ISSN 1070-3632, Russian Journal of General Chemistry, 2009, Vol. 79, No. 3, pp. 500–504. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © B.A. Demidchuk, S.O. Seferov, A.N. Vasilenko, V.S. Brovarets, B.S. Drach, 2009, published in Zhurnal Obshchei Khimii, 2009, Vol. 79, No. 3, pp. 510–514.

Cyclocondensation of 2,2-Dichloroethenylbenzamide and Its Analogs with Amidines and Hydrogen Sulfide in the Presence of Bases

B. A. Demidchuk, S. O. Seferov†, A. N. Vasilenko, V. S. Brovarets, and B. S. Drach

Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 1, Kiev, 02660 Ukraine
e-mail: drach@bpci.kiev.ua

Received July 8, 2008

Abstract—Available chlorine-containing enamides of the general formula Cl_2C=CHNHCOR (**I**) easily react with benzamidine and its derivatives to give 1:1 adducts which under heating with sodium methylate transform to 2-(methoxymethyl)-4,5-diaryl-*s*-triazines. Reaction of compounds (**I**) with hydrogen sulfide in the presence of triethylamine yields a mixture of products. Only the corresponding 3,5-bis(acylaminomethyl)-1,2,4-tritiolanes were isolated from the reaction mixture in moderate yield.

DOI: 10.1134/S1070363209030268

Chlorine-containing enamides **I** presented in the scheme are easily formed from the available adducts of chloral with carboxamides [1, 2]. They were already used for the preparative synthesis of the derivatives of 1,3-oxazole [3], 1,3-thiazole [4, 5], 1,2,4-thiadiazole [6] and fused heterocyclic systems [7].

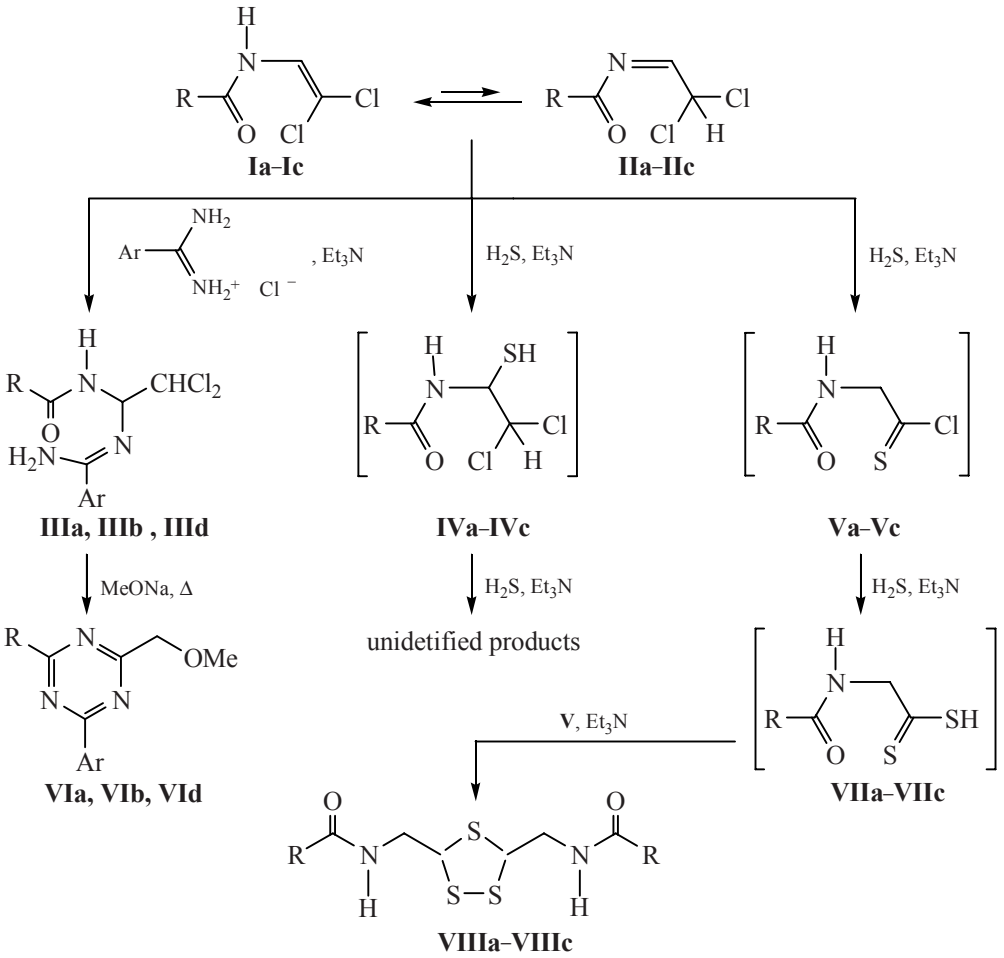
In this work two new applications of reagents **I** for preparing heterocyclic compounds were found (see structures **II–VIII** in the scheme). On the one hand enamides **I** were converted to trisubstituted *s*-triazines **VI**, while on the other hand the unknown previously 3,5-bis(acylaminomethyl)-1,2,4-trithiolanes **VIII** were obtained. An important role in these transformations is played evidently by dichloroacetaldehyde *N*-acylimines **II**, the prototropic tautomers of reagents **I**, which easily react with different nucleophiles [8-10]. Under mild conditions they add various nitrogen-containing bases including amidines. It was shown recently that acetamidine when reacted with the compounds **II** yields the 1:2 adducts. When heated with sodium methylate these substances undergo cyclization to form the new type of 4-functionalyzed oxazoles [11]. At the same time in this study we have found that benzamidine and its nearest analogs in the reaction with compounds **II** give the 1:1 adducts which under treating with sodium methylate yield substituted *s*-triazines **VI** but not the oxazole derivatives.

