A CONVENIENT SYNTHESIS OF METHYL 3-PHENYLHYDRAZONO-2-(2-PYRAZINYLCARBONYLAMINO)PROPANOATES AND THEIR CONVERSION TO SUBSTITUTED PYRAZOL-5(2*H*)-ONES[#]

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Abstract – Methyl 3-dimethylamino-2-(2-pyrazinylcarbonylamino)propenoate (**1**) was transformed into substituted methyl 3-phenylhydrazono-2-(2-pyrazinylcarbonylamino)propanoates (**3**) by treatment with various substituted phenylhydrazine hydrochlorides (**2**) in methanol. In contrast, heating of **1** and **2** in 1-butanol yielded 1,4-disubstituted pyrazol-5(2*H*)-ones (**4**). The latter can also be obtained upon heating of **3** in acetic acid.

Substituted alkyl 2-arylcarbonylamino-3-hydrazonopropanoates are versatile multifunctional synthetic intermediates in the preparation of various heterocyclic systems as recently described for substituted ethyl 2-benzoylamino-3-(phenylhydrazono)propanoates.[1,2] These compounds were prepared from phenylhydrazines and 4-hydroxymethylene-2-phenyl-5(4*H*)-oxazolone or its synthetic equivalent, ethyl *N*-benzoyl-2-formylglycinate, in ethanolic solution, and were further transformed into an oxazinoindole derivative, fused 1,2,4-triazoles, indoles and pyrazoles under different reaction conditions. For example, the transformation into substituted pyrazoles was achieved under alkaline conditions.[2] This is an alternative procedure for the preparation of pyrazolones or their tautomers.[3-6]

Recently, we have investigated amino acid derivatives containing 2-pyrazinylcarbonylamino building block.[6-11] For example, we described transformations of 4-dimethylaminomethylene-2-pyrazinyl-5(4*H*)-oxazolone and its synthetic equivalent, methyl 3-dimethylamino-2-(2-pyrazinylcarbonylamino)propenoate (**1**), into 1,4-disubstituted pyrazol-5(2*H*)-ones by hydrazine hydrate, phenylhydrazines and heterocyclic hydrazines under different conditions.[6] No intermediates were isolated in these transformations. Since we

[#] Dedicated to Professor Teruaki Mukaiyama, Professor of Science University of Tokyo, on the occasion of his 73rd birthday.

believed that substituted alkyl 3-hydrazono-2-(2-pyrazinylcarbonylamino)propanoates might be formed in these conversions, we tried to isolate them as potentially useful synthetic intermediates.

Because of the difference in reactivity of the dimethylamino group toward the nucleophiles only the propenoate (**1**) seemed to be useful for this purpose. The dimethylamino group of 4-dimethylamino-methylene-2-phenyl-5(4*H*)-oxazolone, for example, was described to be very stable towards substitution by nucleophiles since the reaction with potassium methoxide yielded only the product of ring opening reaction, namely, methyl 2-benzoylamino-3-dimethylaminopropenoate. In contrast, the dimethylamino group of the latter can easier be replaced by a nucleophile.[12]

Here we report the transformation of propenoate (**1**) with a series of phenylhydrazine hydrochlorides (**2**) to substituted methyl 3-phenylhydrazono-2-(2-pyrazinylcarbonylamino)propanoates (**3**) and into some pyrazolones (**4**). The structure determination of compounds (**3**) as well as their applicability for the preparation of pyrazolones (**4**) is also discussed. The reactions of propenoate (**1**) with phenylhydrazine hydrochlorides (**2**) were performed under relatively mild reaction conditions (in boiling methanol) and the corresponding propanoates (**3**) were obtained in 64–87% yields (Method A, Scheme 1, Table 1). In contrast, when the reaction was performed in boiling 1-butanol the corresponding pyrazolone derivatives (**4a–d**) or their tautomers were obtained in 62–93% yields (Method B). In order to get an additional information about this reaction, we also carried out transformation of propenoate (**1**) with tolylhydrazine hydrochloride (**2d**) as a two-step procedure. The first step was carried out in boiling methanol (for 40 min), thus forming propanoate (**3d**), then methanol was evaporated, followed by the addition of 1-butanol and further heating for 5 h. The corresponding pyrazolone derivative (**4d**) was obtained in the same yield as by the application of the Method B. An attempt to prepare the pyrazolone derivative (**4e**) from propenoate (**1**) and 2,4-dichlorophenylhydrazine hydrochloride (**2e**) by the two-step procedure failed, and after heating in the second step in 1-butanol for 6 h we isolated the propanoate (**3e**) in 46% yield. For this reason we tested the applicability of propanoates (**3d** and **3e**) for the synthesis of pyrazolones (**4d** and **4e**) in boiling acetic acid. Both pyrazolones were obtained in good yields (Method C).

