AMIDOALKYLATION OF PYRAZINE-2,3-DICARBONITRILE BY THE RADICAL GENERATED FROM *N*-ALKANOYLANILINO-ALKANOIC ACID

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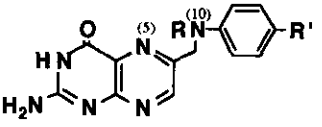
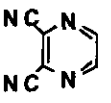
Abstract - *N*-Alkanoylanilinoacetic acid and 2-*N*-alkanoylanilinopropionic acid gave *N*-alkanoylanilinomethyl radical and 1-*N*-alkanoylanilinoethyl radical respectively by the peroxodisulfate oxidation catalized by silver ion. The former radical reacts with pyrazine-2,3-dicarbonitrile to give both monosubstitution product (**6**) and disubstitution product (**7**), whereas the latter radical gives only monosubstitution product due to the steric hindrance for the second radical substitution.

Folic acid (**1**) is an important C_1-carrier in biological systems,[1] in which the tetrahydropteridine having an arylaminomethyl group is an active form, and 5- and 10-nitrogens are the carrying sites of the C_1-unit; -CHO, CH_2OH, and CH_3. We have reported the transformation of pyrazine-2,3-dicarbonitrile (**2**) into 1,2,3,4-tetrahydropteridine-2,4-dione (**3**),[2] a reasonable model system of 3,4-dihydropteridin-4-one moiety of the folate coenzyme. In addition 5-arylaminomethylpyrazine-2,3-dicarbonitrile is a reasonable model of folic acid (**1**).



1 R'=CONH(COOH)CH_2CH_2COOH



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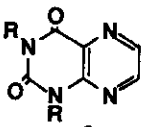

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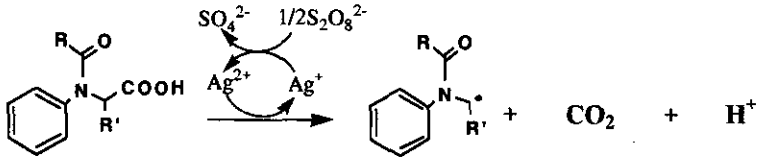
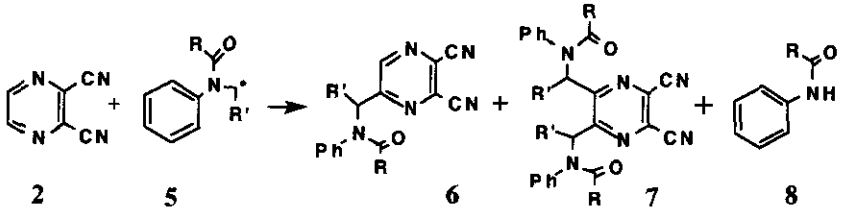
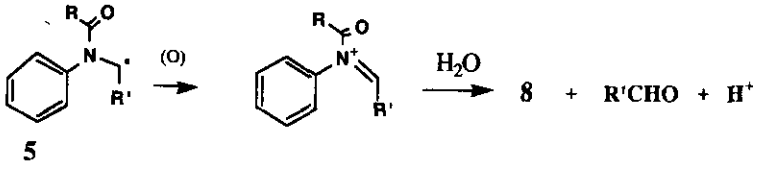
Therefore we have tried the arylaminoalkylation of pyrazine-2,3-dicarbonitrile (**2**) using *N*-alkanoylanilinomethyl radical (**5**) (R'=H) or 1-*N*-alkanoylanilinoethyl radical (**5**) (R'=CH_3) to get 5-*N*-alkanoylanilinoalkylpyrazine-2,3-dicarbonitrile (**6**).



