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SULFUR YLIDES.

2. S,N-TRANSMETHYLATION UPON TREATMENT OF AZOMETHINES WITH DIMETHYLCARBOETHOXYMETHYLIDENESULFURANE, GENERATED UNDER PHASE TRANSFER CATALYSIS CONDITIONS

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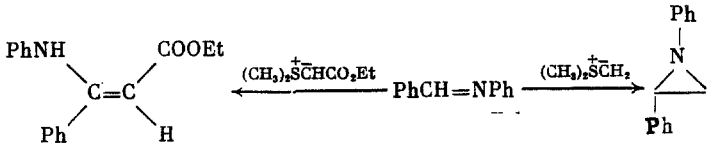
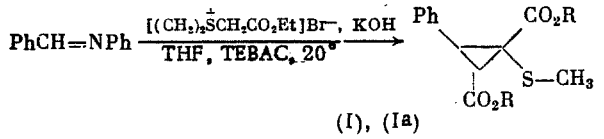
Nonstabilized sulfur ylides add to azomethines to give aziridines [1, 2], whereas the reaction products derived from stabilized ylides are β-aminocinnamic acid type enamines [3].



We have previously demonstrated that a convenient modification for the cyclopropanation of α,β-unsaturated ketones involves treatment of the latter with stabilized sulfur ylides generated from sulfonium salts in a solid–liquid phase system in the presence of a phase transfer catalyst [4]. Applying this method to dimethylcarboethoxymethylidenesulfurane, we recently established that a new type of reaction can occur, namely, formation of the diethyl ester of 1-methylthio-3-phenyl-1,2-cyclopropanedicarboxylic acid (I) [5].



(I), (Ia)

R = Et(I), H(Ia).

It is characteristic that our experiments with this ylide, generated under the conditions used for the formation of dichlorocarbene from chloroform [6], led to the formation of the β-anilinocinnamate mentioned above, in low yield.

The present paper deals with a detailed investigation of this new type of conversion reaction. The reaction apparently involves reaction of the azomethine with two molecules of the sulfur ylide. Compound (I) is formed in 35% yield in THF medium using equimolar amounts of dimethylsulfoniumcarboethoxymethyl bromide (IX), benzalaniline (X), and solid KOH in the presence of 1% triethylbenzylammonium chloride (TEBAC). It should be emphasized that the yield of (I) can be increased to 60% by replacing (X) with benzalmethylamine (XI). Further attempts to increase the yield of (I) by increasing the amounts of sulfonium salt (IX) and KOH were not successful. As can be seen from the data in Table 1, changing the substituent attached to the N atom in the azomethine molecule in the series (XII)-(XIV) leads to a gradual decrease in the yield of compound (I).

The PMR spectrum of (I) contains signals for the two ethoxy group protons, for one thiomethyl group at 1.9 ppm, and for two cyclopropane ring protons at 2.54 and 3.47 ppm. Based on the spin–spin coupling constant values for these signals, we conclude that the C^2-C^3 protons are located in a trans orientation relative to one another, and that the C^2-carboethoxy groups and C^3-phenyl groups are thus also trans to one another. And, in fact, the dicarboxylic acid derivative (Ia) is not converted to an anhydride under standard conditions, which suggests that the two carboxyl groups are also in a trans orientation. The stereochemistry

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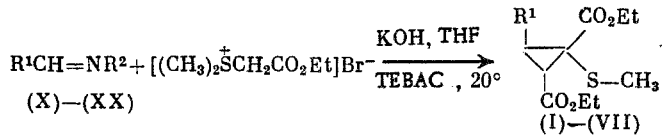
 0568-5230/88/3704-0708$12.50