Introduction of two aryl substituents and the methoxymethyl group in *s*-triazine ring presents the undoubtful interest because many known synthetic procedures for preparing the substituted *s*-triazines cannot be used in this case. But chloromethyl analogs of compounds **VI** were successfully synthesized by condensation of enamides ClCH=C(Ts)NHCOR **IX** with amidines [12]. It was presumable that reagents **IX** might be converted also to compounds **VI**, but this approach is much more complicated than the pathway **II**→**III**→**VI** studied in this work. Absence of these transformations of the N–H bond in the final products was confirmed by the IR spectra, and the presence of the methoxymethyl group in them follows from the ^{1}H NMR data (Table 1).

N-Acylimine tautomers **II** takes up not only various nitrogen-containing bases, but also S-nucleophiles. Thiols and thiophenols in the presence of triethylamine usually give adducts of the general formula Cl_2CHCH·(SR')NHCOR. They were isolated, and their structure was established reliably in [5, 8].

Analogous adducts are also formed evidently in the reaction of tautomers **II** with hydrogen sulfide, but the intermediates **IV** could not be isolated because they quickly transform to other nonidentified compounds.

† Deceased.



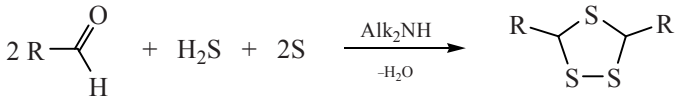
I, II, IV, V, VII, VIII: R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-ClC_6H_4 (**c**). **III, VI**: R = Ar = Ph (**a**), 4-MeC_6H_4 (**b**); R = 4-MeC_6H_4, Ar = 4-BrC_6H_4 (**d**).

