



eq. 13

14. New synthesis of 2-substituted 2-cyclopentenones [18]

2-Substituted 2-cyclopentenones which are important intermediates in prostanoid synthesis can be synthesized by a new route following eq. 14.

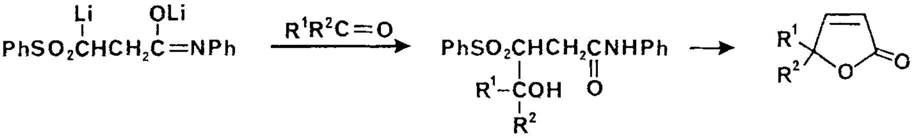


eq. 14

SULFONE

15. New route for the synthesis of γ-substituted butenolides (I) [19]

The dianion of 3-phenylsulfonylpropionanilide reacts with ketones or aldehydes giving an aldol which can be cyclized to 4-substituted 2-butenyrolactones, see eq. 15. When cyclohexanealdehyde was used the overall yield was 67%.



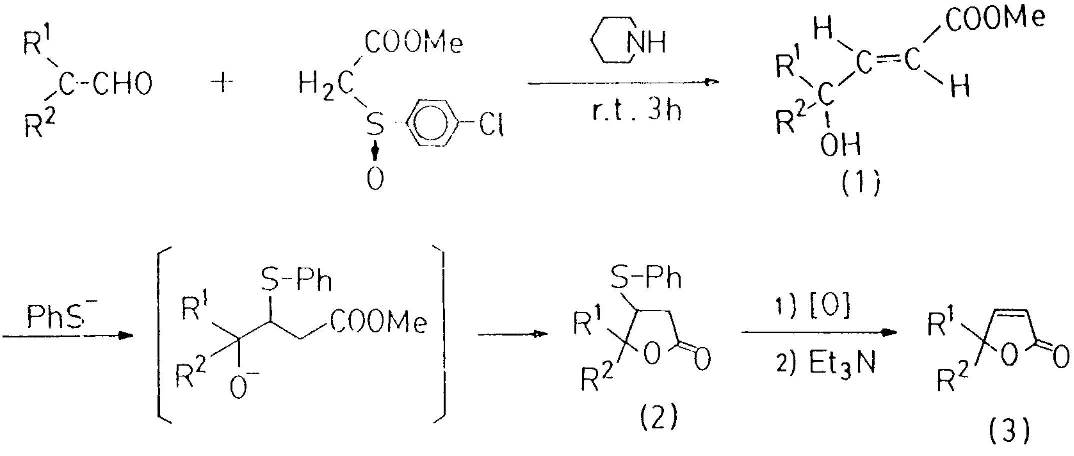
eq. 15

16. New route for the synthesis of γ-substituted butenolides (II) [20]

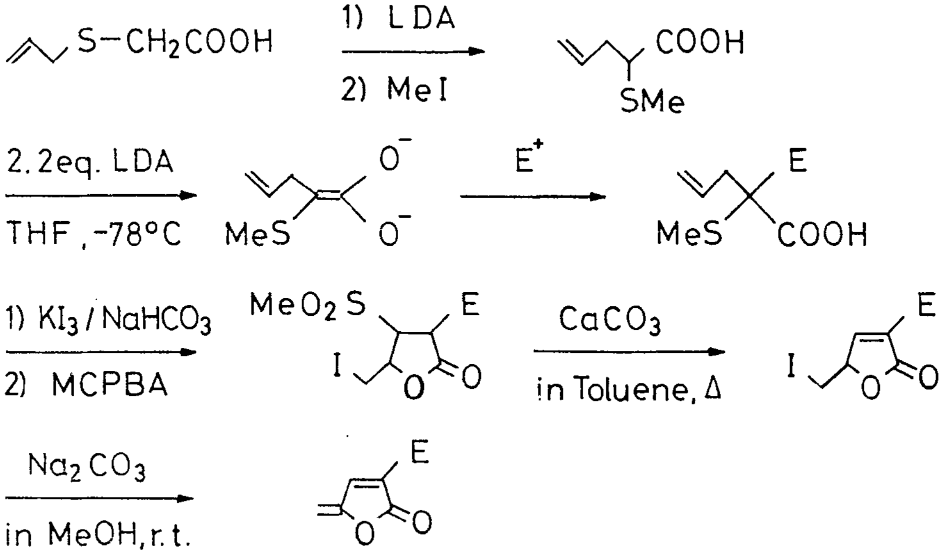
Another route for the synthesis of γ-substituted butenolides has been developed. As mentioned in 12., methyl 4-hydroxy-2-alkenoates can be obtained quite easily. Michael addition of benzenethiolate anion to these esters gives 3-phenylthio-4-substituted γ-butyrolactones. Oxidation of the lactones to sulfones followed by β-elimination with Et_3N gives the desired butenolide in good yields (eq. 16). In the case of R^1 = Et, R^2 = H, the yields of (1), (2) and (3) were 85, 81, 77%, respectively.

17. New synthesis of γ-methylenebutenolides [21]

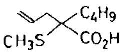
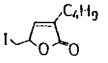
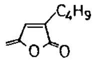
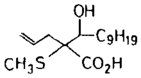
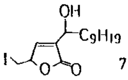
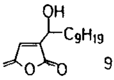
γ-Methylene-α-substituted butenolides can be obtained from S-allylthioglycolic acid following eq. 17.



eq. 16



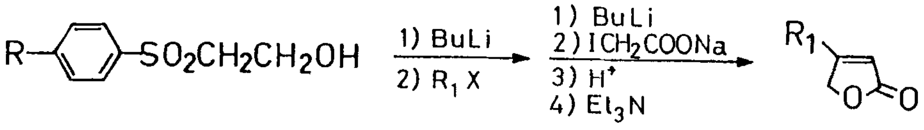
Table

Electrophile	IV	Yield	V	Yield	VI	Yield
n-C_4H_9I		74%		75%		97%
n-$C_9H_{19}CHO$		89%		76%		98%

eq. 17

18. New synthesis of β-substituted butenolides [23]

Certain electrophiles such as alkylhalides or aldehydes can be introduced in the 2-position of 2-(arylsulfonyl) ethanols. The resulting ethanols are good intermediates to give β-substituted butenolides according to eq. 18. This synthesis can be done in a one pot system. When 3-methoxybenzyl bromide was used as electrophile the overall yield was 56%.



eq. 18

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