TABLE 1. Reactions of Azomethines with Dimethylcarboethoxymethylidenesulfurane



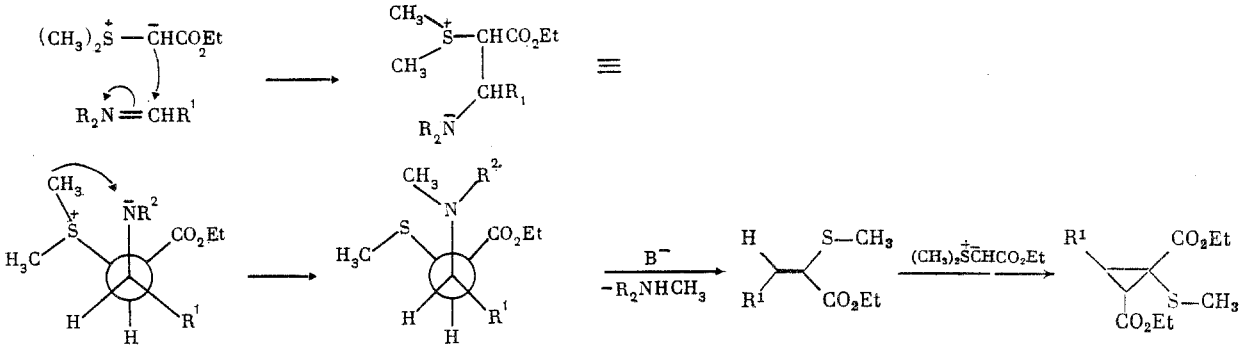
(X)—(XX) (I)—(VII)

Azomethine starting material	R¹	R²	Reaction product	Yield, %	Found, %				Calculated, %			
					C	H	N	S	C	H	N	S
(X)	Ph	Ph	(I)	35	62,28	6,56		10,24	62,3	6,55		10,39
(XI)	Ph	CH_3	(I)	60								
(XII)	Ph	C_2H_5	(I)	50								
(XIII)	Ph	C_3H_7	(I)	45								
(XIV)	Ph	C_5H_{11}	(I)	42								
(XV)	p-$CH_3OC_6H_4$	CH_3	(II)	50	60,2	6,55		9,3	60,35	6,5		9,47
(XVI)	p-$NO_2C_6H_4$	CH_3	(III)	40	56,62	5,31	3,62	8,72	57,2	5,38	3,96	9,00
(XVII)	3-Py	CH_3	(IV)	55	57,76	6,02	3,87	10,3	58,25	6,11	4,53	10,36
(XVIII)	4-Py	CH_3	(V)	50	58,47	5,99	4,53	59,9	58,25	6,11	4,53	10,36
(XIX)	α-Furyl	CH_3	(VI)	20	56,1	6,0		10,5	56,38	6,04		10,74
(XX)	Pr	Ph	(VII)	10	54,5	8,37		12,36	54,96	8,4		12,2

of these molecules, which was suggested on the basis of their chemical behavior and PMR spectra, was confirmed by analysis of the ^{13}C-NMR spectra of compound (I) and its analogs (II)-(V), which were prepared from the corresponding methylamine derivatives. As can be seen from the data in Table 1, replacement of the phenyl substituent by p-anisyl (XV), p-nitrophenyl (XVI), 3-pyridyl (XVII), and 4-pyridyl (XVIII) substituents makes it possible to carry out these reactions with the sulfur ylide quite smoothly and readily. The yields of the corresponding cyclopropanedicarboxylic acid derivatives (II)-(V) are in the 40-55% range.

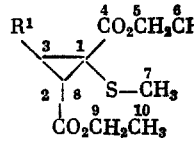
The ^{13}C-NMR spectra of these compounds (Table 2) are noteworthy in terms of the shielding effect of the C^3 substituent on the signal of the C^1 carboxyl group carbon atom; in contrast, the frequency of the C^2 carboxyl group carbon atom changes insubstantially in this transition. Analogous differences were also noted in the signals of the ethoxy group carbon atoms. Also characteristic of these spectra is the observation that the frequency of the thiomethyl group carbon atom remains practically unchanged in this series of compounds. All of these facts lead us to conclude that azomethines react with sulfur ylides to form ester derivatives of trans-1,2-cyclopropanedicarboxylic acid, with a further trans orientation of the substituent at C^3 and the C^1-thiomethyl group.

