Investigation of the regioselectivity of alkylation of 3-nitropyridin-2(1*H*)-ones

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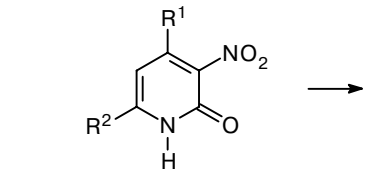
Alkylation of 3-nitropyridin-2(1*H*)-ones in the presence of bases affords *N*-alkylated products and sometimes *O*-alkylated products. The yields and relative amounts of *N*- and *O*-alkylated products depend substantially on the size of the substituent at the C(6) atom of pyridone.

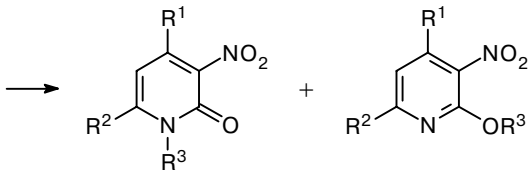
Key words: 3-nitropyridin-2(1*H*)-ones, alkylation, regioselectivity.

In the last few years, a number of derivatives of 3-amino-2-oxopyridin-1-ylacetic acid were covered by patents as inhibitors of thrombin[1,2] and human elastase.[3] An apparent procedure for the synthesis of these compounds involves alkylation of 3-nitropyridin-2(1*H*)-ones followed by hydrogenation of the nitro group to form the amino group. However, alkylation of 3-nitropyridin-2(1*H*)-ones, like alkylation of 3-cyanopyridin-2(1*H*)-ones described previously,[4—6] may afford both *N*- and *O*-alkylation products. Since data on the regioselectivity of alkylation of 3-nitropyridin-2(1*H*)-ones are lacking in the literature, it was of interest to study this problem.



1a—c

$R^1 = R^2 = H$ (**1a**); Me (**1b**);
$R^1 = H$, $R^2 = Ph$ (**1c**)



2a—j **3a—c**

	R^1	R^2	R^3
2a	H	H	Me
2b	H	H	CH_2Ph
2c	H	H	CH_2COPh
2d	H	H	CH_2COOH
2e	Me	Me	Me
2f	Me	Me	CH_2Ph
2g, 3a	Me	Me	CH_2COPh
2h, 3b	Me	Me	CH_2COOEt
2i	Me	Me	CH_2COOH
2j, 3c	H	Ph	Me

We found that alkylation of 3-nitropyridin-2(1*H*)-one (**1a**), which does not contain a substituent at position 6, gave rise only to *N*-alkylation products (**2a—d**), while *O*-alkylation products were not detected. Alkylation was performed in MeOH in the presence of MeONa. The formation of *O*-alkylation products was also not observed upon alkylation of 4,6-dimethyl-3-nitropyridin-2(1*H*)-one (**1b**) with methyl iodide or benzyl bromide performed under the same conditions. The melting points

Table 1. Yields and characteristics of the synthesized compounds

Compound	Yield (%)	M.p. /°C	Molecular formula	Found / Calculated (%)		
				C	H	N
2a	71.7	171—173	$C_6H_6N_2O_3$	47.2 / 46.75	3.7 / 3.92	18.0 / 18.18
2b	53	86—88	$C_{12}H_{10}N_2O_3$	61.9 / 62.61	4.1 / 4.38	12.0 / 12.17
2c	40.8	135—137	$C_{13}H_{10}N_2O_4$	60.5 / 60.47	3.8 / 3.90	10.9 / 10.85
2d	68	205—207	$C_7H_6N_2O_5$	42.4 / 42.43	3.1 / 3.05	14.0 / 14.14
2e	70.3	163—165	$C_8H_{10}N_2O_3$	52.9 / 52.74	5.4 / 5.53	15.0 / 15.38
2f	46.0	116—118	$C_{14}H_{14}N_2O_3$	64.8 / 65.11	5.2 / 5.46	10.3 / 10.85
2g	31	164—166	$C_{15}H_{14}N_2O_4$	62.5 / 62.93	4.7 / 4.93	9.9 / 9.78
2h	52.1	115—116	$C_{11}H_{14}N_2O_5$	51.5 / 51.97	5.7 / 5.55	10.9 / 11.02
2i	25	275—278 (decomp.)	$C_9H_{10}N_2O_5$	47.2 / 47.79	4.9 / 4.45	12.2 / 12.38
2j	17.3	157—158	$C_{12}H_{10}N_2O_3$	62.0 / 62.60	4.6 / 4.37	12.1 / 12.17
3a	3.7	93—95	$C_{15}H_{14}N_2O_4$	62.8 / 62.93	4.9 / 4.93	9.7 / 9.78
3b	2.9	34—36	$C_{11}H_{14}N_2O_5$	51.6 / 51.97	5.6 / 5.55	10.5 / 11.02
3c	50.3	102—103	$C_{12}H_{10}N_2O_3$	61.9 / 62.61	4.5 / 4.38	12.3 / 12.16

