Reaction of Pyrazine-2,3-dicarbonitrile and 1,3-Dimethyllumazine with the Phthalimidoalkyl Radical

Masaru Tada* and Shintaro Totoki

Department of Chemistry, School of Science and Engineering, Waseda University, Shinjuku, Tokyo 160, Japan

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A phthalimidoalkyl radical reacts with pyrazine-2,3-dicarbonitrile (**1**) to give mono- and diphthalimidoalkylpyrazine-2,3-dicarbonitriles **4** and **5**. A similar reaction with 1,3-dimethyllumazine (**2**) gave only monophthalimidoalkyl-1,3-dimethyllumazines **6** or **7**. Hydrazine degradation of 7-(3'-phthalimido)propyl-1,3-dimethyllumazine (**6c**) gave a 7-(3'-amino)propyl derivative **8** but 7-phthalimidomethyl-1,3-dimethyllumazine (**6a**) gave only 1,3-dimethyllumazine (**2**). Thus the phthalimidomethyl group can be used as a protection group of the pteridine nucleus.

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Pyridine and quinoline derivatives react with an alkyl or an acyl radical to give substitution products under acidic conditions [1]. Pyrazine and pteridine derivatives are typical π-deficient heterocycles and react with an alkyl or an acyl radical without acid catalysis to give alkyl- or acyl-substitution products [2-5]. Radical substitutions of pyrazine and pteridine are of increasing importance and a few examples of transformations of the pteridines of biological importance have been reported [4,5].

One electron oxidation of an alkanoic acid (Minisci oxidation) is convenient for the generation of the alkyl radical (Equation 1) [6] and we have reported substitutions of pyrazine-2,3-dicarbonitrile (**1**) and 1,3-dimethyllumazine (**2**) with alkyl radicals generated by Minisci oxidation [2].

Equation 1

$$RCOOH \xrightarrow{S_2O_8^{=} / Ag^+} R\cdot + CO_2 + H^+$$

An *N*-alkylphthalimide is a latent alkylamine since hydrazine degradation of the alkylphthalimide gives alkylamine in a simple manner [7]. Biologically important pteridines such as folic acid and methotrexate have aminomethyl groups [8]. Further we have reported the transformation of pyrazine-2,3-dicarbonitrile into pteridine derivatives [9]. These situations prompted us to investigate the substitution of pyrazine-2,3-dicarbonitrile (**1**) and 1,3-dimethyllumazine (**2**) by phthalimidoalkyl radicals, and the results are reported in this paper.

Results.

Reaction of Pyrazine-2,3-dicarbonitrile.

Minisci oxidation of phthalimidoalkanoic acid **3** [7] in the presence of pyrazine-2,3-dicarbonitrile (**1**) gave 5-(phthalimidoalkyl)pyrazine-2,3-dicarbonitrile **4** and 5,6-di(phthalimidoalkyl)pyrazine-2,3-dicarbonitrile **5** (Scheme I).

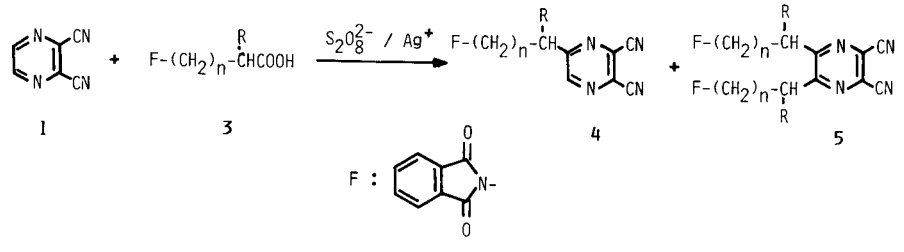
Table

Reaction of Pyrazine-2,3-dicarbonitrile (**1**)

