Vinamidinium salts of *N*-substituted aminoacetic acids

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Formylation of *N*-phthaloylglycine with the $POCl_3$—DMF system afforded *N*,*N*,*N*′,*N*′-tetramethyl-2-(*N*-phthaloyl)vinamidinium perchlorate (**2**). X-ray diffraction study showed that molecule **2** is planar and contains two equivalent nitrogen atoms in the three-carbon vinamidinium fragment. Salt **2** undergoes transamination with primary aromatic amines to give the corresponding bis-azomethines. The reactions with hydrazines produce substituted 4-aminopyrazoles.

Key words: Vilsmeier—Haack reaction, *N*,*N*,*N*′,*N*′-tetramethyl-2-(*N*-phthaloyl)vinamidinium perchlorate, X-ray diffraction study, hindered rotation, synthesis, 4-salicylideneaminopyrazole.

Monosubstituted acetic acids can undergo formylation in the reactions with the Vilsmeier—Haack reagent ($POCl_3$, DMF).[1—4] The unique structures and high reactivity of the resulting salts,[5] whose alkaline hydrolysis affords the three-carbon dicarbonyl fragment, made it possible to synthesize numerous previously unknown compounds and study in detail their structures and chemical properties. The latter compounds, in turn, can form bischelate[6] and macrocyclic molecules[7] and polymeric vinamidines.[5]

The ability of the carboxymethyl group that is directly bound to the nitrogen atom to be involved in the Vilsmeier—Haack reaction was studied for *N*-methyl-, *N*-benzyl-, and *N*-phenyl-substituted glycine derivatives.[8] More recently,[9—10] formylation of various *N*-hetaryl-substituted aminoacetic acids was documented. These investigations substantially extended the scope of the Vilsmeier—Haack reaction. In particular, it became possible to prepare new heterocyclic systems with complex structures.

Studies of the reaction of glycine hydrochloride[8] and *p*-aminophenylacetic acid[5] demonstrated that the free amino group is subjected to formylation along with the methylene group. This substantially narrows the scope of the Vilsmeier—Haack reaction as applied to compounds containing the free amino group.

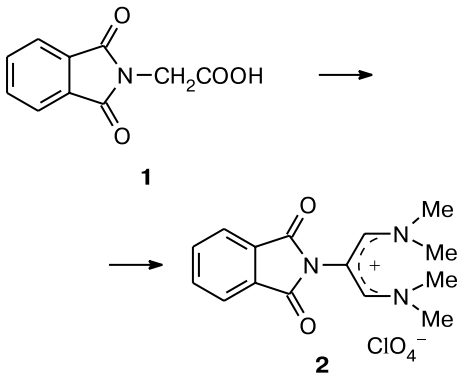
In chemistry of amino acids and peptides, the phthaloyl protecting group is widely used to protect the active amino group. This protective group can easily be removed by treatment with hydrazine hydrate.[11]

In this connection, it was of interest to study formylation of *N*-phthaloyl-substituted glycine and investigate the chemical properties of the resulting salt.

Results and Discussion

We carried out the reaction of the Vilsmeier—Haack reagent ($POCl_3$/DMF, prepared at −5 °C)[2] with *N*-phthalylglycine (**1**).[12] The reaction conditions chosen were similar to those used[1,13] for formylation of phenylacetic acids.

Scheme 1



Reagents and conditions: 1) $POCl_3$/DMF, 90 °C, 25 h; 2) $HClO_4$.

N,*N*,*N*′,*N*′-Tetramethyl-2-(*N*-phthaloyl)vinamidinium perchlorate (**2**) was isolated in individual state after

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the addition of an equimolar amount of perchloric acid to the reaction mixture. The yield of salt **2** was ~40% (white crystalline product).[14] The structure of compound **2** was established by X-ray diffraction.

The vinamidinium fragment of molecule **2** is planar. In the crystal structure, this fragment exists in the open form. The bond length distribution in the vinamidinium fragment is indicative of delocalization of the positive charge between two equivalent nitrogen atoms and is consistent with the data published in the literature.[15—17] The angle between the planes of the phthalimide ring and the vinamidinium fragment is 96.8°, which minimizes steric interactions between these fragments.