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Table 2. ^{1}H NMR and IR spectra of compounds **2a—j** and **3a—c**

Compound	IR (ν/cm^{-1})	^{1}H NMR, δ (J/Hz)
2a	1680 + 1592 (CON)	3.60 (s, 3 H, NMe); 6.40 (t, 1 H, H(5), ^3J = 7.0);
	1540 ($\nu_{as}(NO_2)$)	8.20 (dd, 1 H, H(4), ^3J = 6.7, ^4J = 1.5);
	1376 ($\nu_s(NO_2)$)	8.35 (dd, 1 H, H(6), ^3J = 7.4, ^4J = 1.5)
2b	1672 + 1592 (CON)	5.25 (s, 2 H, CH_2); 6.45 (t, 1 H, H(5), ^3J = 7.0);
	1536 ($\nu_{as}(NO_2)$)	7.30—7.40 (m, 5 H, Ph); 8.30 (dd, 1 H, H(4), ^3J = 6.6, ^4J = 1.5);
	1340 ($\nu_s(NO_2)$)	8.38 (dd, 1 H, H(6), ^3J = 7.4, ^4J = 1.5)
2c	1668 + 1592 (CON)	5.73 (s, 2 H, CH_2CO); 6.50 (t, 1 H, H(5), ^3J = 7.3);
	1536 ($\nu_{as}(NO_2)$)	7.60—8.05 (m, 5 H, Ph); 8.15 (d, 1 H, H(4), ^3J = 6.7, ^4J = 1.8);
	1348 ($\nu_s(NO_2)$)	8.45 (d, 1 H, H(6), ^3J = 7.9, ^4J = 1.8)
2d	1728 (COO)	4.80 (s, 2 H, CH_2COO); 6.45 (t, 1 H, H(5), ^3J = 7.3);
	1688 + 1600 (CON)	8.20 (d, 1 H, H(4), ^3J = 6.7, ^4J = 1.8);
	1516 ($\nu_{as}(NO_2)$)	8.40 (d, 1 H, H(6), ^3J = 8.0, ^4J = 1.8)
	1352 ($\nu_s(NO_2)$)	
2e	1660 + 1595 (CON)	2.18 (s, 3 H, 4-Me); 2.42 (s, 3 H, 6-Me);
	1535 ($\nu_{as}(NO_2)$)	3.50 (s, 3 H, NMe); 6.20 (s, 1 H, H(5))
	1380 ($\nu_s(NO_2)$)	
2f	1665 + 1600 (CON)	2.23, 2.38 (both s, 6 H, Me + Me); 5.35 (s, 2 H, CH_2);
	1525 ($\nu_{as}(NO_2)$)	6.20 (s, 1 H, H(5)); 7.10—7.40 (m, 5 H, Ph)
	1360 ($\nu_s(NO_2)$)	
2g	1680 (CO)	2.25, 2.35 (both s, 6 H, Me + Me);
	1600 (CON)	5.71 (s, 2 H, CH_2CO); 6.30 (s, 1 H, H(5));
	1520 ($\nu_{as}(NO_2)$)	7.50—8.20 (m, 5 H, Ph)
	1360 ($\nu_s(NO_2)$)	
2h	1740 (COO)	1.30 (t, 3 H, $C\underline{H}_3CH_2$, J = 7.1);
	1670 + 1600 (CON)	2.23, 2.38 (both s, 6 H, Me + Me); 4.21 (q, 2 H, CH_2, J = 7.1);
	1530 ($\nu_{as}(NO_2)$)	4.87 (s, 2 H, CH_2COO); 6.27 (s, 1 H, H(5))
	1375 ($\nu_s(NO_2)$)	
2i	1736 (COO)	2.20 (s, 3 H, 4-Me); 2.35 (s, 3 H, 6-Me);
	1660 + 1584 (CON)	4.75 (s, 2 H, CH_2COO); 6.25 (s, 1 H, H(5))
	1524 ($\nu_{as}(NO_2)$)	
	1376 ($\nu_s(NO_2)$)	
2j	1672 + 1600 (CON)	3.40 (s, 3 H, NMe); 6.35 (d, 1 H, H(5), ^3J = 7.9);
	1504 ($\nu_{as}(NO_2)$)	8.40 (d, 1 H, H(4), ^3J = 7.9); 7.55 (m, 5 H, Ph)
	1336 ($\nu_s(NO_2)$)	
3a	1700 (CO)	2.30 (s, 6 H, Me + Me); 5.79 (s, 2 H, OCH_2CO);
	1610 (CON)	6.90 (s, 1 H, H(5); 7.50—8.00 (m, 5 H, Ph)
	1580 ($\nu_{as}(NO_2)$)	
	1380 ($\nu_s(NO_2)$)	
3b	1740 (COO)	1.30 (t, 3 H, $C\underline{H}_3CH_2$, J = 7.2);
	1610 (CON)	2.31, 2.41 (both s, 6 H, Me + Me);
	1575 ($\nu_{as}(NO_2)$)	4.20 (q, 2 H, CH_2, J = 7.2); 4.95 (s, 2 H, CH_2COO);
	1380 ($\nu_s(NO_2)$)	6.95 (s, 1 H, H(5))
3c	1595 + 1576 (CON)	4.15 (s, 3 H, OMe); 7.50—8.20 (m, 5 H, Ph);
	1508 ($\nu_{as}(NO_2)$)	7.75 (d, 1 H, H(5), ^3J = 7.3);
	1344 ($\nu_s(NO_2)$)	8.50 (d, 1 H, H(4), ^3J = 7.3)