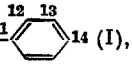
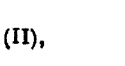
With regard to the mechanism of this novel conversion reaction, the fact that secondary N-methylamines are formed is noteworthy. In our experiments, these amines were N-methylaniline, dimethylamine, methylethylamine, methylpropylamine, and methylpentylamine, all of which were identified in the reaction mixture by GLC. S,N-transmethylation must therefore take place at an intermediate stage in the overall conversion reaction. Taking into account this observation, the following reaction sequence is proposed.

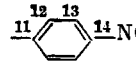
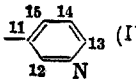
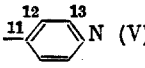


Transmethylation apparently occurs via a conformation which forces the nitrogen- and sulfur-containing functional groups into proximity to one another. Subsequent elimination of a β-amino functional group leads to the corresponding cis-cinnamic acid derivative, which

TABLE 2. Chemical Shifts and Signal Multiplicity in the ^{13}C-NMR Spectra of 1,1,2,3-Tetrasubstituted Cyclopropanes



, where R^1 =  (I),  (II),

 (III),  (IV),  (V)

Compound	C^1	C^2	C^3	C^4	C^5
(I)	42,17s	36,78d	34,01d	169,29s	61,36 t
(II)	42,21s	36,26d	34,32d	169,39s	61,36 t
(III)	42,46s	36,23d	34,53d	167,76s	62,11t
(IV)	42,10s	33,74d	34,24d	168,02s	62,01t
(V)	42,30s	35,58d	33,91d	167,83s	62,08t

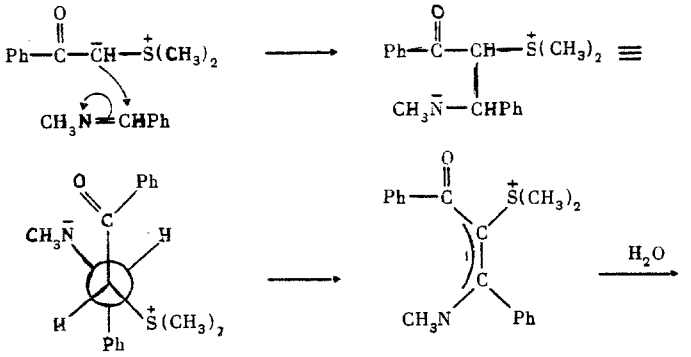
Compound	C^6	C^7	C^8	C^9	C^{10}
(I)	14,17q	15,01q	168,38s	61,72t	14,17q
(II)	14,17q	15,09q	168,55s	61,74t	14,17q
(III)	14,13q	15,18q	168,61s	61,76t	14,13q
(IV)	14,17q	15,08q	168,83s	61,69t	14,17q
(V)	14,13q	15,05q	168,67s	61,72t	14,13q

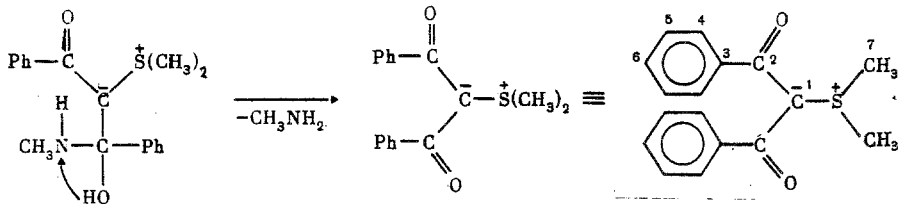
Compound	C^{11}	C^{12}	C^{13}	C^{14}	C^{15}
(I)	133,65s	128,82d	128,01d	127,42d	
(II)	125,67s	129,87,d	113,51d	158,96d	55,24q
(III)	128,73s	129,73d	123,21d	141,39s	
(IV)	129,67s	150,33d	148,73d	122,81d	135,91d
(V)	142,89s	123,93d	149,45d		

then undergoes stereospecific cyclopropanation by means of the ylide; the principle of trans orientation of carboethoxy groups is observed in the latter reaction. α-Furfuralmethylamine (XIX) reacts very rapidly with ylides, although the product yield (VI) is low (does not exceed 20%) due to a great degree of resinification which accrues. The azomethine derived from aniline and butyraldehyde, (XX), also gives a cyclopropane derivative (VII) in 10% yield.