Table 1. Spectral data of the compounds synthesized

Comp. no.	IR spectrum, ν, cm^{-1} (KBr)	^1H NMR spectrum, δ, ppm (DMCO-d_6)
IIIa	1650 (C=O), 3200–3350 (NH_{ac})	5.65 m (1H, CH), 6.20 d (1H, $CHCl_2$, ^3J 7.2 Hz), 6.71 br.s (2H, NH_2), 7.34–7.92 m (10H, $2C_6H_5$), 8.99 d (1H, NH, ^{3}– 8.7 Hz)
IIIb	1640 (C=O), 3200–3400 (NH_{ac})	2.34 s (3H, CH_3), 2.35 s (3H, CH_3), 5.62 m (1H, CH), 6.17 d (1H, $CHCl_2$, ^3J 7.2 Hz), 6.66 br.s (2H, NH_2), 7.15–7.82 m (8H, $2C_6H_4$), 8.91 d (1H, NH, ^3J 8.7 Hz)
IIId	1650 (C=O), 1600 (C=N), 3200–3400 (NH_{ac})	2.37 c (3H, CH_3), 5.62 m (1H, CH), 6.18 d (1H, $CHCl_2$, ^3J 7.2 Hz), 6.79 br.s (2H, NH_2), 7.25–7.80 m (8H, $2C_6H_4$), 8.93 d (1H, NH, ^3J 9.0 Hz)
VIa[a]	–	3.66 s (3H, OCH_3), 4.76 s (2H, CH_2), 7.25–8.67 m (10H, $2C_6H_5$)
VIb	1630–1700, 3050–3500 (bands are absent)	2.45 s (6H, $2CH_3$), 3.55 s (3H, OCH_3), 4.65 s (2H, CH_2), 7.39–8.47 m (8H, $2C_6H_4$)
VId	1630–1700, 3050–3500 (bands are absent)	2.43 s (3H, CH_3), 3.53 s (3H, OCH_3), 4.69 s (2H, CH_2), 7.43–8.48 m (8H, $2C_6H_4$)
VIIIa[b]	1640 (C=O), 3250–3380 (NH_{ac})	3.52 m (4H, $2CH_2$), 5.25 d.d (2H, 2CH, ^3J 5.9, ^3J 8.7 Hz), 7.41–7.87 m (10H, $2C_6H_5$), 8.80 t (2H, 2NH, ^3J 5.6 Hz)
VIIIb	1640 (C=O), 3250–3420 (NH_{ac})	2.35 s (6H, $2CH_3$), 3.44 m (4H, $2CH_2$), 5.28 d.d (2H, 2CH, ^3J 7.1, ^3J 8.1 Hz), 7.29–7.77 m (8H, $2C_6H_4$), 8.84 t (2H, 2NH, ^3J 4.6 Hz)
VIIIc	1640 (C=O), 3300–3390 (NH_{ac})	3.46 m (4H, $2CH_2$), 5.28 d.d (2H, 2CH, ^3J 5.9, ^3J 8.1 Hz), 7.57–7.87 m (8H, $2C_6H_4$), 8.98 t (2H, 2NH, ^3J 4.7 Hz)

[a] ^1H NMR spectrum of compound **VIa** was extracted from the spectrum of reaction mixture. [b] Mass spectrum: *m*/*z* 390 $[M]^+$.

Only the unknown previously 3,5-di(acylaminomethyl)-1,2,4-trithiolanes **VIII** were isolated from the reaction mixture in 32–41% yield. Their formation from adducts **IV** can hardly be imagined. It is probable that the important role is played by the intermediates **V** generated by the substitution of one of the chlorine atoms in dichloromethyl fragment of compounds **II** with the mercapto group. The subsequent intermolecular condensation of products **V** and **VII** in the presence of hydrogen sulfide and triethylamine leads to substituted 1,2,4-trithiolanes **VIII**. The possibilty of formation of 1,2,4-trithiolane ring is doubtless because the reactivity of dichloromethyl fragment resembles that of the aldehyde group. It was shown previously [13] that the latter function can be actually converted to trithiolane system under the treatment with hydrogen sulfide and sulfur in the presence of secondary amines.