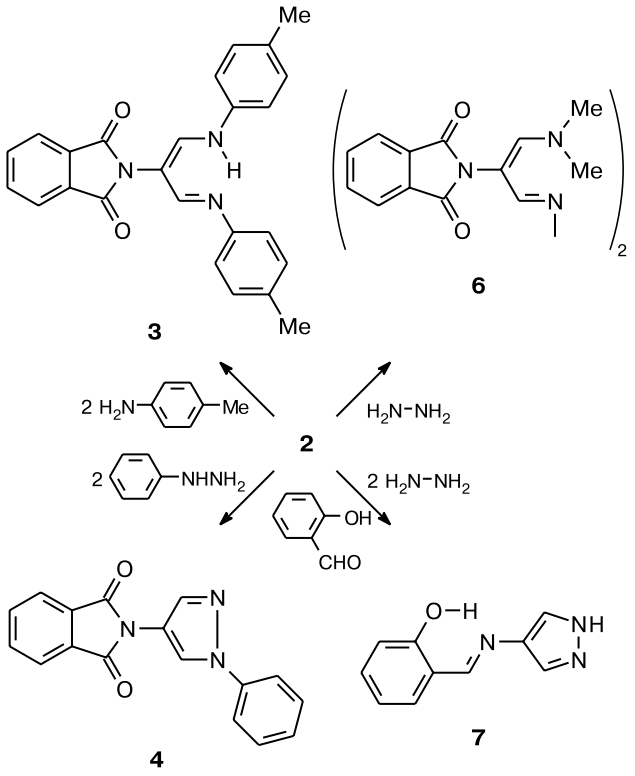
Due to delocalization of the positive charge in the vinamidinium fragment of salt **2** and the planar structure of the resulting cation, pairs of the signals of the methyl groups are nonequivalent and appear as two singlets at δ 2.9 (6 H) and 3.3 (6 H) in the ^{1}H NMR spectrum (D_2O) of **2**.

Investigation of the temperature dependence of the signals of the methyl groups in the ^{1}H NMR spectrum allowed us to estimate the activation parameters of hindered rotation of the *N*-dimethyl fragments. In DMSO-d_6, $\Delta S^{\neq} = -91.1\pm5.2$ J (K mol)$^{-1}$; $\Delta H^{\neq} = 46.7\pm1.8$ kJ mol^{-1}; $\Delta G^{\neq}_{298} = 82.5\pm0.3$ kJ mol^{-1}; $k_{298} = 0.69$ s^{-1}.

Study of the chemical properties of salt **2** demonstrated that this compound can be subjected to transamination.[6] The reaction of salt **2** with two moles of *p*-toluidine produces *N*-[2-phthalimido-3-(*p*-tolylimino)prop-1-enyl]-*p*-toluidine (**3**), and the reaction of this salt with two moles of phenylhydrazine affords 1-phenyl-4-phthalimidopyrazole (**4**). The reaction of bis-azomethine **3** with zinc acetate gives a chelated zinc(II) compound whose coordination unit includes four nitrogen atoms. This assumption agrees well with the ^{1}H NMR spectrum of zinc *N*-[2-phthalimido-3-(*p*-tolylimino)prop-1-enyl]-*p*-toluidinate (**5**), in which the signal for the NH proton at δ 8.6 is absent and the appearance of signals in the aromatic proton region (at δ 6.9—7.9) differs from that observed in the spectrum of ligand **3**.

The reaction of compound **2** with an equimolar amount of hydrazine affords 1,8-bis(dimethylamino)-2,7-bisphthalimido-4,5-diazaocta-1,3,5,7-tetraene (**6**) as a result of transamination of only one *N*-dimethylamino group.