We did not observe reaction of azomethines with tetramethylenecarboethoxymethylidenesulfurane or dimethylcarboethoxyethylidenesulfurane generated under phase transfer catalysis conditions from the following sulfonium salts: tetrahydrothiopheniumcarboethoxymethyl bromide (XXI) and dimethylsulfoniumcarbomethoxypropionate bromide (XXII).

Reaction of (XI) with dimethylphenacylidenesulfurane, generated from dimethylsulfoniumphenacyl bromide (XXIII), occurred via a substantially different reaction pathway. The sole product formed in this case was the two-fold stabilized ylide dimethyldibenzoylmethylidenesulfurane (VIII), which has been prepared previously by benzoylation of dimethylphenacylidenesulfurane [7]. In contrast to the reaction of dimethylcarboethoxymethylidenesulfurane, S,N-transmethylation does not take place in this case.





(VIII)

EXPERIMENTAL

PMR spectra were obtained on a Tesla BS-497 spectrometer (at 100 MHz), while ^{13}C NMR spectra were recorded on a Jeol FX-90Q spectrometer using solutions in $CDCl_3$ or CCl_4 relative to TMS. IR spectra were obtained on a UR-20 spectrophotometer using thin films. GLC analyses were carried out on a Chrom-5 chromatograph (5% SE-30 on N-AW-HMDS chromatone column, column length 1.2 m). Mass spectra were measured on an MX-1306 spectrometer under standard conditions.

Sulfonium salts (IX) and (XXI) were synthesized according to [8], salt (XXII) according to [4], and (XXIII) according to [7]. Azomethines (X) and (XI) were prepared according to [10]. Compounds (XII)-(XIV) were obtained according to [11], (XVI)-(XVIII) according to [12], (XIX) and (XX) according to [13]. Azomethine (XV) was prepared by condensation of p-methoxybenzaldehyde with an aqueous solution of $MeNH_2$ at 25°C for 2 h; yield, 80%, bp 80°C (1 mm Hg). PMR spectrum (δ, ppm): 3.46 s (CH_3), 3.8 s (CH_3), 6.75-7.1 m (CH, CH), 7.55-7.95 m (CH, CH), 8.23 s (CH). IR spectrum (ν, cm^{-1}): 2840, 1650, 1605, 1580, 1515, 1460, 1035, 835.

General Reaction Method. A mixture of 10 mmoles of azomethine, 10 mmoles sulfonium salt, 10 mmoles finely dispersed 85% KOH, and 0.15 mmole TEBAC in 10 ml THF was stirred for 3-4 h at ~20°C; the mixture was filtered to remove the precipitate, and solvent was evaporated. The product was isolated by column chromatography on Al_2O_3 or silica gel.

1-Methylthio-3-phenyl-1,2-cyclopropanedicarboxylic Acid, Diethyl Ester (I). This was prepared from sulfonium salt (IX) and azomethines (X)-(XIV). R_f 0.6 (SiO_2, hexane: ethyl acetate, 7:3). $C_{16}H_{10}O_4S$. PMR spectrum (δ, ppm; J, Hz): 1.2 t (CH_3, J = 7), 1.23 t (CH_3, J = 7), 1.9 s (CH_3), 2.54 d (CH, J = 7), 3.47 d (CH, J = 7), 4.08 q (CH_2, J = 7), 4.15 q (CH, J = 7), 7.17 s (C_6H_5). IR spectrum (ν, cm^{-1}): 1740 br, 1605, 1450, 1330, 1035, 1030, 770, 700. m/z 307 (M^+).