and the spectra of the resulting compounds are given in Tables 1—3.

However, alkylation of compound **1b** with halogenocarbonyl compounds (bromoacetophenone, ethyl bromoacetate, or chloroacetic acid) afforded both *N*- and *O*-alkylation products. In the reactions with bromoacetophenone or ethyl bromoacetate, products of both series were isolated (**2g** and **3a**; or **2h** and **3b**, respectively), whereas the *O*-alkylation product, which was formed in the reaction with chloroacetic acid, decomposed in the course of isolation and attempts to obtain the latter in the pure form failed. Alkylation of 3-nitro-6-phenylpyridin-2(1*H*)-one (**1c**) with methyl iodide was carried out in DMF (due to the low solubility of the initial nitropyridone in MeOH and EtOH). It was found that the latter reaction gave rise to a mixture of products **2j** and **3c**. Later on, it turned out that alkylation in DMF was preparatively much more convenient in the case of nitropyridones **1a,b** as well.

The ratios between the products of *N*- and *O*-alkylation of pyridones **1b** and **1c**, which were determined from the integral intensities of the corresponding signals in the ^{1}H NMR spectra of the reaction mixtures, are given in Table 4. From the data in Table 4 it follows that

Table 3. UV spectra (EtOH) of the initial pyridones **1a—c** and alkylated products **2c, 2e, 2g, 2j, 3a, 3b**, and **3c**

Compound	UV, λ_{max}/nm (ε)		
1a	254 (1410)		360 (5760)
2c	245 (10150)		362 (7250)
1b		309 (3240)	359 (1350)
2e		313 (5400)	362 (3900)
2g	241 (10400)	318 (1900)	359 (730)
3a	244 (5080)	282 (1400)	
1c	264.4 (2090)		390.6 (5690)
2j	258 (3010)		376 (8030)
3c	257.7 (2380)	343.6 (8440)	

the ratio between isomeric products **2** and **3** changes insignificantly on going from MeOH to aqueous DMF, but depends substantially on the nature of the substituents both in the starting pyridone and in the alkylating agent.

Therefore, it can be concluded that the regioselectivity of alkylation of 3-nitropyridin-2(1*H*)-ones depends on a number of factors and primarily on the size of the substituent at the C(6) atom of the initial substrate.