Intermolecular condensation proceeds also when compounds **II** are reacted with hydrogen sulfide as confirmed by the mass spectral evaluation of molecular mass of products **VIII**. At the same time the presence of two symmetrically located $NHCH_2CH$ groups was shown by ^1H NMR spectra (Table 1). The empirical formula of the substance formed was confirmed reliably by the elemental analyses data (Table 2). Besides, COSY, NOESY, HMOC, and HMBC NMR experiments for compounds **VIII** permitted a complete attribution of ^1H and ^{13}C spectral signals. The attribution of signals of protons and carbon atoms of the $4\text{-}ClC_6H_4C(O)$ and $NHCH_2CH$ fragments is easy. The triplet at δ 8.97 ppm (CONH) and the doublet of doublets at δ 5.26 ppm (CH_2) in the COSY spectrum show only one interaction with the signals at δ 3.50 and δ 3.43 ppm (CH_2) what is confirmed by the sequence of atoms in the $NHCH_2CH$ group. Note that the proton giving signal at δ 5.26 ppm correlates with the carbon atom having δ_C 63.46 ppm in the HMBC spectrum what unambiguously proves the structure of the molecule **VIIIc**. The attributiuon of the carbon atom signal at δ_C 63.46 ppm to the trithiolane fragment agrees with the published data [14].

Consider finally the general stoichiometric equation presented below. It shows that in the course of complex pathway leading to the compounds **VIII** not only nucleophilic substitution of the reactive chlorine atoms by the sulfur-containing groups, but the redox reactions also occur because alongside compounds **VIII** elemental sulfur is formed.

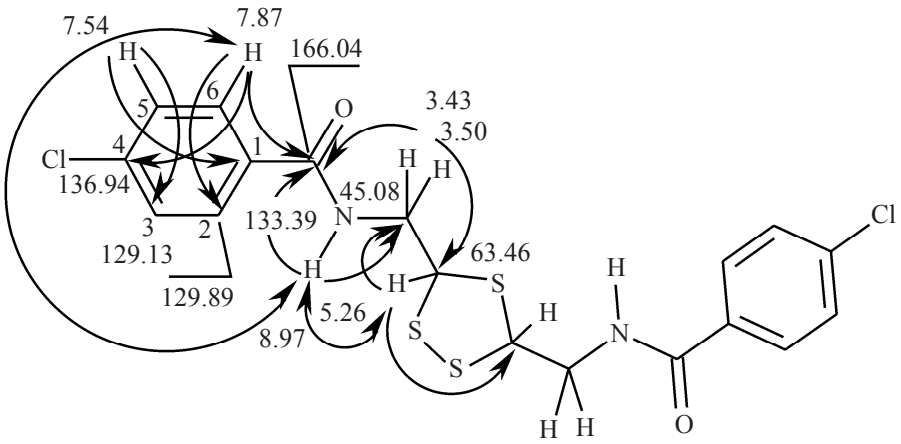
$$2\mathbf{II} + 4\ Et_3N + 4\ H_2S \rightarrow \mathbf{VIII} + 4\ Et_3NH^+\ Cl^- + S.$$

Finally note that the application sphere of the transformations **I→VI** and **I→VIII** is probably much wider than cited in this work.

Table 2. Yields, melting points, and elemental analysis data of the compounds synthesized **III–VIII**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, **%**		Formula	Calculated, **%**	
			Cl (Br)	N		Cl (Br)	N
IIIa	97	145–147[a] (MeOH)	21.17	12.31	$C_{16}H_{15}Cl_2N_3O$	21.09	12.50
IIIb	82	158–159 (MeCN–H_2O, 3:1)	19.40	11.20	$C_{18}H_{19}Cl_2N_3O$	19.46	11.54
IIId	88	155–160 (MeCN)	16.04 (18.95)	9.43	$C_{17}H_{16}BrCl_2N_3O$	16.52 (18.62)	9.79
VIa	85	–[b]	–	13.98	$C_{17}H_{15}N_3O$	–	15.15
VIb	80	104–105 (EtOH)	–	13.71	$C_{19}H_{19}N_3O$	–	13.76
VId	82	125–126 (MeOH)	(21.49)	11.10	$C_{18}H_{16}BrN_3O$	(21.58)	11.35
VIIIa	41[c]	215–216 (MeCOOH)	–	6.81	$C_{18}H_{18}N_2O_2S_3$[d]	–	7.17
VIIIb	32	226–227 (MeCOOH)	–	6.63	$C_{20}H_{22}N_2O_2S_3$[e]	–	6.69
VIIIc	35	235–236 (MeCOOH)	15.98	5.88	$C_{18}H_{16}Cl_2N_2O_2S_3$[f]	15.43	6.10