1-Methylthio-3-(p-methoxyphenyl)-1,2-cyclopropanedicarboxylic Acid, Diethyl Ester (II). From salt (IX) and azomethine (XV). R_f 0.65 (Al_2O_3, CH_2Cl_2:benzene, 7:3). $C_{17}H_{22}O_5S$. PMR spectrum (δ, ppm; J, Hz): 1.28 t (CH_3, J = 7), 1.31 t (CH_3, J = 7), 2.05 s (CH_3), 2.6 d (CH, J = 7), 3.58 d (CH, J = 7), 3.68 s (CH_3), 4.25 q (CH_2, J = 7), 4.3 q (CH_2, J = 7), 6.88-7.25 m (CH, CH), 7.25-7.45 m (CH, CH). IR spectrum (ν, cm^{-1}): 2840, 1730 br, 1605, 1580, 1515, 1460, 1325, 1030 br, 840.

1-Methylthio-3-(p-nitrophenyl)-1,2-cyclopropanedicarboxylic Acid, Diethyl Ester (III). From salt (IX) and azomethine (XVI). R_f 0.8 (Al_2O_3, CH_2Cl_2:benzene, 7:3). $C_{16}H_{19}NO_6S$. PMR spectrum (δ, ppm; J, Hz): 1.28 t (CH_3, J = 7), 1.31 t (CH_3, J = 7), 2.0 s (CH_3), 2.67 d (CH, J = 7), 3.61 d (CH, J = 7), 4.19 q (CH_2, J = 7), 4.23 q (CH_2, J = 7), 7.21-7.55 m (CH, CH), 8.0-8.27 m (CH, CH). IR spectrum (ν, cm^{-1}): 1740 br, 1650, 1605, 1515, 1460, 1340, 1320, 840.

1-Methylthio-3-(3-pyridyl)-1,2-cyclopropanedicarboxylic Acid, Diethyl Ester (IV). From salt (IX) and azomethine (XVII). R_f 0.5 (SiO_2, hexane:ethyl acetate, 7:3). $C_{15}H_{19}NO_4S$. PMR spectrum (δ, ppm; J, Hz): 1.28 t (CH_3, J = 7), 1.32 t (CH_3, J = 7), 2.0 s (CH_3), 2.63 d (CH, J = 7), 3.55 d (CH, J = 7), 4.2 q (CH_2, J = 7), 4.25 q (CH_2, J = 7), 7.13-7.4 m, 7.53-7.77 m, 8.43-8.77 m (CH, CH, CH). IR spectrum (ν, cm^{-1}): 1730 br, 1590, 1570, 1455, 1420, 1320, 1030, 715.

1-Methylthio-3-(4-pyridyl)-1,2-cyclopropanedicarboxylic Acid, Diethyl Ester (V). From salt (IX) and azomethine (XVIII). R_f 0.55 (hexane:ethyl acetate, 7:3). $C_{15}H_{19}NO_4S$. PMR spectrum (δ, ppm; J, Hz): 1.28 t (CH_3, J = 7), 1.31 t (CH_3, J = 7), 1.98 s (CH_3), 2.67 d (CH, J = 7), 3.61 d (CH, J = 7), 4.19 q (CH_2, J = 7), 4.23 q (CH_2, J = 7), 7.2-7.55 m (CH, CH), 8.0-8.27 m (CH, CH). IR spectra (ν, cm^{-1}): 1730 br, 1600, 1560, 1455, 1415, 1320, 1030, 1000.

1-Methylthio-3-(α-furyl)-1,2-cyclopropanedicarboxylic Acid, Diethyl Ester (VI). From salt (IX) and azomethine (XIX). R_f 0.65 (SiO_2, hexane:ethyl acetate, 7:3). $C_{14}H_{19}O_5S$. PMR

spectrum (δ, ppm; J, Hz): 1.28 t (CH_3, J = 7), 1.3 t (CH_3, J = 7), 2.07 s (CH_3), 2.61 d (CH, J = 7), 3.48 d (CH, J = 7), 4.18 q (CH_2, J = 7), 4.23 q (CH_2, J = 7), 6.3-6.33 m (CH, CH), 7.27-7.43 m (CH). IR spectra (ν, cm^{-1}): 1740 br, 1500, 1325, 1030, 810.

