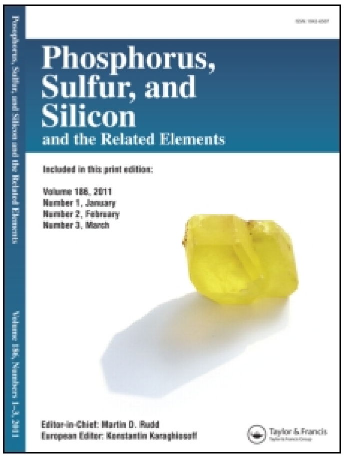

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S,N-Heterocyclic Compounds from 2,2-Dichlorovinyl-Sulfonylacetic Acid and Bifunctional Nucleophiles

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S,N-HETEROCYCLIC COMPOUNDS FROM 2,2-DICHLOROVINYLSULFONYLACETIC ACID AND BIFUNCTIONAL NUCLEOPHILES

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Abstract. Reactions of 2,2-dichlorovinylsulfonylacetic acid with bifunctional nucleophiles such as aminoalcohols, aminothiols, semi- and thiocarbazide, aminoguanide have been studied. A series of thiazolyl-, oxadiazolyl-, triazolyl-, benzimidazolyl-, imidazolyl-, benzox- and benzothioazolylmethyllsulfonylacetic acids, very promising biologically active compounds have been prepared.

INTRODUCTION

Investigation of the properties of heterylsulfonylalkane carboxylic acids and their derivatives which show a wide scope of biological action is hindered due to unavailability of convenient preparatory methods. Most heterocycles are unstable to oxidants, therefore sometimes it is not possible to make use of conventional syntheses, in particular, oxidation reactions, for the preparation of corresponding derivatives with sulfur(IV) or sulfur(VI) atoms.

Continuing our research on the synthesis of biologically active organylthioacetic acid derivatives[1] and with a goal to prepare compounds containing a heterocyclic, sulfonyl and carboxyl fragment, we have synthesized heterylmethylsulfonylacetic acids by reaction of 2,2-dichlorovinylsulfonylacetic acid with arylamines, aminoalcohols, aminothiols, diamines, semi- and thiosemicarbazide, aminoguanidine.

2,2-Dichlorovinylsulfonylacetic acid having several reaction centers such as double bond, carboxylic and sulfonyl groups, labile halogen atoms activated with an electro-negative SO_2 group, can be assigned to the most promising reagents for fine organic synthesis.

Previously it has been shown that 2,2-dichlorovinylalkyl(aryl)sulfones and ketones react with diverse S,N,O-nucleophiles including bifunctional nucleophiles, to form the products of simultaneous substitution of two halogen atoms[2-6].

In order to avoid heterocyclization of the carboxy group[7] we have elaborated a method for the preparation of methyl ester of dichlorovinylsulfonylacetic acid.

The initial thio derivatives were obtained by use of the known developed by us reaction of chlorovinylation of thiols[8]. Dichlorovinylthioacetic acid and its methyl ester were obtained in 79% yield from trichloroethylene, thioglycolic acid or its methyl ester by irradiation with simultaneous boiling of the reagents for 39 hours, the thiol:trichloroethylene ratio being 1 to 4. Further increase in both the amount of trichloroethylene and the reaction time does not affect the yield of end products.

Dichlorovinylsulfonylacetic acid and its methyl ester were prepared by oxidation of the corresponding sulfides with 30% hydrogen peroxide in glacial acetic acid[9].

$$CCl_2{=}CHCl + HSCH_2COOR \xrightarrow{h\nu,\ t} CCl_2{=}CHSCH_2COOR \longrightarrow$$

$$R{=}H\ (I),\ CH_3\ (II) \qquad (1)$$

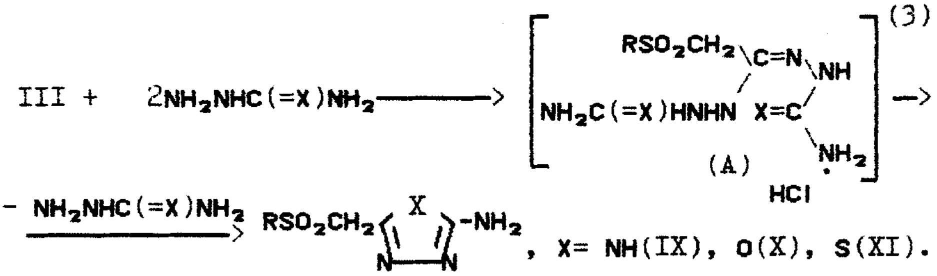
$$\xrightarrow{H_2O_2,\ CH_3COOH} CCl_2{=}CHSO_2CH_2COOR,\ R{=}H(III),\ CH_3(IV)$$