Scheme 1

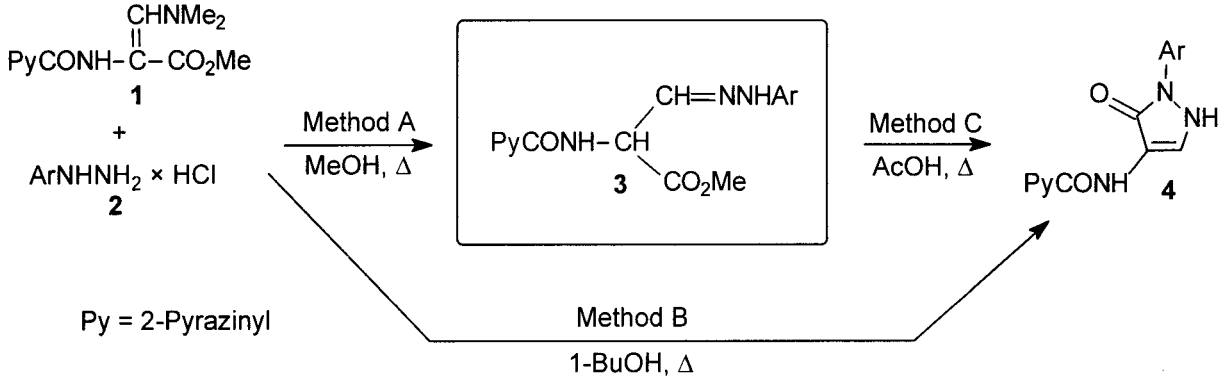
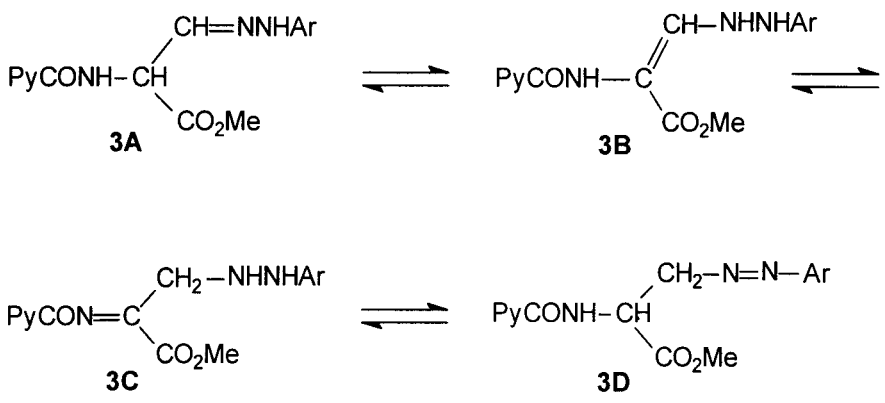


Table 1. The Synthesis of Propanoates (**3a–g**) and Pyrazolones (**4a–e**):

Ar-NHNH$_2$ · HCl (2, Ar=)	Product (3)	Method A (r. time; yield)	Product (4)	Method B (r. time; yield)	Method C (r. time; yield)
Ph	**3a**	60 min; 77%	**4a**[6]	5 h; 93%	
4-chlorophenyl	**3b**	60 min; 87%	**4b**	5 h; 78%	
4-bromophenyl	**3c**	60 min; 70%	**4c**	5 h; 67%	
3-tolyl	**3d**	40 min; 67%	**4d**	5 h; 62%	3 h; 68%
2,4-dichlorophenyl	**3e**	40 min; 86%	**4e**		5 h; 80%
4-nitrophenyl	**3f**	90 min; 64%			
2,4-difluorophenyl	**3g**	60 min; 87%			

