Russian Journal of General Chemistry, Vol. 71, No. 11, 2001, pp. 1734–1736. Translated from Zhurnal Obshchei Khimii, Vol. 71, No. 11, 2001, pp. 1830–1832.
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Phosphonium Ylides Stabilized with Cyano Group and 5-Acylamino-4-phenyl-2-thiazolyl Residue

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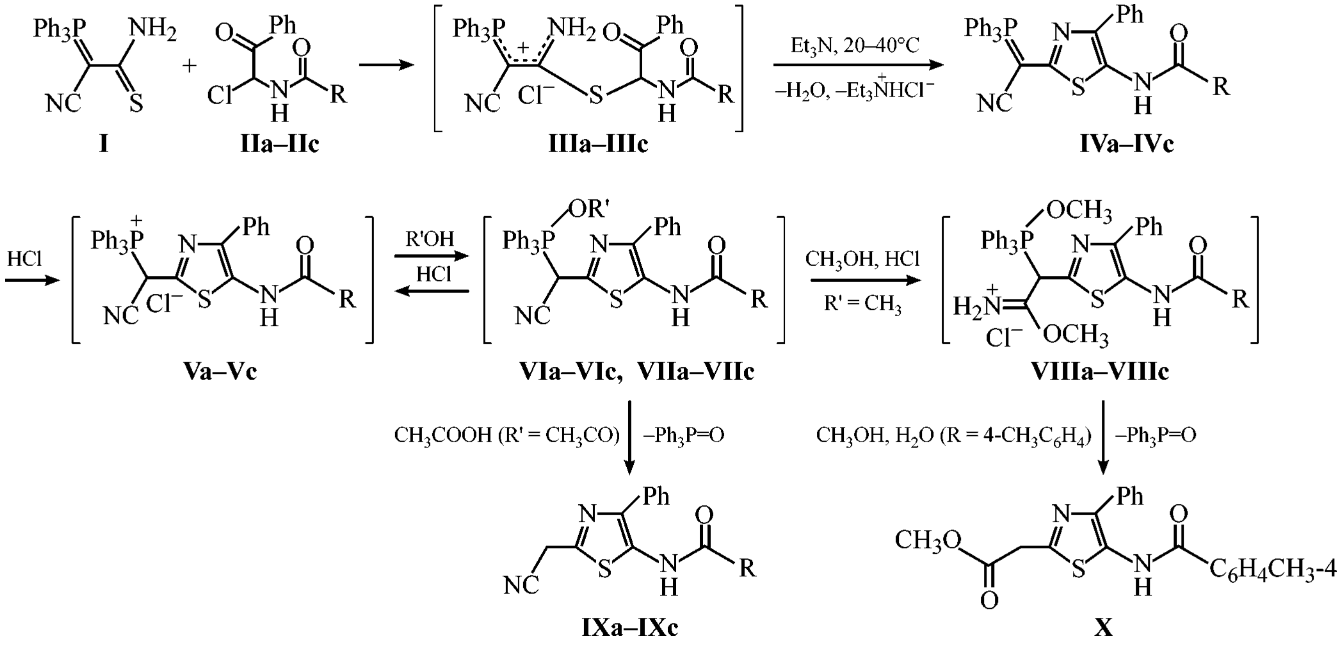
Received June 21, 2000

Abstract—Available ylide reagent $Ph_3P=C(CN)C(S)NH_2$ readily enters cyclocondensation with *N*-(chlorophenacyl)benzamide and its analogs. By this route were prepared new stabilized phosphonium ylides containing cyano group and the corresponding 5-acylamino-4-phenyl-2-thiazolyl fragment. All these compounds even under standard conditions are dephosphorylated under the action of hydrogen chloride in acetic acid to form 5-acylamino-4-phenyl-2-cyanomethylthiazoles in high yields. Their structure was proved by spectroscopic studies and independent synthesis.

Recently we have developed a convenient procedure for preparing a series of *C*-thiocarbamoyl-substituted phosphonium ylides of the general formula $Ph_3P=C(X)C(S)NH_2$ [1]. The most important of them is triphenylphosphoranylidenecyanothioacetamide **I**, which readily reacts with methyl chloroacetate and chloroacetonitrile [1]. In this work we found that reagent **I** under mild conditions enters cyclocondensation with available polyfunctional electrophilic substrates **II** containing the characteristic COCHClNHCO group.



$R = C_6H_5$ (**a**), $4\text{-}CH_3C_6H_4$ (**b**), $4\text{-}ClC_6H_4$ (**c**); $R' = CH_3CO$ (**VI**), CH_3 (**VII**).