Virtually all known procedures for the synthesis of 4-aminopyrazoles are based on reduction of the corresponding nitro derivatives.[18] However, this method is applicable only to the synthesis of a narrow range of 4-aminopyrazoles. This is due to the fact that nitration of the pyrazole ring can be performed only under severe conditions, because the pyrazolium cation generated in the first step of the reaction hinders subsequent electrophilic attack.[19]



In this connection, the ability of compound **2** to be involved in Ing—Manske's reaction[20] (removal of the phthaloyl protecting group) with two moles of hydrazine is, in our opinion, very promising. The resulting 4-aminopyrazole was identified by the reaction with salicylaldehyde giving rise to 4-salicylideneaminopyrazole (**7**).

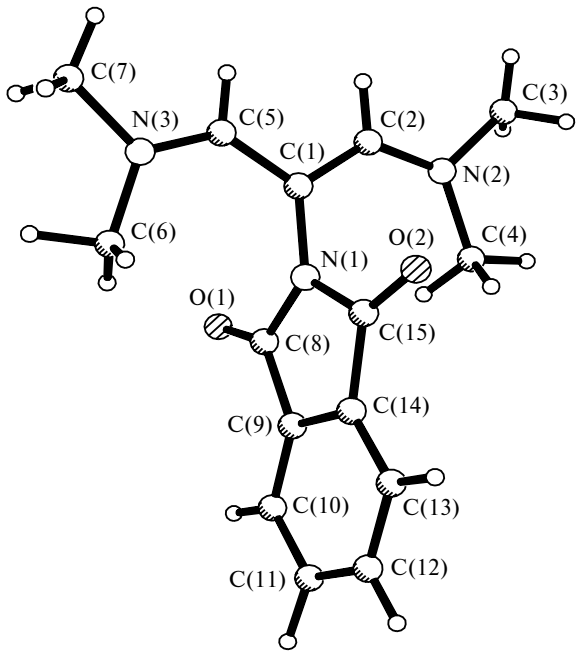


Fig. 1. Molecular structure of salt **2**.

The ^{1}H NMR spectrum ($CDCl_3$) of azomethine **7** shows an averaged broadened signal for the NH protons (at δ 7.8) of the five-membered heterocyclic ring due to a fast (at room temperature) intermolecular exchange between the hydrogen atom of the NH bond and the nitrogen atom of the adjacent molecule, resulting in the equivalence of the nitrogen atoms of the pyrazole ring.[21]

To conclude, we demonstrated that *N*-phthaloylglycine can be subjected to Vilsmeier—Haack formylation with the involvement of the carboxymethyl group. The resulting vinamidinium cation can react with primary aromatic amines and hydrazines to form bis-azomethines and substituted 4-aminopyrazoles, respectively. Formylation of amino acids at the carboxy group provides a new approach to the synthesis of complex heterocyclic compounds, including nitrogen macroheterocycles and metal complexes on their basis. The latter compounds are widely used as catalysts.[22]

Experimental

The ^{1}H NMR spectra were recorded on a Varian Unity-300 instrument operating at 300 MHz using $SiMe_4$ as the internal standard with an accuracy of 0.01 ppm. The IR spectra were measured on a Specord-75IR spectrometer in Nujol mulls. Column chromatography was performed on L 5/40 μ silica gel (Chemapol, Czech Republic). The course of the reactions was monitored and the purity of the reaction products was checked by TLC on Silufol plates (visualization with iodine vapor).

Formylation was carried out with the use of purified DMF and freshly distilled $POCl_3$. 1,8-Bis(dimethylamino)-2,7-bisphthalimido-4,5-diazaocta-1,3,5,7-tetraene (**6**) was prepared with the use of hydrazine hydrate (98%) purchased from Lancaster. *N*-Phthaloylglycine was prepared in toluene in the presence of triethylamine according to a known procedure.[12]

The unit cell parameters were determined and the three-dimensional X-ray data set was collected from poor-quality white transparent single crystals on an automated four-circle KM-4 diffractometer (Kuma Diffraction, MoKα radiation, graphite monochromator); a = 11.291(2) Å, b = 10.330(2) Å, c = 15.227(3) Å, β = 103.57(3)°, space group $P2_1/c$.