Scheme I



Scheme II



Scheme III

These radicals were generated by Minisci oxidation[3] ($S_2O_8^{2-}/Ag^+$) of the corresponding 2-*N*-alkanoylanilinoalkanoic acid (**4**) in aqueous acetonitrile (Scheme I). The reactions of thus formed 1-amidoalkyl radical (**5**) with pyrazine-2,3-dicarbonitrile (**2**) gave monoamidoalkylpyrazines (**6**), diamidoalkylpyrazine (**7**), and alkanoylanilide (**8**) (Scherme II). The anilide (**8**) must be produced by the oxidative dealkylation of the radical (**5**) under the reaction conditions (Scheme III). The reaction conditions and yields of the products are listed in Table 1.

Table 1. The Reaction of *N*-alkanoylanilinoalkyl Radical (**5**) with Pyrazine- 2,3-dicarbonitrile (**2**).

Run	R	R'	[4] / [2][a]	$[S_2O_8^{2-}]$ / [2]	$[Ag^+]$ / [2]	Product (yield/%)[b]		
1	CH_3	H	2.0	1.0	0.1	**6a**(26)	**7a**(6)	**8**(20)
2	CH_3	H	2.0	2.0	0.2	**6a**(34)	**7a**(16)	**8**(24)
3	CH_3	H	3.0	2.0	0.2	**6a**(37)	**7a**(38)	**8**(2)
4	CH_3	H	3.0	3.0	0.3	**6a**(30)	**7a**(60)	**8**(31)
5	CH_3	CH_3	2.0	1.0	1.0	**6c**(22)	--	**8**(8)
6	CH_3	CH_3	5.0	2.5	0.25	**6c**(9)	--	**8**(15)
7	CH_3	CH_3	5.0	2.5	2.5	**6c**(65)	--	**8**(27)
8	CH_3	CH_3	5.0	5.0	2.5	**6c**(83)	--	**8**(51)
9	H	H	2.0	2.0	0.2	**6b**(45)	**7b**(9)	**8**(21)
10	H	H	2.0	3.0	0.3	**6b**(29)	**7b**(9)	**8**(5)
11	H	H	2.0	4.0	0.4	**6b**(36)	**7b**(6)	**8**(5)
12	H	CH_3	2.0	2.0	0.2	**6d**(7)	--	**8**(33)
13	H	CH_3	2.0	2.0[c]	0.2	**6d**(20)	--	**8**(12)
14	H	CH_3	2.0	2.0[d]	0.2	**6d**(11)	--	**8**(20)

[a] [2] = 1.0 mmol/l.

[b] Yields of **6** and **7** are based on the amount of the starting material (**2**), and those of **8** are based on the starting material (**4**).

[c] A mixture of ammonium peroxodisulfate and silver nitrate in water was added to the mixture of **2** and **4**.

[d] Potassium peroxodisulfate was used instead of the ammonium salt.

Structures of the products were determined straightforwardly by the characteristic ^{1}H-nmr signals due to the hydrogen on pyrazine ring and also by the signals due to the formyl or acetyl group. Molecular peaks and reasonable fragment peaks are also seen in the mass spectra of the products (see Experimental).

The carboxyl group of 2-amidoalkanoic acid is easily oxidized by the single electron oxidant Ag^{2+} [3] to give a 1-amidoalkyl radical, which attacks the pyrazine ring having electrophilic property. Acetanilinomethyl radical (**5a**) (R=CH_3, R'=H) and formanilinomethyl radical (**5b**) (R=H, R'=H) gave both monosubstitution and disubstitution products (**6** and **7**) of pyrazine-2,3-dicarbonitrile on the use of an excess amount of the alkanoic acid and oxidant, whereas 1-acetanilinoethyl radical (**5c**) (R=CH_3, R'=CH_3) and 1-formanilinoethyl radical (**5d**) (R=H, R'=CH_3) gave only the monosubstitution product (**6**).