As the chlorine in this group is very labile [2], it can be suggested that initially intermediate acyclic products **III** are formed, which under the action of triethylamine and insignificant heating undergo Hansch cyclization to form previously unknown stable phosphonium ylides of the thiazole series **IV**, stabilized by the nitrile group and the corresponding 5-acylamino-4-phenyl-2-thiazolyl residue. The presence of the cy-

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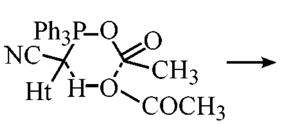
ano group and amide bond in compounds **IV** was proved by IR spectroscopy (see Experimental). Furthermore, their structure was finally confirmed in experiments on their dephosphorylation, which occurs under mild conditions when treating solutions of compounds **IV** in acetic acid or methanol with hydrogen chloride. Most probably, the initial protonation of the ylide center of compounds **IV** gives tertiary phosphonium salts **V**, which, in turn, are evidently related to phosphorane structures **VI**–**VIII**. Further stabilization of such structures by elimination of triphenylphosphine oxide has some analogs [3] and seems quite possible. In particular, phosphoranes **VI** must exhibit strong acylating power, and their reaction with acetic acid can proceed through the cyclic transition state of type **A**.



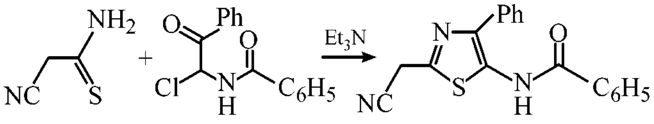
A

+ $Ph_3P{=}O$ + $(CH_3CO)_2O$

Ht = 5-acylamino-4-phenylthiazol-2-yl.

It is not appropriate to discuss in detail the alternative mechanisms of transformations **VI** → **IX** and **VII** → **VIII** → **X** without additional experimental data. Note only that in formation of substituted phosphoranes **VI** and **VII** an important role may be played not only by tertiary phosphonium salts **V**, but also by the related phosphoranes of the general formula $Ph_3P(Cl)CH(CN)Ht$, which under the action of acetic acid or methanol must be converted to intermediates **VI** and **VII**. It is interesting that the P–C bond is cleaved not only in anhydrous acetic acid when passing thoroughly dried hydrogen chloride, but also on addition of phosphorus trichloride, phosphorus oxychloride, or acetyl chloride. At the same time, no dephosphorylation occurs in a mixture of acetic acid and acetic anhydride in the absence of hydrogen chloride.

Finally, it cannot be ruled out that intermediates **VII** first undergo dephosphorylation, which is followed by conversion of the cyano group to the methoxycarbonyl group. Thus, the stages of transformations of ylides **IV** presented in the scheme cannot be regarded as the only possible, but the structure of dephosphorylation products **IX** and **X** is doubtless, because the presence of the methylene group in them was proved by the ^1H NMR spectra (see Experimental), and one of these substituted thiazoles was prepared by an independent procedure.



XI **IXa**

The possible applications of this convenient method for dephosphorylation of ylides stabilized with heterocyclic fragments will be considered in subsequent papers.

EXPERIMENTAL

The IR spectrum of **IVa** was recorded on a UR-20 spectrometer in KBr pellets, and that of **X**, on a Specord IR-71 spectrometer (0.1 M CH_2Cl_2 solution). The ^1H NMR spectra of **IXa**–**IXc** and **X** were measured on a Varian VXR-300 spectrometer relative to TMS. The constants, yields, and elemental analyses of **IV**, **IX**, and **X** are given in the table.

5-Acylamino-4-phenylthiazol-2-yl(cyano)methylenetriphenylphosphoranes IVa–**IVc.** Compound **I** [1], 0.01 mol, and 0.01 mol of triethylamine were added to a suspension of 0.01 mol of **IIa**–**IIc** in 30 ml

Constants, yields, and elemental analyses of new thiazole derivatives

Comp. no.	Yield, %	mp, °C (solvent for recrystallization)	Found, %			Formula	Calculated, %		
			H (S)	C (P)	N		H (S)	C (P)	N
IVa	71	178–180 dec. (acetonitrile)	(5.59)	(5.61)	7.34	$C_{36}H_{26}N_3OPS$	(5.34)	(5.53)	7.25
IVb	69	190–192 dec. (ethanol)	(5.01)	(5.32)	7.25	$C_{37}H_{28}N_3OPS$	(5.22)	(5.40)	7.08
IVc	76	210–211 dec. (acetonitrile)	(5.25)	(5.41)	7.02	$C_{36}H_{25}ClN_3OPS$	(5.04)	(5.22)	6.84
IXa	82[a]	196–197 (ethanol)	67.67	3.94	13.10	$C_{18}H_{13}N_3OS$	67.69	4.10	13.16
IXb	86[a]	193–194 (acetonitrile)	68.58	4.70	12.81	$C_{19}H_{15}N_3OS$	68.45	4.53	12.60
IXc	85[a]	192–193 (acetonitrile)	61.18	3.56	11.71	$C_{18}H_{12}ClN_3OS$	61.10	3.42	11.88
X	72	126–127 (ethanol)	65.59	5.03	7.81	$C_{20}H_{18}N_2O_3S$	65.56	4.95	7.64