It should be noted that alkylation of 3-cyanopyridin-2(1*H*)-ones described in the literature is characterized by similar features. Thus, the reactions of 3-cyanopyridin-2(1*H*)-ones containing the hydrogen atom or the alkyl group at the C(6) atom performed in EtOH (or in mixtures of EtOH and DMSO) afford predominantly *N*-alkylation products, although the content of *O*-alkylated compounds increases as the size of the substituent becomes larger (simultaneously, the reaction time increases and the total yield of the products decreases).[4] Alkylation of 3-cyano-4,6-diphenylpyridin-2(1*H*)-one with methyl iodide in DMF gave rise only to the *O*-alkylation product.[5] However, it should be noted that the avaialble data are inadequate to quantitatively compare the regioselectivity of alkylation of 3-cyano- and 3-nitropyridin-2(1*H*)-ones and there is a need to perform special studies in which identically substituted pyridones will be alkylated under strictly standard conditions.

The structures of the resulting compounds were established by ^{1}H NMR and UV spectroscopy. Previously,[4,6] it was proposed to use the chemical shift of the methylene group at the nitrogen or oxygen atom in the case of 3-cyanopyridin-2(1*H*)-ones and it was stated that the signal of the OCH_2 group is shifted downfield with respect to the signal of the NCH_2 group by 0.6—1.0 ppm. In the case under consideration, the difference between the chemical shifts of the methyl groups at the nitrogen and oxygen atoms in compounds **2j** and **3c** is actually 0.75 ppm. However, the differences between the chemical shifts of the OCH_2 and NCH_2 groups for the pair **2g** and **3a** and for the pair **2h** and **3b** are small (less than 0.1 ppm). Hence, this method is in reality usable only if two isomers are present. The chemical shift for the proton at the C(5) atom proves to be much more informative. In the *N*-alkylated isomer of pyridone, the signal for this proton is insignificantly shifted downfield (by 0.05—0.2 ppm) relative to the signal for the H(5) proton in the initial pyridone, whereas the signal for this proton in *O*-alkylated pyridine is substantially shifted (by 0.6—1.4 ppm) downfield compared to that of the initial pyridone. The strong downfield shift is attributable to the appearance of the "aromatic" ring current on going from the pyridone to pyridine structure. Analogous differences are observed in the UV spectra of *N*- and *O*-alkylated pyridones (Table 3). The long-wavelength band with λ_{max} = 360—390 nm typical of nitropyridones is retained in the spectrum of the *N*-alkylated pyridone isomer and disappears in the spectra of *O*-alkylated aromatic structures **3a** and **3c**. The difference in the UV spectra is clearly seen in TLC plates using an indicator with the absorption maximum at 254 nm. Thus, the initial pyridone and the *N*-alkylated product were yellow, while the *O*-alkylated pyridine isomers were colorless and were observed as dark-blue spots under UV light.

Therefore, alkylation of 3-nitropyridin-2(1*H*)-ones affords primarily *N*-alkylation products, whereas the relative amounts of *O*-alkylation products depend substantially on the size of the substituent at the C(6) atom of pyridone.

Table 4. Ratios between the *N*- and *O*-alkylation products of 3-nitropyridin-2(1*H*)-ones

Pyridone	Alkylating agent	Solvent	Base	Ratio between *N*- and *O*-alkylation products	
1b	$BrCH_2COPh$	MeOH	MeONa	**2g** : **3a**	86.7 : 13.3
		DMF + H_2O	KOH	**2g** : **3a**	91.2 : 8.8
1b	$BrCH_2COOEt$	MeOH	MeONa	**2h** : **3b**	82.5 : 17.5
		DMF + MeOH	MeONa	**2h** : **3b**	80.3 : 19.7
1c	MeI	DMF + H_2O	KOH	**2j** : **3c**	35.7 : 64.3

Experimental

The ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument (250.13 MHz) in DMSO-d_6. The IR spectra were measured on a Specord M80 instrument in KBr pellets. The UV spectra were obtained on a Specord UV VIS instrument in EtOH. The yields and the melting points are listed in Table 1. The spectra are given in Tables 2 and 3.

The ratios between the *N*- and *O*-alkylation products were determined based on the intensity ratios for the corresponding signals in the ^{1}H NMR spectra of the reaction mixtures (see Table 2).