Propanoates (**3**) might exist in several tautomeric forms (Scheme 2). Their ^{1}H NMR spectra, recorded in DMSO-d_6 solution, indicate that **3A** is the most stable tautomer. This statement is based on the coupling constants obtained for the fragment –NH–CH–CH=. Namely, the proton at the position 2 is a typical doublet of doublets with coupling constants about 5.6 and 7.5 Hz, respectively. On the other hand, signals for 3-H and NH proton are doublets with previously mentioned coupling constants, thus supporting structure **3A**.

Scheme 2



In conclusion, we synthesized substituted methyl 3-phenylhydrazono-2-(2-pyrazinylcarbonylamino)-propanoates (**3**), an interesting class of synthetic intermediates, determined their predominant tautomeric structure and demonstrated their use for the preparation of some pyrazolone derivatives.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DPX 300 in DMSO-d_6 using TMS as an internal standard. IR spectra were performed with a Perkin-Elmer 1310 spectrophotometer. MS spectra were obtained with a VG-Analytical AutospecQ spectrometer. Elemental analyses (C, H, N) were taken on a Perkin-Elmer 2400 CHN Analyzer. TLC was carried out on Fluka silica gel TLC-cards. Propenoate (**1**) was prepared as described in the literature.[6] All other compounds and solvents were used as received from commercial sources.

General procedure for the preparation of methyl 3-phenylhydrazono-2-(2-pyrazinylcarbonylamino)propanoates (3): Method A.

A mixture of methyl 3-dimethylamino-2-(pyrazinylcarbonylamino)propenoate (**1**) (250 mg, 1 mmol) and 1 mmol of a phenylhydrazine hydrochloride derivative (**2**) in 2 mL of methanol was refluxed for 40–90 min. Upon cooling, the separated product was filtered off and washed with 1 mL of methanol. Yields of TLC-pure products are given in Table 1.

The following products were obtained by this method:

Methyl 3-phenylhydrazono-2-(2-pyrazinylcarbonylamino)propanoate (3a): mp 148–151 °C (MeOH); ^{1}H NMR (300 MHz) δ 3.72 (s, 3H, Me), 5.26 (dd, J = 5.6 and 7.5 Hz, 1H, 2-H), 6.73 (m, 1H, Ph), 6.92 (m, 2H, Ph), 7.18 (m, 2H, Ph), 7.37 (d, J = 5.6 Hz, 1H, 3-H), 8.80 (dd, J = 1.5 and 2.6 Hz, 1H, 6'-H), 8.93 (d, J = 2.6 Hz, 1H, 5'-H), 9.22 (d, J = 1.5 Hz, 1H, 3'-H), 9.50 (d, J = 7.5 Hz, 1H, N*H*CH), 10.22 (br s, 1H, NH); MS (m/z, %) 313 (M^+, 56), 281 (63), 206 (46), 107 (63), 93 (85), 79 (100), 65 (40); IR (KBr) 3380, 3280, 1728, 1668, 1595, 1490 br cm^{-1}. Anal. Calcd for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.83; N, 22.35. Found: C, 57.50; H, 4.86; N, 22.33.

Methyl 3-(4-chlorophenylhydrazono)-2-(2-pyrazinylcarbonylamino)propanoate (3b): mp 161–163 °C (MeOH); ^{1}H NMR (300 MHz) δ 3.72 (s, 3H, Me), 5.26 (dd, J = 5.6 and 7.5 Hz, 1H, 2-H), 6.92 (m, 2H, Ph), 7.22 (m, 2H, Ph), 7.39 (d, J = 5.6 Hz, 1H, 3-H), 8.80 (dd, J = 1.5 and 2.6 Hz, 1H, 6'-H), 8.93 (d, J = 2.6 Hz, 1H, 5'-H), 9.21 (d, J = 1.5 Hz, 1H, 3'-H), 9.52 (d, J = 7.5 Hz, 1H, N*H*CH), 10.36 (br s, 1H, NH); MS (m/z, %) 349 (M^+ + 2, 15, ^{37}Cl), 347 (M^+, 40, ^{35}Cl), 315 (44), 240 (26), 162 (38), 127 (71), 107 (71), 79 (100); IR (KBr) 3380, 3280, 1730, 1670, 1597, 1490 br cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_5O_3Cl$: C, 51.81; H, 4.06; N, 20.14. Found: C, 51.69; H, 3.91; N, 20.23.