[a] Yields of **IVa–IVc** in procedure *b*.

of anhydrous acetonitrile. The mixture was heated to 40°C until a clear solution formed, and then it was left for 24 h at 20°C. The resulting precipitate was filtered off, washed with acetonitrile (5 ml) and water (2 × 20 ml), and recrystallized. IR spectrum of **IVa**, ν, cm^{-1}: 1670 (C=O), 2150 (C≡N), 3390 (NH$_{assoc}$).

5-Acylamino-4-phenyl-2-cyanomethylthiazoles IXa–IXb. *a*. A suspension of 0.001 mol of **IVa**–**IVc** in 10 ml of anhydrous acetic acid (double-distilled from P_2O_5) was saturated with dry hydrogen chloride for 20 min. The resulting precipitate was filtered off, washed with 1 ml of anhydrous acetic acid, and recrystallized. Yields of **IXa**–**IXc** 80–85%. IR spectrum of **IXa**, ν, cm^{-1}: 1670 (C=O), 2270 (C≡N), 3350 (NH$_{assoc}$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: **IXa**: 4.55 s (2H, CH_2), 7.37–7.98 m (10H, $2C_6H_5$), 10.96 s (1H, NH); **IXb**: 2.39 s (3H, CH_3), 4.55 s (2H, CH_2), 7.37–7.87 m (9H, C_6H_5, C_6H_4), 10.88 s (1H, NH); **IXc**: 4.56 s (2H, CH_2), 7.39–7.97 m (9H, C_6H_5, C_6H_4), 11.07 (1H, NH).

b. To a solution of 0.001 mol of **IVa**–**IVc** in 10 ml of glacial acetic acid was added 0.002 mol of acetyl chloride. The resulting mixture was left for 20 min at 20–25°C, and the resulting precipitate was filtered off and recrystallized. Phosphorus trichloride, tribromide, or oxychloride can be used instead of acetyl chloride. Yields of **IXa**–**IXc** are approximately the same as in the case of acetyl chloride. Mixed samples of compounds obtained by procedures *a* and *b* gave no depression of the melting point. The identity of the compounds obtained by procedures *a* and *b* was also proved by TLC and ^{1}H NMR spectra.

c. To a solution of 0.002 mol of compound **IIa** in 10 ml of anhydrous THF was added 0.002 mol of thiocyanoacetamide [4]. The reaction mixture was kept for 24 h at 20–25°C, and the resulting precipitate was filtered off, washed with 2 ml of THF, and dissolved in 10 ml of methanol. Triethylamine, 0.003 mol, was added, and the mixture was refluxed for 15 min and left for 2 h at 20–25°C. The resulting precipitate was filtered off and recrystallized from ethanol; yield 79%. A mixed sample of 5-benzoylamino-4-phenyl-2-cyanomethylthiazole **IXa** obtained by procedures *a* and *b* gave no depression of the melting point.

2-Methoxycarbonylmethyl-5-*p*-toluylamino-4-phenylthiazole X. A suspension of 0.002 mol of **IVb** in 10 ml of absolute methanol was saturated with anhydrous hydrogen chloride for 20 min. The resulting precipitate was quickly filtered off and kept in a water-jet-pump vacuum for 30 min. Then it was suspended in 5 ml of methanol, 5 ml of water was added, and the mixture was kept for 1 h at 20°C. The resulting precipitate was filtered off, washed with water, and recrystallized. IR spectrum, ν, cm^{-1}: 1675 (C=O), 1750 (C=O), 3420 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.43 s (3H, CH_3), 3.78 s (3H, OCH_3), 4.07 s (2H, CH_2), 7.28–7.70 m (9H, C_6H_5, C_6H_4), 8.67 s (1H, NH).

ACKNOWLEDGMENTS

The study was carried out in the framework of INTAS grant no. 96-1115 under the guidance of Prof. G. Reiners (Louvain-la-Nueve Catholic University, Belgium) to whom the authors express their gratitude.

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