Synthesis and addition-nucleophilic reactions of 2-chloro- and 2,6-dimethyl-4-chloro-3-pyridyl isocyanates

D. KOŠČÍK, P. KUTSCHY, M. DZURILLA, and P. KRISTIAN

Department of Organic Chemistry and Biochemistry, Faculty of Natural Sciences, P. J. Šafárik University, CS-041 67 Košice

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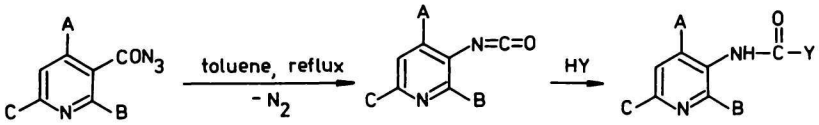
2-Chloro-3-pyridyl isocyanate and 2,6-dimethyl-4-chloro-3-pyridyl isocyanate, prepared by decomposition of the corresponding acyl azides, react with amines, benzyl alcohol, and phenylmethanethiol under formation of the respective ureas and esters of carbamic acids, respectively. On heating in solvents of different polarities, in alkaline or acidic media intramolecular cyclization of the obtained products to derivatives of pyridoimidazole and pyridooxazole does not proceed, while photolysis of *N*-phenyl-*N'*-(2,6-dimethyl-4-chloro-3-pyridyl)urea affords a pyridoimidazole derivative. Treatment of the prepared ureas with potassium thiocyanate in acidic medium results in 2-aminopyrido[3,2-*d*]thiazole and 2-amino-4,6-dimethylpyrido[3,4-*d*]thiazole.

2-Хлор-3-пиридилизоцианат и 2,6-диметил-4-хлор-3-пиридилизоцианат, полученные при разложении соответствующих ацилазидов, реагируют с аминами, бензиловым спиртом и бензилмеркаптаном с образованием соответствующих мочевин или эфиров карбамовых кислот. При нагревании в растворителях различной полярности, в щелочной или кислой среде не происходит внутримолекулярная циклизация полученных продуктов присоединения в производные пиридоимидазола или пиридооксазола, в то время как фотолиз *N*-фенил-*N'*-(2,6-диметил-4-хлор-3-пиридил)мочевины приводит к производному пиридоимидазола. Под действием роданистого калия в кислой среде из полученных мочевин образуются 2-аминопирido[3,2-*d*]тиазол или 2-амино-4,6-диметилпирido[3,4-*d*]тиазол.

In the framework of study of addition-cyclization reactions of pyrido heterocumulenes, in our previous works we have dealt with synthesis and reactions of 2-chloro- and 2,6-dimethyl-4-chloronicotinoyl isothiocyanates and isoselenocyanates with *N*- and *S*-nucleophiles, resulting in pyridothiazines [1, 2], pyridopyrimidines, and pyridoselenazines [3, 4].



I, II *III, IV* *V–XXI*

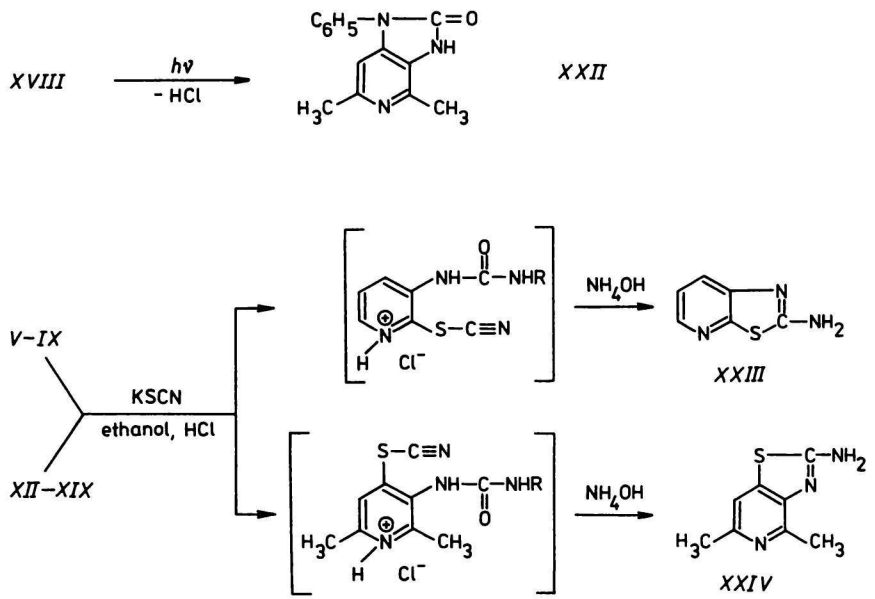
I, III, V–XI: A = C = H, B = Cl; *II, IV, XII–XXI*: B = C = CH_3, A = Cl

