Chemistry of Heterocyclic Compounds, Vol. 29, No. 12, 1993

TWO DIRECTIONS IN THE HETEROCYCLIZATION OF THIOCARBAMOYLPYRIDINIUM(ISOQUINOLINIUM)YLIDES IN THEIR INTERACTION WITH ESTERS OF ACETYLENECARBOXYLIC ACIDS

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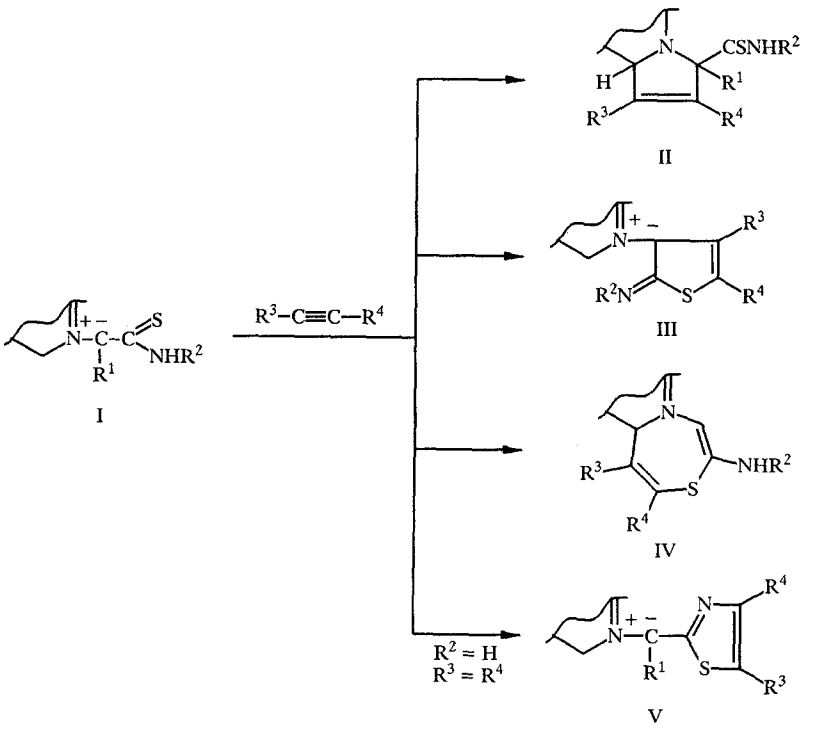
It has been found that pyridinium- and isoquinoliniumthiocarbamoylazomethinylides react with esters of acetylenedicarboxylic and propiolic acids in two directions. The first direction is heterocyclization of the thioamide fragment of the ylide; under the influence of dimethyl acetylenedicarboxylate, a thiazolyl-4-one ring is formed, and by the interaction of the pyridiniumylide with methyl propiolate, a thiazin-4-one ring is formed. The second direction consists of annelation of the imidazole ring to the isoquinoline system upon reaction with methyl propiolate.

It is known that acetylene derivatives interact readily with heterocyclic azomethinylides stabilized by carbonyl and cyano groups, forming polycyclic pyrroles [1-6]. This method is now used extensively in synthesis, including applications in the preparation of compounds with potential biological activity [6]. However, the circle of reactions that have been investigated does not include the reactions of heterocyclic thiocarbamoylazomethinylides – compounds in which the molecules contain several nucleophilic centers and hence can interact with acetylene derivatives in several directions, forming sulfur- and nitrogen-containing heterocycles.

Scheme 1



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 0009-3122/93/2912-1458$12.50