Synthesis of 1-R-3-nitropyridin-2(1*H*)-ones (general procedure for alkylation of compounds 2a—2c, 2e, and 2f). Nitropyridone **1a,b** (10 mmol) was dissolved in DMF (5—10 mL). Then a 10% aqueous solution of KOH (15 mmol) and haloalkane (20 mmol) were successively added to the reaction mixture. After 1—2 days, the initial pyridone was not detected in the mixture (TLC data). Then DMF was evaporated to one-third of the initial volume on a rotary evaporator (50—70 °C). Water (10 mL) and benzene (20—30 mL) were added to the residue. The benzene layer was separated and dried over $MgSO_4$ and the solvent was evaporated. The resulting products were recrystallized from a 1 : 1 benzene—hexane mixture.

Alkylation of nitropyridinones 1a,b in methanol (general procedure). Nitropyridone **1a,b** (10 mmol) was suspended in MeOH (200 mL) containing MeONa (14 mmol). Then the corresponding halogenocarbonyl compound (15 mmol) was added, the mixture was refluxed with stirring for 10 h, and the methanol was evaporated. Water (10 mL) and benzene (20—30 mL) were added to the residue, the benzene layer was separated and dried over $MgSO_4$, and the solvent was evaporated. The resulting products were recrystallized from a 1 : 1 benzene—hexane mixture.

4,6-Dimethyl-3-nitro-1-(2-oxo-2-phenylethyl)pyridin-2(1*H*)-one (2g) and 4,6-dimethyl-3-nitro-2-(2-oxo-2-phenylethoxy)pyridine (3a). The reactions were carried out according to the general procedure for alkylation (see above). Then the benzene solution was diluted threefold with hexane and the pyridone (**2g**) was filtered off. The mother liquor was concentrated to dryness in the presence of silica gel and the powder that formed was transferred on a Schott filter. Chromatographic separation was performed according to a procedure reported previously[7] to isolate pyridine **3a**.

Ethyl (4,6-dimethyl-3-nitro-2-oxopyridin-1-yl)acetate (2h) and ethyl (4,6-dimethyl-3-nitropyridin-2-yloxy)acetate (3b). Finely dispersed pyridone **1b** (5.0 g, 36.9 mmol) and $BrCH_2CO_2Et$ (7 g) were successively added to a solution of MeONa, which was prepared from MeOH (40 mL) and Na (0.85 g). The mixture was heated on a water bath at 70 °C for 4 h. Then MeOH was evaporated on a rotary evaporator and water (20 mL) was added to the residue. After a time, the precipitate was filtered off and recrystallized from toluene. Compound **2h** was obtained in a yield of 3.95 g (52.1%). The mother liquor was concentrated together with silica gel (1 g) and the powder that formed was transferred on a Schott filter. Chromatographic separation was performed according to a procedure reported previously[7] to obtain compound **3b** in a yield of 0.22 g (2.9%).

1-Methyl-3-nitro-6-phenylpyridin-2(1*H*)-one (2j) and 2-methoxy-3-nitro-6-phenylpyridine (3c). Pyridone **1c** (200 mg, 0.92 mmol) was dissolved in DMF (10 mL). Then MeI (0.5 mL, 8 mmol) and a solution of KOH (70 mg, 1.25 mmol) in water (1 mL) were added. After 24 h, DMF was evaporated on a rotary evaporator (50—70 °C). Water (5 mL) and benzene (20 mL) were added to the residue, the benzene layer was separated and dried over $MgSO_4$, and the solvent was evaporated on a rotary evaporator in the presence of silica gel (1 g). The powder that formed was transferred on a Schott filter. Chromatographic separation was performed according to a procedure reported previously[7] to obtain compounds **2j** and **3c** in yields of 37.3 mg (17.3%) and 107.1 mg (50.3%), respectively.

Alkylation of nitropyridones with chloroacetic acid (general procedure for compounds 2d and 2i). Water (30 mL) was added to a mixture of pyridone **1b** (10 mmol) and $ClCH_2CO_2H$ (20 mmol). Then $NaHCO_3$ (4.2 g, 50 mmol) was added portionwise with stirring. The reaction mixture was refluxed (15 min for **2d** and 4 h for **2i**), cooled, and acidified to pH 7. The unconsumed nitropyridone was filtered off and the reaction mixture was acidified to pH 1 and kept at +4 °C for 12 h. The crystals that formed were filtered off, washed with cold water, and dried at 50—60 °C to obtain products **2d** and **2i**.

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