Compound	*V* / *XII*	*VI* / *XIII*	*VII* / *XIV*	*VIII* / *XV*	*IX* / *XVI*
Y	NH_2	morpholino	C_2H_5NH	$4\text{-}CH_3\text{-}C_6H_4NH$	$4\text{-}CH_3O\text{-}C_6H_4NH$
Compound	*XVII*	*XVIII*	*XIX*	*X* / *XX*	*XI* / *XXI*
Y	$(CH_3)_2CHNH$	C_6H_5NH	$C_6H_5CH_2NH$	$C_6H_5CH_2O$	$C_6H_5CH_2S$

Scheme 1

In the present work we devoted our attention to synthesis of 2-chloro-3--pyridyl isocyanate (*III*) and 2,6-dimethyl-4-chloro-3-pyridyl isocyanate (*IV*) with primary amines, morpholine, benzyl alcohol, and phenylmethanethiol (*V—XXI*; Scheme 1). Isocyanates *III* and *IV* were prepared by Curtius degradation of acyl azides (*I, II*) which were obtained from the respective acyl chlorides [2, 5] and carbohydrazides [6], respectively. The prepared ureas *V—IX* and *XII—XIX* as well as the *O*- and *S*-benzyl carbamates *X, XI, XX, XXI* are, contrary to the similar type of acylthioureas, very stable compounds. On heating in solvents of different polarities, in alkaline or acidic media intramolecular cyclization, utilizing reactive chlorine in the position 2 or 4 on the pyridine ring, did not proceed. Unsuccessful was also the attempt to substitute chlorine with cyanide ion by treatment with CuCN and $Pb(CN)_2$ where we assumed the formation of the corresponding nitriles which, having bound urea residue in the vicinity, are known to give in alkaline medium pyridopyrimidines [7]. When studying the possibilities of cyclization of the prepared ureas we investigated also their photoreactivity. In the case of urea *XVIII* ($\lambda_{max} = 246$ nm, $\log\{\varepsilon\} = 4.2$) we succeeded in photocyclization to 1-phenyl-2-oxo-4,6-dimethylpyrido[3,4--*d*]imidazole (*XXII*; Scheme 2), the structure of which was proved by IR and mass spectra. Due to insolubility, it was impossible to measure its ^1H and ^{13}C NMR spectra. In the IR spectrum the absorption band $\nu(C=O)$ appearing at $\tilde{\nu} = 1670\,cm^{-1}$ proved that cyclization occurred through the nitrogen atom, since the corresponding band with urea appeared at $\tilde{\nu} = 1635\,cm^{-1}$. The

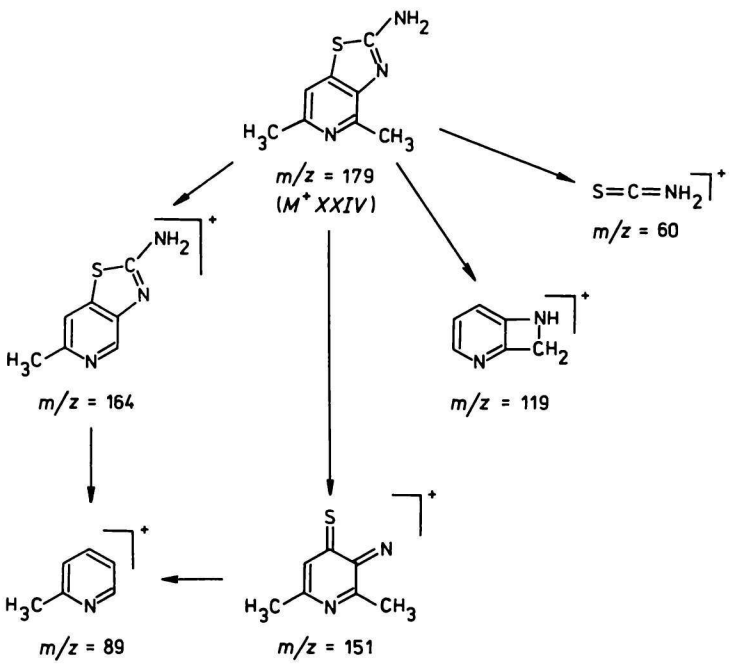
presence of the intense peak of the molecular ion in the mass spectrum points to stability of pyridoimidazole *XXII* and the presence of peaks of low intensity at *m/z* 196 and 119 proves the suggested structure. Photocyclization of the other ureas studied resulted in mixtures of products which we failed to identify.