TABLE 1. PMR Spectra of Synthesized Compounds

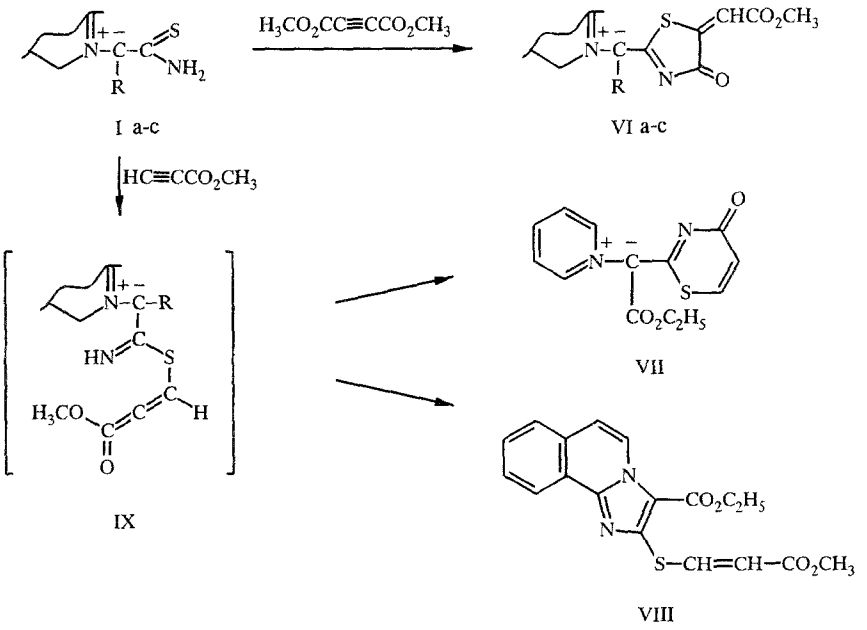
Compound	Empirical formula	δ, ppm (and J, Hz)
Ia		8.78 (2H,d); 8,5 (1H. t); 7,95 (2H. t): 3,95 (2H,q. CH_2); 1.0 (3H, t, CH_3)
Ic		9,93 (1H, s, 1-H); 8,39 (6H,m); 3,93 (2H, q, CH_2); 1,0 (3H, t, CH_3)
VIa	$C_{15}H_{14}N_2O_5S$	9,1 (2H, d); 8,55 (1H, t); 8,15 (2H, t); 6,5 (1H, s, =CH—); 4,15 (2H,q, CH_2); 3,75 (3H, s, CH_3); 1,15 (3H, t, CH_3)
VIb	$C_{19}H_{15}N_3O_4S$	12,0 (1H, s, NH); 9,2 (2H,d); 8,8 (1H, t); 8,3 (2H, t,); 7,3 (5H, m); 6,55 (1H, s, =CH—); 3,7 (3H, s, CH_3)
VIe	$C_{13}H_{12}N_2O_3S$	10,1 (1H, c, 1-H); 8,4 (6H,m); 6,45 (1H, s, =CH—); 4,2 (2H,q, CH_2); 3,7 (3H, s, CH_3); 1,1 (3H, t, CH_3)
VII	$C_{13}H_{12}N_2O_3S$	8,85 (2H,d); 8,5 (1H, t); 8,1 (2H, t); 7,62 (1H,d, J = 10,4, =CH); 6,1 (1H, d, J = 10,4, CH=); 3,9 (2H,q, CH_2); 1,04 (3H, t, CH_3)
VIII	$C_{18}H_{16}N_2O_4S$	8,94 (1H,d, J = 7,5, 5-H); 8,87 (1H,d, J = 10,3, CH=CH); 8,4 (1H, m); 7,8 (3H,m); 7,55 (1H, d, J = 7,5 6-H); 6,29 (1H, d, J = 10,3, CH=CH); 4,42 (2H,q., CH_2); 3,75 (3H,s, CH_3); 1,43 (3H, t, CH_3)

In the work reported here, we investigated the interaction of pyridinium and isoquinolinium thiocarbamoylazomethinylides with dimethyl acetylenedicarboxylate and methyl propiolate; we established the dependence of the direction of the heterocyclization reaction on the nature of the azinium part of the ylide molecule and on the nature of the acetylenic dipolarophile.

We found that the reaction of the pyridiniumylides Ia,b with acetylenedicarboxylic ester does not involve the ylide fragment of the molecule: The products are not the expected cycloadducts, pyrrolo[2,1-a]pyridines, but rather the bicyclic ylides VIa,b. Analogously, from the isoquinoliniumylide Ic, the thiazolin-4-one VIc is obtained.

The zwitterion structure of compounds VIa-c is confirmed by their PMR spectra, in which the signals of the protons of the azinium part of the molecule in the weak-field region remain unchanged in comparison with the ylides Ia-c. The appearance of a singlet signal at 6.45-6.55 ppm can be attributed to the proton of the methylene group in position 5 of the thiazolinone ring [7].

Scheme 1



a,b) pyridine; c) isoquinoline; R = $CO_2C_2H_5$, $CONHC_6H_5$.

Replacement of the acetylenedicarboxylate by an ester of acetylenemonocarboxylic acid changes the direction of heterocyclization of the thiocarbamoylazomethinylide. Thus, the reaction of the ylide Ia with methyl propiolate leads to the formation of a new derivative with the ylide structure: 1-(4-oxo-1,3-thiazin-2-yl)-1-carbethoxymethylenepyridiniumylide (VII). The same as in the previous cases, in the PMR spectrum of compound VII, the chemical shifts of the signals from the pyridine ring protons remain unchanged in comparison with the analogous signals of the ylide Ia. On the basis of the SSCC of the two doublets at 7.62 and 6.11 ppm (J = 10.4 Hz), we can assign these signals to 5-H and 6-H protons of the newly formed thiazinone ring.

The formation of two different heterocycles – thiazole and thiazine – in the interaction of thioamides of azomethinylides with esters of acetylenemonocarboxylic acid and acetylenedicarboxylic acid is entirely consistent with information reported in the literature on reactions of acetylene derivatives with enaminothioamides [7].