Those behaviors are in good accordance with those of the radical alkylation of pyrazine-2,3-dicarbonitrile with alkyl radicals[4] and *N*-phthaliminoalkyl radical.[5] Simple secondary alkyl radicals can give disubstitution products by stepwise alkylation but secondary *N*-phthaliminoalkyl radicals cause only monoalkylation. These properties of 1-amidoalkyl radical and phthaliminoalkyl radical must be mainly due to the steric bulkiness of the amide or imide groups. We recorded rather high total yields of mono- and disubstitution products from 1-acetanilinoalkyl radical when an excess amount of the alkanoic acids and the oxidant were used, 90% for **6a** + **7a** (R=CH_3, R'=H) (run 4) and 83% for **6c** (R=R'=CH_3) (run 8). The yields of the formanilinoalkylation, however, remain modrate even under the use of an excess amount of the reagents. This must be attributable to the instability of the formyl group under the present oxidative conditions since the use of ecxess reagent further reduced the yields.

We could not use large amount of the oxidation reagent and silver salt for this reason and the yields of **6b** and **6d** (R=H, R'=H, CH_3) are moderate. The catalytic cycle between silver(I) and silver(II) ion (Scheme II) seems not efficient and the equimolar mixture of peroxodisulfate and silver nitrate (run 7) gave the better results than the catalytic reaction (run 6). Generally the yields of **6** and **7** from amidomethyl radical (**5**) (R'=H) is better than those from 1-amidoethyl radical (**5**) (R'=CH_3) (run 9 *vs* 13 and 14). The reactivity of secondary alkyl radical is higher than primary alkyl radical. Therefore, this difference in the yields of the substitution products can be accounted for by the oxidative decay of the intermediate radical (**5**) (Scheme III).

In conclusion, the models of the folate carrying an *N*-CHO (C_1-unit) were prepared in 45% with **6b** (R=H, R'=H) (run 9) and 20% with **6a** (R=CH_3, R'=H) at best (run 13), but the folate models carrying *N*-acetyl group were obtained in higher yields.

EXPERIMENTAL

Materials and Spectra

Ir spectra were measured in chloroform by a Shimadzu IR-400 spectrometer. ^{1}H-nmr spectra were measured by a Hitachi R-24 (60 MHz) or a Hitachi R-90 (90 MHz) spectrometer in deuteriochloroform. Chemical shifts and coupling constants are recorded in δ value and Hz

respectively. Mass spectra were measured by a JEOL JMS-DX306 spectrometer by electron impact ionization at 70eV.

Pyrazine-2,3-dicarbonitrile (mp 126-127 °C),[6] acetoanilinoacetic acid (mp 189 °C), 2-Acetoanilinopropionic acid (mp 138 °C), formanilinoacetic acid (mp 122 °C), and 2-formanilinopropionic acid (mp 93-94 °C) were prepared by the reported methods[7] and those acids were fully characterized by spectroscopic data.

General Procedure for the Reaction of Pyrazine-2,3-dicarbonitrile (2) with N-Alkanoylanilinoacetic Acid (4, R'=H) or 2-N-Alkanoylanilinopropionic Acid (4, R'=CH3) under Oxidative Conditions.

To a two necked flask was placed a mixture of pyrazine-2,3-dicarbonitrile (130 mg, 1.0 mmol), 2-alkanoylanilinoalkanoic acid (2.0 - 5.0 mmol), silver nitrate (17.0 - 425 mg, 0.1 - 2.5 mmol), and 7 - 10 ml of the mixed solvent of acetonitrile-water (3:5) (degassed by bubbling argon in an ultrasonic bath) in the ratio listed in Table 1. The mixture was treated with 1 ml of aqueous solution of ammonium peroxodisulfate (228 mg - 1.41 g, 1.0 - 5.0 mmol) by a syringe during 10 min at 80-90 °C and the reaction mixture was kept at the same temperature for 40 min under argon. After cooling and addition of 5% aqueous ammonia to ajust pH 8 - 9, the products were extracted with chloroform. Washing with water, drying over sodium sulfate, and condensation of the extract gave the crude products. The crude products were separated by a preparative tlc on silica gel (5mm x 20cm x 20cm) using hexane-ethyl ether (4:1). Homogeneity of non-crystalline products was checked by tlc and ^{1}H-nmr spectra. High resolution mass spectra of those products gave the correct molecular peaks.