Table 1. Interatomic distances (d) in compound **2**

Bond	d/Å	Bond	d/Å
N(1)—C(8)	1.407(3)	C(9)—C(10)	1.379(3)
N(1)—C(15)	1.410(3)	C(9)—C(14)	1.397(3)
N(1)—C(1)	1.420(3)	C(10)—C(11)	1.384(4)
C(1)—C(2)	1.400(3)	C(11)—C(12)	1.392(4)
C(1)—C(5)	1.405(3)	C(12)—C(13)	1.379(3)
C(2)—N(2)	1.311(3)	C(13)—C(14)	1.389(3)
N(2)—C(4)	1.456(4)	C(14)—C(15)	1.477(3)
N(2)—C(3)	1.468(3)	C(15)—O(2)	1.191(3)
C(5)—N(3)	1.310(3)	Cl—O(3)	1.368(3)
N(3)—C(7)	1.466(4)	Cl—O(6)	1.371(4)
N(3)—C(6)	1.476(4)	Cl—O(4)	1.408(3)
C(8)—O(1)	1.207(3)	Cl—O(5)	1.425(4)
C(8)—C(9)	1.478(3)		

The intensities of 3652 reflections were measured in the angle range θ ≤ 27° using the ω/2θ scanning technique. The systematic absences were excluded and the intensities of the equivalent reflections were merged, after which the measured $F^2(hkl)$ set contained 3511 independent reflections, and these reflections were used in subsequent calculations. The structure was solved by direct methods and refined anisotropically by the full-matrix least-squares method against F^2 with the use of the SHELXL-97 program package[23] to R = 6.26%. The interatomic distances and the bond angles are given in Tables 1 and 2, respectively.

***N*,*N*,*N*′,*N*′-Tetramethyl-2-(*N*-phthaloyl)vinamidinium perchlorate (2).** Phosphorus oxychloride (28 mL, 0.3 mol) was added dropwise with stirring and ice-salt cooling to DMF (39 mL, 0.5 mol) at a rate such that the temperature in the flask was maintained no higher than −5 °C. The solution was stirred for 30 min, and then *N*-phthaloylglycine (20 g, 0.1 mol) was added. The reaction mixture was stirred at 90 °C for 25 h and then poured onto ice. The precipitate of the starting *N*-phthaloylglycine that formed was filtered off and washed with a small amount of cold water. Then 57% $HClO_4$ (12 mL, 0.1 mol) was added to the mother liquor and the reaction mixture was kept at 0 °C for 2—3 h. The white crystals that formed were filtered off,

Table 2. Bond angles (ω) in compound **2**

Angle	ω/deg	Angle	ω/deg	Angle	ω/deg
C(8)—N(1)—C(15)	112.2(2)	C(5)—N(3)—C(6)	125.3(2)	C(13)—C(14)—C(9)	121.0(2)
C(8)—N(1)—C(1)	124.5(2)	C(7)—N(3)—C(6)	115.3(3)	C(13)—C(14)—C(15)	130.2(2)
C(15)—N(1)—C(1)	123.1(2)	O(1)—C(8)—N(1)	124.3(2)	C(9)—C(14)—C(15)	108.9(2)
C(2)—C(1)—C(5)	115.0(2)	O(1)—C(8)—C(9)	130.2(2)	O(2)—C(15)—N(1)	124.4(2)
C(2)—C(1)—N(1)	122.5(2)	N(1)—C(8)—C(9)	105.4(2)	O(2)—C(15)—C(14)	130.5(2)
C(5)—C(1)—N(1)	122.4(2)	C(10)—C(9)—C(14)	121.2(2)	N(1)—C(15)—C(14)	105.0(2)
N(2)—C(2)—C(1)	130.5(2)	C(10)—C(9)—C(8)	130.5(2)	O(3)—Cl—O(6)	110.7(4)
C(2)—N(2)—C(4)	126.3(2)	C(14)—C(9)—C(8)	108.3(2)	O(3)—Cl—O(4)	107.0(2)
C(2)—N(2)—C(3)	119.6(2)	C(9)—C(10)—C(11)	117.3(2)	O(6)—Cl—O(4)	109.7(3)
C(4)—N(2)—C(3)	114.1(2)	C(10)—C(11)—C(12)	122.1(2)	O(3)—Cl—O(5)	112.5(3)
N(3)—C(5)—C(1)	131.5(2)	C(13)—C(12)—C(11)	120.4(3)	O(6)—Cl—O(5)	105.0(2)
C(5)—N(3)—C(7)	119.4(3)	C(12)—C(13)—C(14)	118.1(2)	O(4)—Cl—O(5)	111.9(2)