Scheme 2

In 1977 *Atland* [8] published the synthesis of 2-amino[3,2-*d*]pyridothiazole from 2-chloro-3-aminopyridine and five-fold mole excess of potassium thiocyanate in ethanol in the presence of hydrochloric acid. It was assumed that protonization of the amino group or nitrogen in pyridine enabled nucleophilic substitution of chlorine in the vicinal *ortho*-position by the thiocyanate ion. Then followed the addition of the amino group to the C≡N bond of the thiocyanate group under formation of the thiazole ring. We found that analogous reaction proceeded in low yields also with compounds *V—IX* and *XII—XIX*. We assume that this cyclization proceeded by a similar mechanism as suggested by Atland and the respective pyridothiazoles (*XXIII*, *XXIV*; Scheme 2) were formed under simultaneous elimination of the CONHR residue. Cyclization of *O*- and *S*-benzyl carbamates *X*, *XI*, *XX*, *XXI* under similar conditions did not occur. In these cases only small amounts of the starting compounds and their unidentified decomposition products were isolated from the reaction mixture. After conversion of ureas *V—IX* and *XII—XIX* to pyri-

dothiazoles *XXIII* and *XXIV*, the stretching vibrations ν(NH—C=O) at $\tilde{\nu} = 1630$—$1675\ cm^{-1}$ were absent in the IR spectra, present were only the bands belonging to vibrations of free and bound NH_2 groups. The structures of pyridothiazoles *XXIII* and *XXIV* were proved unambiguosly by mass spectra (Scheme 3). Intense peaks of molecular ions pointed to stability of these compounds. The suggested structure of the compound *XXIV* was confirmed also by its ^{13}C NMR spectrum.



Scheme 3

Experimental

Infrared absorption spectra were measured with a Specord IR-75 (Zeiss, Jena) spectrometer. The compounds *V*—*VII*, *XII*—*XIV*, *XVII*, and *XIX* were measured in $CHCl_3$, the others by KBr technique. ^1H and ^{13}C NMR spectra were measured with a Tesla BS 487 A (80 MHz) and Tesla BS 567 (25.15 MHz) spectrometers using tetramethylsilane as internal standard. The spectra were measured in the mixture of deuteriochloroform and hexadeuteriodimethyl sulfoxide. UV spectrum of the compound *XVIII*

Table 1

Physicochemical characteristics of the derivatives *V*—*XXI*

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.
			C	H	N	%	°C
V	$C_6H_6ClN_3O$	171.6	41.99	3.52	24.49	42	160
			41.84	3.39	24.45		
VI	$C_{10}H_{12}ClN_3O_2$	241.7	49.69	5.00	17.38	33	181
			49.75	5.04	17.52		
VII	$C_8H_{10}ClN_3O$	199.6	48.12	5.04	21.04	40	221
			48.23	5.08	21.06		
VIII	$C_{13}H_{12}ClN_3O$	261.7	59.65	4.62	16.05	35	240—242
			59.42	4.67	16.07		
IX	$C_{13}H_{12}ClN_3O_2$	277.7	56.22	4.35	15.13	39	249
			56.43	4.54	15.28		
X	$C_{11}H_{11}ClN_2O_2$	238.7	55.35	4.64	11.73	30	256—258
			55.27	4.52	11.61		
XI	$C_{11}H_{11}ClN_2OS$	254.7	51.86	4.35	10.99	28	251—253
			52.01	4.52	11.02		
XII	$C_8H_{10}ClN_3O$	199.5	48.12	5.01	21.05	42	262—265
			47.96	4.89	21.00		
XIII	$C_{12}H_{16}ClN_3O_2$	269.5	53.43	5.94	15.58	31	142—144
			53.46	6.04	15.51		
XIV	$C_{10}H_{14}ClN_3O$	227.5	52.74	6.15	18.46	41	230—232
			52.66	6.27	18.26		
XV	$C_{15}H_{16}ClN_3O$	289.5	62.18	5.53	14.51	38	242—243
			61.95	5.77	14.39		
XVI	$C_{15}H_{16}ClN_3O_2$	305.5	58.92	5.23	13.75	37	240—241
			59.03	5.31	13.51		
XVII	$C_{11}H_{16}ClN_3O$	241.5	54.66	6.62	17.39	43	230—232
			54.95	6.76	17.67		
XVIII	$C_{14}H_{15}ClN_3O$	275.5	60.98	5.08	15.24	40	244.5
			61.11	5.21	15.36		
XIX	$C_{15}H_{16}ClN_3O$	289.5	62.18	5.53	14.51	39	246
			61.98	5.71	14.29		
XX	$C_{15}H_{15}ClN_2OS$	306.5	58.73	4.89	9.14	26	305
			58.78	5.10	9.05		
XXI	$C_{15}H_{15}ClN_2O_2$	290.5	61.96	5.16	9.64	28	310—311
			62.01	4.98	9.56		