2,2-Dichlorovinylsulfonylacetic acid and its methyl ester are involved in reactions with aromatic amines either with excess amine or in the presence of a dehydrochlorinating agent, triethylamine, to form the corresponding formamidines as the only reaction products.

$$III(IV) + XC_6H_4NH_2 \longrightarrow XC_6H_4NH(XC_6H_4NH{=})CCH_2SO_2CH_2COOH \qquad (2)$$

$$R{=}H,\ X{=}H(V),\ 4\text{-}CH_3(VI),\ 2\text{-}CH_3(VII),\ R{=}CH_3,\ X{=}2\text{-}CH_3O(VIII)$$

The reactions of 2,2-dichlorovinylsulfonylacetic acid and its methyl ester with thiosemicarbazide, semicarbazide and aminoguanidine lead to only one type of products, the derivatives of 1,3,4-thiadiazole, oxadiazole and triazole. The mechanism of the reaction of 2,2-dichlorovinylsulfonylacetic acid with thiosemicarbazide, semicarbazide and aminoguanidine seems to involve a successive substitution of the chlorine atoms in the dichlorovinyl fragment to form salt (**A**) and cyclization of the latter by intramolecular attack of the heteroatom X at the C_β-atom leading to the isolation of the products (IX-XI). The fact that the cyclization involves the atom of sulfur, nitrogen or oxygen, rather than the amino group, to form triazoles is expained by a reduced activity of the amino group in salts (**A**).



A treatment of 2,2-dichlorovinylsulfonylacetic acid with equimolar quantity of o-phenylenediamine at 20^o for 1 hour leads to dihydrochloride of {[(2,3-dihydrobenzimidazol-2-ylidene)-methyl]sulfonyl}acetic acid (XII).

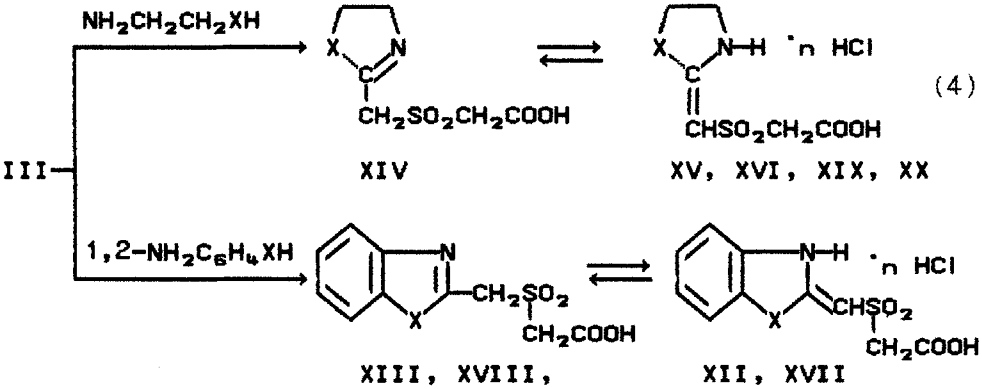
In order to prove the structure of (XII) this compound was treated with two-fold excess of 5% aqueous NaCO$_3$. The reaction was carried out with pH monitoring until CO$_2$ stopped liberating. When the mixture was allowed to stand for a long time the acid (XIII) precipitated.

It has been shown that HCl abstraction causes tautomerization of the acid (XII) to (benzimidazol-2-yl)methylsulfonylacetic acid and this is supported by ^{1}H NMR spectroscopy.

In order to increase the yield of (benzimidazol-2-yl)-methylsulfonylacetic acid and to reduce the reaction time, the reaction of 2,2-dichlorovinylsulfonylacetic acid with o-phenylenediamine was carried out in ether in the 1:1 ratio of the initial reagents in the presence of triethylamine as a dehydrochlorinating agent. The reaction proceeded exothermally and after stirring the boiling reaction mixture for 0.5 h the benzimidazol-2-yl)methylsulfonylacetic acid (XIII) was isolated in 76% yield.