Methyl 3-(4-bromophenylhydrazono)-2-(2-pyrazinylcarbonylamino)propanoate (3c): mp 159–161 °C (MeOH); ^{1}H NMR (300 MHz) δ 3.72 (s, 3H, Me), 5.26 (dd, *J* = 5.6 and 7.5 Hz, 1H, 2-H), 6.88 (m, 2H, Ph), 7.34 (m, 2H, Ph), 7.39 (d, *J* = 5.6 Hz, 1H, 3-H), 8.80 (dd, *J* = 1.5 and 2.6 Hz, 1H, 6'-H), 8.93 (d, *J* = 2.6 Hz, 1H, 5'-H), 9.21 (d, *J* = 1.5 Hz, 1H, 3'-H), 9.52 (d, *J* = 7.5 Hz, 1H, N*H*CH), 10.38 (br s, 1H, NH); MS (m/z, %) 393 (M^+ + 2, 39, ^{81}Br), 391 (M^+, 39, ^{79}Br), 361 (38), 359 (38), 171 (64), 162 (42), 107 (60), 79 (100); IR (KBr) 3375, 3280, 1732, 1673, 1592, 1500, 1482 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_5O_3Br$: C, 45.94; H, 3.60; N, 17.86. Found: C, 45.63; H, 3.44; N, 17.64.

Methyl 2-(2-pyrazinylcarbonylamino)-3-(3-tolylhydrazono)propanoate (3d): mp 126–129 °C (MeOH); ^{1}H NMR (300 MHz) δ 2.23 (s, 3H, Me), 3.72 (s, 3H, OMe), 5.25 (dd, *J* = 5.6 and 7.5 Hz, 1H, 2-H), 6.55 (m, 1H, Ph), 6.71 (m, 1H, Ph), 6.77 (br s, 1H, Ph), 7.06 (deg t, 1H, Ph), 7.36 (d, *J* = 5.6 Hz, 1H, 3-H), 8.80 (dd, *J* = 1.5 and 2.6 Hz, 1H, 6'-H), 8.93 (d, *J* = 2.6 Hz, 1H, 5'-H), 9.22 (d, *J* = 1.5 Hz, 1H, 3'-H), 9.50 (d, *J* = 7.5 Hz, 1H, N*H*CH), 10.16 (br s, 1H, NH); MS (m/z, %) 327 (M^+, 53), 295 (46), 107 (100), 79 (72), 69 (81), 57 (72); IR (KBr) 3385, 3305, 1745, 1690, 1615, 1605, 1520 br cm^{-1}. Anal. Calcd for $C_{16}H_{17}N_5O_3$: C, 58.71; H, 5.23; N, 21.39. Found: C, 59.09; H, 5.13; N, 21.73.

Methyl 3-(2,4-dichlorophenylhydrazono)-2-(2-pyrazinylcarbonylamino)propanoate (3e): mp 135-137 °C (MeOH); ^{1}H NMR (300 MHz) δ 3.73 (s, 3H, Me), 5.28 (dd, *J* = 5.6 and 7.5 Hz, 1H, 2-H), 7.31 (m, 2H, Ph), 7.44 (deg dd, 1H, Ph), 7.82 (d, *J* = 5.6 Hz, 1H, 3-H), 8.81 (dd, *J* = 1.5 and 2.6 Hz, 1H, 6'-H), 8.93 (d, *J* = 2.6 Hz, 1H, 5'-H), 9.22 (d, *J* = 1.5 Hz, 1H, 3'-H), 9.53 (d, *J* = 7.5 Hz, 1H, N*H*CH), 10.05 (br s, 1H, NH); MS (m/z, %) 385 (M^+ + 4, 7, two ^{37}Cl), 383 (M^+ + 2, 35, ^{37}Cl and ^{35}Cl), 381 (M^+, 51, two ^{35}Cl), 349 (41), 274 (35), 161 (72), 107 (78), 79 (100); IR (KBr) 3370, 3275, 1730, 1670, 1590, 1500 br cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_5O_3Cl_2$: C, 47.14; H, 3.43; N, 18.32. Found: C, 47.22; H, 3.39; N, 18.25.