was recorded with a Perkin—Elmer 402 spectrometer in ethanol at 1×10^{-4} mol dm^{-3} concentration. Mass spectra were measured with an MS 902-S (AEI, Manchester) spectrometer at ionizing energy 70 eV and ionizing chamber temperature 155 and 180 °C. The

Table 2

Spectral data of the derivatives *V*—*XXI*

Compound	IR, $\tilde{\nu}$/cm^{-1}				^{1}H NMR, δ/ppm				
	ν(C=O)	ν(N—H)$_{free}$	ν(N···H)$_{bound}$	ν(C—Cl)	CH_3	H_α	H_β	H_γ	NH
V	1640	3370	3200	795	—	7.81	7.32	7.70	9.50
VI	1645	3370	3100	840	—	7.86	7.41	7.85	9.60
VII	1645	3440	3220	850	—	8.21	7.40	7.76	9.40
VIII	1650	*a*	*a*	825	—	8.31	7.45	7.75	9.20
IX	1650	*a*	*a*	800	—	8.35	7.44	7.71	*b*
X	1640	*a*	*a*	845	—	8.21	7.40	7.77	9.50
XI	1640	*a*	*a*	845	—	8.23	7.40	7.77	9.20
XII	1640	3370	3200	795	2.85	—	7.41	—	7.91; 6.15
XIII	1660	3440	3150	846	2.42	—	7.13	—	7.40
XIV	1670	3440	3200	850	2.75	—	7.40	—	8.50; 7.67
XV	1640	*a*	*a*	800	2.62	—	7.56	—	9.00; 8.15
XVI	1635	*a*	*a*	825	2.41	—	7.25	—	8.50; 7.60
XVII	1670	3425	3100	795	2.41	—	6.88	—	7.23; 5.66
XVIII	1635	*a*	*a*	856	2.38	—	7.03	—	8.40; 7.63
XIX	1645	3460	3100	835	2.45	—	7.20	—	8.60; 7.82
XX	1640	*a*	*a*	845	2.81	—	7.17	—	8.16
XXI	1640	*a*	*a*	845	2.68	—	7.15	—	8.01

a) The respective band could not be resolved since the spectrum was measured in KBr; *b*) the signal has not appeared in the spectrum.

progress of reactions was checked by thin-layer chromatography on Silufol plates (Kavalier).

2-Chloronicotinoyl azide (*I*) and 2,6-dimethyl-4-chloronicotinoyl azide (*II*) were prepared according to Ref. [9, 10].

2-Chloro-3-pyridyl isocyanate (III) and 2,6-dimethyl-4-chloro-3-pyridyl isocyanate (IV)

Azide *I* or *II* (20 mmol) was dissolved in anhydrous toluene (200 cm^3) and heated at 120 °C for 2 h. Then charcoal was added, filtered, and toluene was distilled off *in vacuo*. The formed crude isocyanates *III* and *IV* were used in subsequent reactions.

N-Substituted N'-(2-chloro-3-pyridyl)ureas (V—IX) and N-substituted N'-(2,6-dimethyl-4-chloro-3-pyridyl)ureas (XII—XIX)

Into freshly prepared solution of isocyanate *III* or *IV* (25 mmol) in toluene cooled solution of the respective amine (25 mmol) in toluene or ether (100 cm^3) was added with stirring. The reaction mixture was allowed to stand at room temperature for 1 h while the corresponding ureas precipitated. These were dissolved in methanol, boiled with charcoal and, after evaporation of methanol, crystallized from the mixture of methanol—water (Tables 1 and 2).