washed with cold water, and recrystallized from 50% aqueous MeOH. Salt **2** was obtained in a yield of 13 g (0.035 mol, 35%), m.p. 245—246 °C. Found (%): C, 48.56; H, 4.82; Cl, 9.39; N, 11.28. $C_{15}H_{18}ClN_3O_6$. Calculated (%): C, 48.52; H, 4.85; Cl, 9.43; N, 11.32. ^{1}H NMR (D_2O), δ: 2.9 (s, 6 H, 2 NMe); 3.3 (s, 6 H, 2 NMe); 7.8 (s, 2 H, CH azometh.); 8.0 (dm, 4 H, arom.). IR (Nujol mulls), ν/cm^{-1}: 1780 (C=O), 1600 (C=N), 1100 br (ClO_4^-), 1710 (C=O).

***N*-[2-Phthalimido-3-(*p*-tolyl)prop-1-enyl]-*p*-toluidine (3).** A mixture of perchlorate **2** (556 mg, 1.5 mmol), *p*-toluidine (321 mg, 3 mmol), and triethylamine (0.21 mL, 1.5 mmol) was refluxed in MeOH (100 mL) for 3 h. The yellow precipitate that formed was filtered off and washed with hot MeOH (2×25 mL). The mother liquor was refluxed for 3 h, concentrated, and cooled. The yellow precipitate that formed was filtered off and washed with hot methanol (2×25 mL). The combined precipitates were dried in a drying oven at 40—50 °C. Toluidine **3** was obtained in a yield of 0.495 g (1.25 mmol, 85%), m.p. 275 °C. Found (%): C, 76.02; H, 5.26; N, 10.57. $C_{25}H_{21}N_3O_2$. Calculated (%): C, 75.95; H, 5.31; N, 10.63. ^{1}H NMR ($CDCl_3$), δ: 2.3 (s, 6 H, 2 Me); 7.2 and 7.4 (both d, 4 H each, arom. toluid., J = 8.3 Hz); 7.7 (d, 2 H, arom. phthal., J = 7.5 Hz); 7.9 (d, 2 H, arom. phthal., J = 7.5 Hz); 8.6 (s, 2 H, CH azometh.). IR (Nujol mulls), ν/cm^{-1}: 3170 br. (NH), 1710 (C=O), 1680 (C=O), 1610 (C=N), 1580 (C=C).

1-Phenyl-4-phthalimidopyrazole (4). A mixture of perchlorate **2** (742 mg, 2 mmol), phenylhydrazine sulfate (842 mg, 4 mmol), and triethylamine (0.84 mL, 6 mmol) was refluxed in methanol (50 mL) for 10 h. The precipitate that formed upon cooling was filtered off and dried in air. Recrystallization from benzene (100 mL) afforded pyrazole **4** in a yield of 0.135 g (0.47 mmol, 23.5%), m.p. 157—159 °C. Found (%): C, 70.66; H, 3.75; N, 14.47. $C_{17}H_{11}N_3O_2$. Calculated (%): C, 70.59; H, 3.81; N, 14.5. ^{1}H NMR ($CDCl_3$), δ: 7.3, 7.5, and 7.9 (all m, 2 H each, CH, toluid.); 7.8 (m, 4 H, CH, arom. phthal.); 8.4 and 8.6 (both s, 1 H each, CH, pyrazole). IR (Nujol mulls), ν/cm^{-1}: 1870 (C=O), 1740 (C=O), 1690 (C=N), 1580 (C=C).