[a] Corresponds to the reported data [10]. [b] Compound **VIa** was obtained in a mixture with another compounds as a viscous oil. [c] Yield according to the procedure *a*. [d] Found, %: S 25.12. Calculated, %: S 24.63. [e] Found, %: S 23.41. Calculated, %: S 22.98. [f] Found, %: S 20.91. Calculated, %: S 20.94.



Main correlations (shown by arrows) and the attribution of signals (ppm) in the ^{1}H and ^{13}C NMR spectra of compound **VIIIc**.

Meanwhile, our attempts to involve *N*-2,2-dichloroethenylacetamide in this reaction failed.

EXPERIMENTAL

IR spectra of compounds were recorded on a Specord M-80 spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were taken on a Varian Mercury-400 spectrometer in DMSO-d_6 against internal TMS. Mass spectrum of compound **VIIIa** was registered on an Agilent 1100 LC/MSD instrument.

***N*-(1-Benzoylamino-2,2-dichloroethyl)benzamidine (IIIa)** was obtained as described above [10].

***N*-(1-*p*-toluylamino-2,2-dichloroethyl)-4-methylbenzamidine (IIIb)** was obtained analogously to compound **IIIa** from *N*-2,2-dichloroethenyl-4-methylbenzamide **Ib** and 4-methylbenzamidine hydrochloride.

***N*-(1-*p*-Toluylamino-2,2-dichloroethyl)-4-bromobenzamidine (IIId)** was prepared analogously to compound **IIIa** from *N*-2,2-dichloroethenyl-4-methylbenzamide **Ib** and 4-bromobenzamidine hydrochloride.

4,6-Diaryl-2-methoxymethyl-1,3,5-triazines (VIa, VIb, VId). To a solution of 0.005 mol of one of the compounds **IIIa, IIIb,** and **IIId** in 50 ml of anhydrous methanol 0.015 mol of sodium methylate in 5 ml of methanol was added, and the resulting mixture was refluxed for 4 h. The mixture obtained was cooled, NaCl precipitate was filtered off, solvent was removed in a vacuum, and the residue was treated with water. The crystals formed were filtered off, dried in a vacuum desiccator over phosphorus pentoxide, and compounds **VIb** and **VId** were purified by crystallization. For the isolation of compound **VIa** the reaction mixture was treated with water and then extracted with chloroform (3×10 ml), and the extract was dried over magnesium sulfate. Chloroform was removed in a vacuum, and compound **VIa** was isolated together with the impurities as a viscous oil which was analyzed without further purification.

Table 3. List of correlations in the COSY, NOESY, HMQC, and HMBC spectra of compound **VIIIc**[a]

^{1}H NMR spectrum, δ, ppm	^{1}H NMR spectrum, δ, ppm		^{13}C NMR spectrum, δ, ppm	
	COSY	NOESY	HMQC	HMBC
7.54 (C^3H, C^5H)	7.87	7.87	129.13	129.13 (C^3, C^5), 133.39 (C^1)
7.87 (C^2H, C^6H)	7.54	7.54, 8.97	129.89	128.89 (C^2, C^6), 136.94 (C^4), 166.04 (CO)
8.97 (CONH)	3.50, 3.43	7.87, 3.50, 3.43, 5.26	–	166.04 (CO), 45.08 (CH_2)
3.50, 3.43 (CH_2)	5.26, 8.97	5.26, 8.97	45.08	63.46 (CH), 166.04 (CO)
5.26 (CH)	3.50, 3.43	3.50, 3.43, 8.97	63.46	45.08 (CH_2), 63.46 (CH)

[a] Numbering of carbon atoms in the structure **VIIIc** is shown in the figure.