Methyl 3-(4-nitrophenylhydrazono)-2-(2-pyrazinylcarbonylamino)propanoate (3f): mp 182–184 °C (DMF/MeOH); ^{1}H NMR (300 MHz) δ 3.74 (s, 3H, Me), 5.33 (dd, *J* = 5.65 and 7.5 Hz, 1H, 2-H), 7.03 (m, 2H, Ph), 7.59 (d, *J* = 5.65 Hz, 1H, 3-H), 8.12 (m, 2H, Ph), 8.81 (dd, *J* = 1.5 and 2.3 Hz, 1H, 6'-H), 8.94 (d, *J* = 2.3 Hz, 1H, 5'-H), 9.22 (d, *J* = 1.5 Hz, 1H, 3'-H), 9.62 (d, *J* = 7.5 Hz, 1H, N*H*CH), 11.20 (br s, 1H, NH); MS (m/z, %) 358 (M^+, 31), 326 (62), 251 (32), 107 (77), 79 (100), 69 (47), 57 (58); IR (KBr) 3355, 3245, 1720, 1680, 1590, 1497 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_6O_5$: C, 50.28; H, 3.94; N, 23.45. Found: C, 50.29; H, 3.87; N, 23.54.

Methyl 3-(2,4-difluorophenylhydrazono)-2-(2-pyrazinylcarbonylamino)propanoate (3g): mp 148-

150 °C (MeOH); ^{1}H NMR (300 MHz) δ 3.72 (s, 3H, Me), 5.27 (dd, *J* = 5.65 and 7.5 Hz, 1H, 2-H), 6.97 (m, 1H, Ph), 7.22 (m, 2H, Ph), 7.61 (d, *J* = 5.65 Hz, 1H, 3-H), 8.80 (dd, *J* = 1.5 and 2.3 Hz, 1H, 6'-H), 8.93 (d, *J* = 2.3 Hz, 1H, 5'-H), 9.21 (d, *J* = 1.5 Hz, 1H, 3'-H), 9.50 (d, *J* = 7.5 Hz, 1H, N*H*CH), 10.14 (br s, 1H, NH); MS (m/z, %) 349 (M^+, 44), 317 (46), 129 (72), 107 (72), 79 (100); IR (KBr) 3385, 3290, 1733, 1672, 1500 br cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_5O_3F_2$: C, 51.58; H, 3.75; N, 20.05. Found: C, 51.37; H, 3.76; N, 20.11.

General procedure for the preparation of pyrazolone derivatives (4a–d): Method B.

A mixture of methyl 3-dimethylamino-2-(pyrazinylcarbonylamino)propenoate (**1**) (250 mg, 1 mmol) and 1 mmol of a phenylhydrazine hydrochloride derivative (**2**) in 2 mL of 1-butanol was refluxed for 5 h. Upon cooling, the separated product was filtered off and washed with 1 mL of ethanol. Yields of TLC-pure products are given in Table 1.

The following products were obtained by this method:

***N*-(1,2-Dihydro-5-oxo-1-phenyl-5*H*-pyrazol-4-yl)pyrazine-2-carboxamide (4a):** mp 235–239 °C (decomp, DMF/EtOH); lit.,[6] mp 235–239 (decomp).

***N*-[1-(4-Chlorophenyl)-1,2-dihydro-5-oxo-5*H*-pyrazol-4-yl]pyrazine-2-carboxamide (4b):** mp 250-252 °C (DMF/MeOH); ^{1}H NMR (300 MHz) δ 7.55 (m, 2H, Ph), 7.81 (m, 2H, Ph), 7.96 (br s, 1H, 3'-H), 8.82 (dd, *J* = 1.5 and 2.6 Hz, 1H, 6-H), 8.94 (d, *J* = 2.6 Hz, 1H, 5-H), 9.28 (d, *J* = 1.5 Hz, 1H, 3-H), 10.37 (br s, 1H, NH), 11.82 (br s, 1H, NH); MS (m/z, %) 317 (M^+ + 2, 33, ^{37}Cl), 315 (M^+, 88, ^{35}Cl), 107 (100), 79 (81); IR (KBr) 3370, 1674, 1622, 1600 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_5O_2Cl$: C, 53.26; H, 3.19; N, 22.18. Found: C, 53.10; H, 3.23; N, 21.78.