N-(2-Chloro-3-pyridyl)-O- and -S-benzyl carbamates (X, XI) and N-(4-chloro-2,6-dimethyl-3-pyridyl)-O- and -S-benzyl carbamates (XX, XXI)

Into the solution of freshly prepared isocyanate *III* or *IV* (15 mmol) in toluene (100 cm^3) benzyl alcohol or phenylmethanethiol (15 mmol) in toluene (100 cm^3) was added dropwise with stirring and after 2 h a precipitate was formed. It was filtered off, boiled in methanol with charcoal, and crystallized from the mixture of methanol—water (Tables 1 and 2).

1-Phenyl-2-oxo-4,6-dimethylpyrido[3,4-d]imidazole (XXII)

The solution of urea *XVIII* (1 g; 3.63 mmol) in acetone (250 cm^3) was irradiated for 22 h under bubbling with nitrogen and stirring by using a high-pressure mercury lamp TQ 150 (Original Hanau) in an immersion equipment with the lamp placed in a quartz, water-cooled jacket. The product precipitated during the reaction and partially deposited also on the quartz jacket of the lamp. Therefore, photolysis was always interrupted after 3—4 h, the solution was filtered and the precipitate was removed from the jacket. Yield

of the product after combining the individual portions obtained on filtration of the reaction mixture was 0.5 g (57 %). M.p. = 307—310 °C (ethanol, decomposition).

For $C_{12}H_{13}N_3C$ (M_r = 239.3) w_i(calc.): 70.27 % C, 5.48 % H, 17.56 % N; w_i(found): 70.39 % C, 5.32 % H, 17.61 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 1670 (C = O). Mass spectrum, m/z (I_r/%): M^+ 239 (100), $[M - HOCN]^+$ 196 (1), $[C_6H_5NCO]^+$ 119 (6).

2-Aminopyrido[3,2-d]thiazole (XXIII)

Urea *V—IX* (20 mmol) and KSCN (7.6 g; 80 mmol) were dissolved in absolute ethanol under reflux and 37 % hydrochloric acid was added dropwise during 8 h up to pH = 1. After completion of the reaction ethanol was distilled off *in vacuo* and the formed solid was dissolved in water (250 cm^3). Then 24 % ammonium hydroxide was added up to pH = 10 and the precipitate formed was filtered off, dried, and crystallized from methanol. Yield of pyridothiazole *XXIII* was approximately 15 % with all thioureas used. M.p. = 240 °C (decomposition).

For $C_6H_5N_3S$ (M_r = 151.3) w_i(calc.): 47.68 % C, 3.34 % H, 27.81 % N; w_i(found): 48.01 % C, 3.62 % H, 27.89 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 1650 (C=N). ^{1}H NMR spectrum, δ/ppm: 7.80 (s, NH_2), 7.76 (m, C_5H_3N). Mass spectrum, m/z (I_r/%): M^+ 151 (100), $[M - HNCS]^+$ 92 (12), [pyridyl]$^+$ 76 (18).

2-Amino-4,6-dimethylpyrido[3,4-d]thiazole (XXIV)

Urea *XII—XIX* (10 mmol) and KSCN (3.8 g; 40 mmol) were dissolved under reflux in ethanol (100 cm^3) and the further procedure was as in the previous case. Yield of pyridothiazole *XXIV* was approximately 25 % with all thioureas used. M.p. = 275 °C (decomposition).

For $C_8H_9N_3S$ (M_r = 179.2) w_i(calc.): 53.69 % C, 5.02 % H, 23.46 % N; w_i(found): 53.51 % C, 5.32 % H, 23.56 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 1650 (C=N), 1575 (NH_2). ^{1}H NMR spectrum, δ/ppm: 2.61 (s, CH_3), 2.72 (s, CH_3), 7.53 (s, H_β), 7.81 (s, NH_2). ^{13}C NMR spectrum, δ/ppm: 21.00 and 23.11 (t, t, CH_3), 119.10, 140.72, 146.17, 149.72, and 156.58 (d, s, s, s, s, C_6HN), 165.60 (s, C=N).

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