3,5-Di(acylaminomethyl)-1,2,4-trithiolanes (VIIIa–VIIIc). *a*. A mixture of 0.01 mol of one of the compounds **Ia–Ic** and 0.02 mol of triethylamine in 20 ml of diethyl ether was saturated with hydrogen sulfide for 1 h. The precipitate formed was filtered off, washed with 10 ml of acetone, then with 10 ml of water, and dried. Compounds **VIIIa–VIIIc** were purified by crystallization.

b. To a solution of 0.01 mol of compound **Ia** in 20 ml of anhydrous methanol 0.05 mol of sodium hydrosulfide was added, and the mixture formed was stirred for 7 days at 20°C. After that 50 ml of water was added, the precipitate formed was filtered off, washed with 20 ml of ethanol, and compound **VIIIa** was purified by crystallization from acetic acid, yield 33%. The mixed sample of compound **VIIIa** prepared according to the procedures *a* and *b* gave no depression of the melting poimt, and their IR and ^{1}H NMR spectra were identical.

REFERENCES

1. Yelburgi, B.H. and Wheeler, T.S., *J. Indian Chem. Soc*., 1934, no 11, p. 217.
2. Drach, B.S., Brovarets, V.S., and Smolii, O.B., *Sintezy azotsoderzhashchikh geterotsiklicheskikh soedinenii na osnove amidoalkiliruyushchikh agentov* (Syntheses of the Nitrogen-containing Heterocyclic Compounds on the Basis of Amidoalkylating Agents), Kiev: Naukova Dumka, 1992, p. 66.
3. Vinogradova ,T.K., Turov, V.V., and Drach, B.S., *Zh. Org. Khim*., 1990, vol. 26, no. 6, p. 1302.
4. Vinogradova, T.K., Martynyuk, A.P., and Drach, B.S., *Zh. Org, Khim*., 1980, vol. 16, no. 8, p. 1783.
5. Demidchuk, B.A., Brovarets, V.S., and Drach, B.S., *Zh. Org. Farm. Khim*., 2006, vol. 4, no. 1, p. 55.
6. Zyabrev, V.S., Popovich, T.K., Kiselev, V.V., Kisilenko, A.A., Kalinin, V.N., Kharchenko, A.V., and Drach, B.S., *Ukr. Khim. Zh.,* 1995, vol. 61, no. 5, p. 55.
7. Vinogradova, T.K., Drach, B.S., Kukhar', V.P., *Dokl. Akad. Nauk USSR, Ser. B*, 1987, no. 12, p. 37.
8. Mironova, A.N., Zorina, E.F., and Atavin, A.S., *Zh. Org. Khim*., 1972, vol. 8, no. 6, p. 1150.
9. Drach, B.S., Sviridov, E.P., Kisilenko, A.A., and Kirsanov, A.V., *Zh. Org. Khim*., 1973, vo.l 9, no. 9, p. 1818.
10. Vinogradova, T.K., Mis'kevich, G.N., and Drach, B.S., *Zh. Org. Khim*., 1980, vol. 16, no. 9, p. 1869.
11. Demidchuk, B.A., Brovarets, V.S., and Drach, B.S., *Zh. Obshch. Khim*., 2008, vol. 78, no. 2, p. 349.
12. Rudenko, E.A., Kharchenko, A.V., and Drach, B.S., *Ukr. Khim. Zh*., 1992, vol. 58, no. 7, p. 585.
13. Asinger, F., Thiel, M., and Lipfert, G., *Chem. Ber*., 1959, vol. 627, p. 195.
14. Akihiko, I., Takenori, O., Kazuyo, U., and Juzo, N., *Bull. Chem. Soc. Japan*, 2000, vol. 73, no. 3, p. 729.