When the reaction of 2,2-dichlorovinylsulfonylacetic acid with ethylenediamine was carried out in ether at 20-22°C in the 1:1 ratio of reagents, it was possible to isolate and separate by fractional recrystallization {[(2,3,4,5-tetrahydroimidazole-2-ylidene)methyl]sulfonyl}-acetic acid (XIV) and of its structural isomer,hydrochloride {[(4,5-dihydroimidazol-2-yl)methyl]sulfonyl}acetic acid (XV). A temperature decrease to 10-12°C in the reaction of 2,2-dichlorovinylsulfonylacetic acid with ethylenediamine leads to only one product, dihydrochloride (XVI) in a yield up to 80%

At the same time, a change in the ratio of reagents to 1:2 leads to a mixture of imidazoline dihydrochlorides (XVI) and hydrochlorides (XV) and ethylenediamine.



(4)

X=NH, n=2(XII), X=NH(XIII); X=NH (XIV); X=NH, n=1 (XV);X=NH n=2(XVI); X=S, n=0 (XVII); X=O (XVIII); X=O (XIX); X=S (XX).

After stirring for 3-4 h of 2,2-dichlorovinylsulfonyl acetic acid with o-aminothiophenol and o-aminophenol at 70-75°C the corresponding acids (XVII, XVIII) were isolated in various tautomeric forms. Whereas the reaction of 2,2-dichlorovinylsulfonylacetic acid with o-aminothiophenol gave the benzothiazol-2-yl)methylsulfonylacetic acid (XVII), the reaction with o-aminophenol afforded {[(3,4- dihydrobenzoxazol-2-yl)methylene]sulfonyl}acetic acid (XVIII).

The reaction of 2,2-dichlorovinylsulfonylacetic acid with ethanolamine and mercamine was carried out also by heating to 70-75°C in alcohol. Due to close solubilities of the reaction products on the one hand and ethanolamine and mercamine hydrochlorides on the other hand, the corresponding acids could not be isolated; however, the formation of these products was fixed by appearance of the corresponding signals in the ^{1}H NMR spectra of reaction mixtures.

No products of heterocyclization involving carboxyl groups of 2,2-dichlorovinylsulfonylacetic acid were isolated under all the reaction conditions studied.

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TABLE Physicochemical data of compounds obtained

№	Yield (%)	Melting point (^{o}C)	^{1}H NMR in DMSO-d_6 δ (ppm)
II	71	(bp 138–141/3 mm)	3.75 (OCH_3), 3.79 (SCH_2), 6.51 (=CH)
IV	82	(bp 143–145/3 mm)	3.79(OCH), 4.20(SO_2CH_2), 7.04(=CH)
V	45	145–147	3.83 (CH_2SO_2), 4.48 (CH_2COO), 7.12–7.33 m (Ar), 7.58 (NH), 10.40 (OH)
VI	47	164–166	4.49 (CH_2COO), 7.46 (NH), 10.19 (COOH).
VII	50	158–160	3.65 (CH_2SO_2), 4.72 (CH_2COO), 7.00–7.31 m (Ar), 8.04 (NH), 9.78 (OH)
VIII	66	76–78	3.57 (CH_2SO_2), 4.23 (CH_2COO), 6.66–6.92 m (Ar), 8.12 (NH).
IX	55	149–151	4.70 (CH_2SO_2), 4.53 (CH_2COO), 7.27 (NH_2).
X	45	129(dec.)	4.37 (CH_2SO_2), 4.18 (CH_2COO), 7.25 (NH_2).
XI	75	190–192	4.96 (CH_2SO_2), 4.35 (CH_2COO), 7.35 (NH_2).
XII	84	135–137	4.43 (CH_2COO), 6.63 m (Het), 7.75 (=$CHSO_2$),
XIII	76	192–194	5.02 (CH_2SO_2), 4.54 (CH_2COO), 7.58–7.30 m (Het), 9.65 (NH).
XV	45	153–157	3.48 (CH_2SO_2), 3.07 (CH_2COO), 3.97 m (Het), 7.89 (NH).
XVI	80	121-124	3.05(CH_2COO), 7.41 (=$CHSO_2$), 2.87 m (Het).
XVII	56	282–283	4.67 (CH_2COO), 7.92 (=$CHSO_2$), 6.93 m (Het), 9.69 (NH).
XVIII	95	199–201	5.33 (CH_2SO_2), 4.31 (CH_2COO), 8.15 m 7.59 m (Het).