1-Methylthio-3-propyl-1,2-cyclopropanedicarboxylic Acid, Diethyl Ester (VII). From salt (IX) and azomethine (XX). R_f 0.7 (SiO_2, hexane: ethyl acetate, 7:3). $C_{13}H_{22}O_4S$. PMR spectrum (δ, ppm; J, Hz): 0.98 t (CH_3, J = 7), 1.19 t (CH_3, J = 7), 1.22 t (CH_3, J = 7), 1.2-1.31 m (CH_2, CH_2), 2.0 s (CH_3), 2.53 d (CH, J = 7), 3.3 d (CH, J = 7), 4.05 q (CH_2, J = 7), 4.13 q (CH_2, J = 7). IR spectrum (ν, cm^{-1}): 1730 br, 1380, 1320, 1035.

N-Carboethoxycinnamylaniline. A mixture of 0.63 g (2.76 mmoles) sulfonium salt (IX), 0.5 g (2.76 mmoles) benzalaniline, 2.7 ml 50% NaOH solution, and 0.15 g (0.41 mmole) Bu_4NI in 15 ml CH_2Cl_2 was stirred at 40°C for 48 h. The organic layer was washed several times with water, with an HCl solution, and then again with water and dried over $MgSO_4$. After solvent removal 0.15 g (20%) of product was obtained, mp 67°C (petroleum ether). Spectral data were completely consistent with the literature data [3].

Dimethyldibenzoylmethylidenesulfurane (VIII). A mixture of 0.5 g (4.2 mmoles) (XI), 1.1 g (4.2 mmoles) sulfonium salt (XXIII), 0.28 g (4.2 mmoles) finely dispersed 85% KOH, and a catalytic quantity of TEBAC was stirred at reflux for 6 h, cooled, and filtered. The filtrate was evaporated. The product was isolated by column chromatography on silica gel, R_f 0.67 (cyclohexane:ethyl acetate, 7:3). Yield 0.4 g (34%) of crystalline (VIII), mp 211-212°C. PMR spectrum (δ, ppm): 2.98 s (CH_3), 7.2-7.8 m (C_6H_5). IR spectrum (ν, cm^{-1}): 1655, 1590, 1580, 1450, 1210, 750, 690. ^{13}C NMR spectrum (δ, ppm): 51.50 s (C^1), 183.10 s (C^2), 140.87 s (C_3), 126.34 d (C^4), 127.88 d (C^5), 129.51 d (C^6), 28.49 q (C^7). Found: C 72.1; H 5.6; S 11.0%. $C_{17}H_{16}O_2S$. Calculated: C 71.83; H 5.67; S 11.26%.

1-Methylthio-3-phenyl-1,2-cyclopropanedicarboxylic Acid (Ia). A mixture of 1.5 g (5 mmoles) diethyl ester (I), 7 ml MeOH, and 5 ml of 2 N NaOH solution was refluxed for 4 h; the solvent MeOH was evaporated under vacuum, and the mixture was washed with $NaHCO_3$ solution, followed by water. The mixture was extracted into chloroform and dried over Na_2SO_4, then evaporated. Yield 1 g (80%) (Ia) as a viscous oil. IR spectrum (ν, cm^{-1}): 2600-2800, 1710, 1690, 1605, 1450, 1330, 1040, 1030, 910.

Attempt to Form an Anhydride from Acid (Ia). A mixture of 1 g (4 mmoles) acid (Ia) in 20 ml Ac_2O was refluxed for 10 h. Excess Ac_2O was removed by washing with water, and the residue was extracted into chloroform and dried over Na_2SO_4. After solvent removal 0.8 g of (Ia) was recovered.

CONCLUSIONS

A method has been developed for the preparation of methylthiocyclopropanedicarboxylic acid derivatives based on reactions of azomethines with dimethylcarboethoxymethylidenesulfurane, which is generated *in situ* from its sulfonium salt precursor and KOH in the presence of a phase transfer catalyst.

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