It could be assumed that in the reaction of the isoquinoliniumylide Ic with methyl propiolate, a bicyclic ylide containing a thiazinone ring, analogous to compound VII, would likewise be formed. However, upon interaction of the thioamide Ic with methyl propiolate, we obtained a derivative of imidazo[1,2-a]isoquinoline (VIII), the same as in the reaction of the thioamides I with methyl iodide [8]. In the PMR spectrum of compound VIII, in comparison with the original thioamide Ic, we observe an upfield shift of the signals of the heterocyclic part of the molecule (8.9-7.5 ppm) and disappearance of the singlet signal of the 1-H proton of the isoquinoline at δ 9.93 ppm. In addition, a doublet of signals appears corresponding to the AB system of protons 5-H and 6-H of the isoquinoline part of the heterocycle, with SSCC 7.5 Hz — a signal that does not appear in the case of the isoquinoliniumylides. The presence of the olefin group is proven by the corresponding doublet of the AB system with J = 10.4 Hz. The presence of the methoxycarbonyl group is evidenced by the singlet at 3.75 ppm.

Thus, we have discovered two directions in the heterocyclization of thiocarbamoylylides under the action of methyl propiolate. Both conversions apparently proceed through the intermediate IX. The change in direction of the reaction upon changing the heterocyclic part of the ylide molecule in compounds Ia and Ic can be explained as follows. In the first place, the degree of aromaticity and the energy of the transition state for derivatives of isoquinoline is lower; in the second place, the isoquinolinium cation has a greater π-deficiency in comparison with pyridine, and the magnitude of the positive charge on the C_1 atom of the isoquinoline is greater than that on the α-carbon atom of pyridine [9]. Both factors act in the same direction, lowering the activation energy of electrocyclization in the case of the isoquinoliniumylide Ic, leading to the formation of the condensed heterocycle VIII.

From the data obtained in these studies, we can draw a conclusion regarding the direction taken in the heterocyclization of pyridinium- and isoquinoliniumthiocarbamoylylides as influenced by the nature of the reactants: Interaction with esters of acetylenemonocarboxylic acid and acetylenedicarboxylic acid can be accomplished either through the sole participation of the thioamide group, forming a thiazole or thiazine ring, or with the participation of both the thioamide group and the azinium part of the ylide molecule, forming an imidazole ring.

EXPERIMENTAL

PMR spectra were obtained in Tesla-100 (100 MHz) and Bruker WP-80 (80 MHz) instruments in DMSO-d_6, internal standard TMS. The course of the reaction and the individuality of the compounds were monitored by means of TLC on Silufol UV-254 plates in a solvent system consisting of 9:1 chloroform–ethanol (A) or 15:9:1 chloroform–ethanol–ammonia (B). The mass spectra were recorded in a Varian-311A mass spectrometer under standard conditions.

The PMR spectra of the compounds are shown in Table 1.

Elemental analyses of the compounds matched the calculated values.

The thioamides Ia-c were synthesized by procedures given in [8].

1-(4-Oxo-5-carbomethoxymethylenethiazol-2-yl)-1-carbethoxymethylenepyridiniumylide (VIa). To a solution of 0.5 g (2.2 mmoles) of the pyridiniumylide Ia in 30 ml of chloroform, 0.43 g (3 mmoles) of acetylenedicarboxylic ester was added. In 30 min, a precipitate was formed; this was filtered off and crystallized from ethanol. Bright-yellow crystals, yield 36%, mp 290°C (decomp.), R_f (A) 0.74. M^+ 334.

1-(4-Oxo-5-carbomethoxymethylenethiazol-2-yl)-1-N-phenylcarbamoylmethylenepyridiniumylide (VIb). Obtained by analogy with VIa, in acetonitrile. Yellow crystals, yield 22%, mp 270-273°C (decomp.), R_f (B) 0.74. M^+ 381.

1-(4-Oxo-5-carboxymethylmethylenethiazol-2-yl)-1-carboxymethyleneisoquinoliniumylide (VIc). Obtained by analogy with VIa. Reaction time 2 h. Yellow crystals, yield 20%, mp 258-260°C, R_f (A) 0.8. M^+ 384.

1-(4-Oxo-1,3-thiazin-2-yl)-1-carbethoxymethylenepyridiniumylide (VII). To a solution of 0.45 g (0.2 mmole) of the pyridiniumylide Ia in 25 ml of methanol, 0.21 g (2.5 mmoles) of methyl propiolate was added. The reaction mixture was refluxed for 4.5 h. The precipitate was filtered off, treated with ether, and crystallized from methanol. Yellow crystals, yield 15%, mp 230-231°C (decomp.), R_f (B) 0.56. M^+ 276.

2-Methoxycarbonylvinylthio-3-carbethoxyimidazo[1,2-a]isoquinoline (VIII). To a solution of 0.3 g (1.1 mmoles) of the ylide Ic in 20 ml of methanol, 0.13 g (1.6 mmoles) of methyl propiolate was added. The mixture was refluxed for 2.5 h. The precipitate was filtered off and crystallized from methanol. Colorless crystals, yield 15%, mp 130-132°C, R_f (A) 0.77. M^+ 536.

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