Zinc *N*-[2-phthalimido-3-(*p*-tolyl)prop-1-enyl]-*p*-toluidinate (5). A solution of anhydrous $ZnCl_2$ (136 mg, 0.1 mol) in methanol (10 mL) was added to a suspension of compound **3** (395 mg, 0.1 mol) in methanol (50 mL). The reaction mixture was refluxed for 30 min. Then a solution of NaOH (40 mg, 0.1 mol) in methanol (10 mL) was added. The precipitate of the complex that formed was filtered off, washed with hot methanol, and dried in air. The product was obtained in a yield of 196 mg (46%), m.p. 280—282 °C. Found (%): C, 70.39; H, 4.63; N, 9.78; Zn, 7.68. $C_{50}H_{40}N_6O_4Zn$. Calculated (%): C, 70,34; H, 4.69; N, 9.85; Zn, 7.62. ^{1}H NMR ($CDCl_3$), δ: 2.2 (s, 6 H, 2 Me); 6.9 and 7.1 (both d, 4 H each, arom. toluid., J = 8.3 Hz); 7.7 (s, 2 H, azometh.); 7.8 and 8.0 (m, 2 H, arom., phthal.). IR (Nujol mulls), ν/cm^{-1}: 1780 (C=O), 1700 (C=O), 1600 (C=N).

1,8-Bis(dimethylamino)-2,7-bisphthalimido-4,5-diazaocta-1,3,5,7-tetraene (6). A mixture of perchlorate **2** (742 mg, 2 mmol) and hydrazine hydrate (0.12 mL, 2 mmol) in MeOH (25 mL) was refluxed for 1 h. The red precipitate that formed was filtered off, washed with hot methanol, and dried in air. Compound **6** was obtained in a yield of 0.157 g (0.326 mmol, 32.6%), m.p. 242 °C. Found (%): C, 64.51; H, 4.9; N, 17.32. $C_{26}H_{24}N_6O_4$. Calculated (%): C, 64.46; H, 4.96; N, 17.32. ^{1}H NMR ($CDCl_3$), δ: 2.9 (s, 12 H, Me); 6.8 and 7.8 (both s, 2 H each, azometh.); 7.8 (dm, 8 H, arom.). IR (Nujol mulls), ν/cm^{-1}: 1780 (C=O), 1710 (C=O), 1640 (C=N), 1600 (C=C).

4-Salicylideneaminopyrazole (7). A mixture of perchlorate **2** (1.113 g, 3 mmol) and hydrazine hydrate (0.68 mL, 12 mmol) was refluxed in methanol (100 mL) for 10 h. Then methanol was evaporated. The residue was dissolved in benzene (50 mL) and refluxed with salicylaldehyde (0.31 mL, 3 mmol) for 12 h. The reaction mixture was chromatographed on silica gel (benzene), and the fraction with R_f 0.2 (TLC control) was collected. Pyrazole **7** was obtained in a yield of 0.01 g (0.054 mmol, 18%), m.p. 188—190 °C. Found (%): C, 64.25; H, 4.76; N, 22.39. $C_{10}H_9N_3O$. Calculated (%): C, 64.17; H, 4.81; N, 22.46. ^{1}H NMR ($CDCl_3$), δ: 6.8 (t, 2 H, CH arom., J = 7.6 Hz); 7.3 (t, 1 H, arom., J = 7.8 Hz); 7.4 (d, 1 H, arom., J = 8.1 Hz); 7.8 (s, 2 H, CH, pyrazole); 8.8 (s, 1 H, CH, azometh.); 12.80 (br.s, 1 H, NH); 12.94 (s, 1 H, OH). IR (Nujol mulls), ν/cm^{-1}: 3150 (NH), 3100 (OH), 1610 (C=N), 1570 (C=C).

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