Compound **6a** (R=CH_3, R'=H), mp 90 °C (hexane); ^{1}H-nmr 1.95(s, 3H), 5.07(s, 2H), 7.25-7.48(m, 5H), 8.95(s, 1H); ir 3010, 2250, 1659 cm^{-1}; ms m/z(%) 277(M^+, 1.8), 235(M^+-$COCH_2$, 15), 106($C_6H_5NHCH_2^+$, 25), 77(21), 51(11), 43(100). *Anal. Calcd for* $C_{15}H_{11}N_5O$: C, 64.93; H, 4.00; N, 25.26. *Found*: C, 65.22; H, 3.89; N, 25.52.

Compound **7a** (R=CH_3, R'=H), viscous oil; ^{1}H-nmr 1.91(s, 6H), 5.13(s, 4H), 7.36(diffused s, 10H); ir 3010, 2255, 1656 cm^{-1}; ms m/z(%) 424(M^+, 39), 332(M^+- C_6H_5NH, 100), 249(22), 247(31), 136(30), 93($C_6H_5NH_2$, 89), 43(24); high resolution mass, *Calcd for* $C_{24}H_{20}N_6O_2$: 424.1648. *Found*: 424.1647.

Compound **6b** (R=H, R'=H), mp 111 °C (hexane); ^{1}H-nmr 5.14(s, 2H), 7.19-7.35(m, 5H), 8.41(s, 1H), 8.79(s, 1H); ir 3005, 2260, 1677 cm^{-1}; ms m/z(%) 263(M^+, 9.4), 235(M^+- CO, 26), 106($C_6H_5NHCH_2$, 100), 59(12%); high resolution mass, *Calcd for* $C_{14}H_9N_5O$: 263.0807. *Found*: 263.0789.

Compound **7b** (R=H, R'=H), viscous oil; ^{1}H-nmr 5.41(s, 4H), 7.17-7.34(m, 10H), 8.34(s, 2H); ir 3005, 2265, 1674 cm^{-1}; ms m/z(%) 396(M^+, 7.3), 368(M^+- CO, 100), 247(59), 122(18), 93(100); high resolution mass, *Calcd for* $C_{22}H_{16}N_6O_2$: 396.1334. *Found*: 396.1321.

Compound **6c** (R=CH_3, R'=CH_3), mp 89-90°C (chloroform-hexane); ^{1}H-nmr 1.50 (d, J=8, 3H), 1.81(s, 3H), 5.71(q, J=8, 1H), 7.10-7.61(m, 5H), 9.10(s, 1H); ir 3050, 2260, 1650 cm^{-1}; ms m/z(%) 291(M^+, 5.8), 249(99), 234(100), 157(5.9), 131(2.5), 120(82), 104(14), 93(13), 77(43), 65(11); high resolution mass, *Calcd for* $C_{16}H_{13}N_5O$: 291.1093. *Found*: 291.1107. *Anal. Calcd for* $C_{16}H_{13}N_5O$: C, 65.97; H, 4.50; N, 24.04. *Found*: C, 66.31; H, 4.90; N, 24.09.

Compound **6d** (R=H, R'=CH_3), powdery solid; ^{1}H-nmr 1.70(d, J=8, 3H), 5.70(q, J=8, 1H), 7.05-7.60(m, 5H), 8.30(s, 1H), 9.05(s, 1H); ir 3050, 2265, 1670 cm^{-1}; ms m/z(%) 277(M^+, 9.4), 260(2.6), 249(55), 234(91), 158(27), 148(2.4), 131(4.4), 120(100), 104(16), 93(21), 77(52), 65(22); high resolution mass, *Calcd for* $C_{15}H_{11}N_5O$: 277.0963. *Found*: 277.0969.

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