***N*-[1-(4-Bromophenyl)-1,2-dihydro-5-oxo-5*H*-pyrazol-4-yl]pyrazine-2-carboxamide (4c):** mp 249-251 °C (DMF/MeOH); ^{1}H NMR (300 MHz) δ 7.68 (m, 2H, Ph), 7.76 (m, 2H, Ph), 7.96 (br s, 1H, 3'-H), 8.81 (dd, *J* = 1.5 and 2.6 Hz, 1H, 6-H), 8.94 (d, *J* = 2.6 Hz, 1H, 5-H), 9.28 (d, *J* = 1.5 Hz, 1H, 3-H), 10.37 (br s, 1H, NH), 11.84 (br s, 1H, NH); MS (m/z, %) 361 (M^+ + 2, 65, ^{81}Br), 359 (M^+, 65, ^{79}Br), 107 (100), 79 (79); IR (KBr) 3370, 1675, 1625, 1600 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_5O_2Br$: C, 46.69; H, 2.80; N, 19.44. Found: C, 46.54; H, 2.76; N, 19.38.

***N*-[1,2-Dihydro-5-oxo-1-(3-tolyl)-5*H*-pyrazol-4-yl]pyrazine-2-carboxamide (4d):** mp 191–194 °C (DMF/MeOH); ^{1}H NMR (300 MHz) δ 2.37 (s, 3H, Me), 7.11 (m, 1H, Ph), 7.36 (deg t, 1H, Ph), 7.56 (m,

1H, Ph), 7.58 (br s, 1H, Ph), 7.93 (br s, 1H, 3'-H), 8.81 (dd, J = 1.5 and 2.5 Hz, 1H, 6-H), 8.94 (d, J = 2.5 Hz, 1H, 5-H), 9.28 (d, J = 1.5 Hz, 1H, 3-H), 10.36 (br s, 1H, NH), 11.60 (br s, 1H, NH); MS (m/z, %) 295 (M^+, 100), 188 (20), 107 (56), 91 (50), 79 (52); IR (KBr) 3395, 1690, 1630 br, 1535 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 60.93; H, 4.58; N, 23.89.

General procedure for the preparation of pyrazolone derivatives (4d–e): Method C.

A mixture of a propanoate (**3d–e**) (1 mmol) in 4–6 mL of acetic acid was refluxed for 3 h (for product **4d**) or 5 h (for **4e**). After evaporation a small amount of ethanol (1–2 mL) was added and, upon cooling, the separated product was filtered off and washed with 1 mL of ethanol. Yields of TLC-pure products are given in Table 1.

***N*-[1-(2,4-Dichlorophenyl)-1,2-dihydro-5-oxo-5*H*-pyrazol-4-yl]pyrazine-2-carboxamide (4e):** mp 225–230 °C (decomp, DMF/MeOH); ^{1}H NMR (300 MHz) δ 7.57 (m, 2H, Ph), 7.86 (m, 1H, Ph), 7.97 (br s, 1H, 3'-H), 8.81 (dd, J = 1.5 and 2.4 Hz, 1H, 6-H), 8.93 (d, J = 2.4 Hz, 1H, 5-H), 9.28 (d, J = 1.4 Hz, 1H, 3-H), 10.45 (br s, 1H, NH), 11.55 (br s, 1H, NH); MS (m/z, %) 353 (M^+ + 4, 18, two ^{37}Cl), 351 (M^+ + 2, 68, ^{37}Cl and ^{35}Cl), 349 (M^+, 90, two ^{35}Cl), 107 (100), 79 (87); IR (KBr) 3360, 1675, 1615, 1500 br cm^{-1}. HRMS Calcd for $C_{14}H_9N_5O_2Cl_2$ 349.0139. Found 349.0133.

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