Starting Material	n	R	3/1	Yield (%) 4	5
3a	0	H	3.3	trace	58
			1.7	26	25
			1.1	48	0
3b	1	H	3.3	7	67
			1.1	55	10
3c	2	H	3.3	8	46
			1.1	55	11
3d	0	CH_3	3.3	98	0
			1.1	55	0

The strong ir absorptions due to the phthalimide group in the products appear at *ca.* 1780 and 1720 cm^{-1} but the absorptions due to the cyano group are weak or not seen since the carbonyl absorptions have strong intensities in ordinary spectra. Nevertheless the structures of products **4**

Scheme I



and **5** are easily assigned by elemental analyses and nmr spectra. Products **4** are characterized by signals at δ = 8.2-8.8 due to the pyrazine ring protons and by the coupling pattern of signals due to the methylene group between the pyrazine and phthalimide groups. Products **5** are characterized by replacement of the signals due to the pyrazine ring proton by the signals due to the second methylene group.

In all reactions we used 1:1.5 molar mixtures of phthalimidoalkanoic acid **3** and ammonium peroxodisulfate with catalytic amount of silver nitrate, but the ratio of **3**/**1** was changed from 3.3:1 to 1:1 and the yields of products are listed in the Table.

Reaction of 1,3-Dimethyllumazine.

1,3-Dimethyllumazine (**2**) was reacted with the radical generated from phthalimidoalkanoic acid **3** as in the case of pyrazine-2,3-dicarbonitrile (**1**). Primary radicals gave only 7-substituted lumazines in 80% (**6a**), 79% (**6b**), and 80% (**6c**), but the secondary radical from acid **3a** gave both 7- (**6d**) and 6-substituted lumazine (**7d**) in 58% and 14% yield respectivley (Scheme II).

Structure assignment of product **6** and **7** was based on elemental analyses, nmr spectra, and analogy of the reactivity of **2** to the alkyl radical [2]. 1,3-Dimethyllumazines substituted at C-7 with a primary or secondary alkyl group show the singlet signals between δ = 8.36-8.49 due to the ring proton (C-6-H) [2]. The C-6-H protons of **6a-6c** show signals in this region. Discrimination of **6d** and **7d** was made by ^{1}H-nmr and ^{13}C-nmr. The chemical shift of the ring proton is higher for **6d** (8.58) than for **7d** (8.78). The ^{13}C-nmr signal due to C-6 shifts from 157.8 for **6d** to 145.7 for **7d** whereas the signal due to C-7 shifts from 150.3 for **7d** to 137.7 for **6d**. These shifts to higher field are accounted for by ring substitution at C-7 for **6d** and C-6 for **7d**.

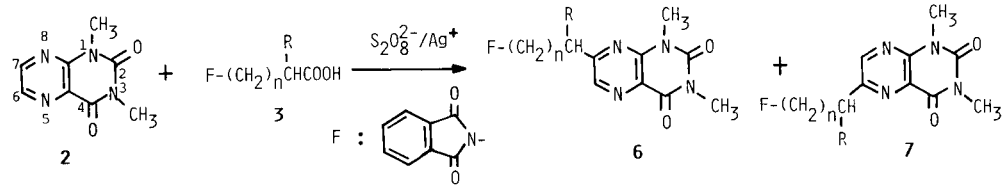
This behavior is explained by the variation of the π-electron density at C-6 due to the carbonyl group at the *para*-position.

Next we tried the conversion of the phthalimidoalkyl group of **6** to aminoalkyl. Treatment of 7-(3'-phthalimidopropyl)-1,3-dimethyllumazine (**6c**) with hydrazine in ethanenitrile gave 7-(3'-aminopropyl)-1,3-dimethyllumazine (**8**) in 72% yield. Hydrazine degradation of 7-(phthalimidomethyl)-1,3-dimethyllumazine (**6a**), however, gave only **2** (55%) which formed by the loss of the phthalimidomethyl group. Radical methylation of **6a** gave product **9** and hydrazine degradation of **9** gave 1,3,6-trimethyllumazine [10] (Scheme III).

Discussion.

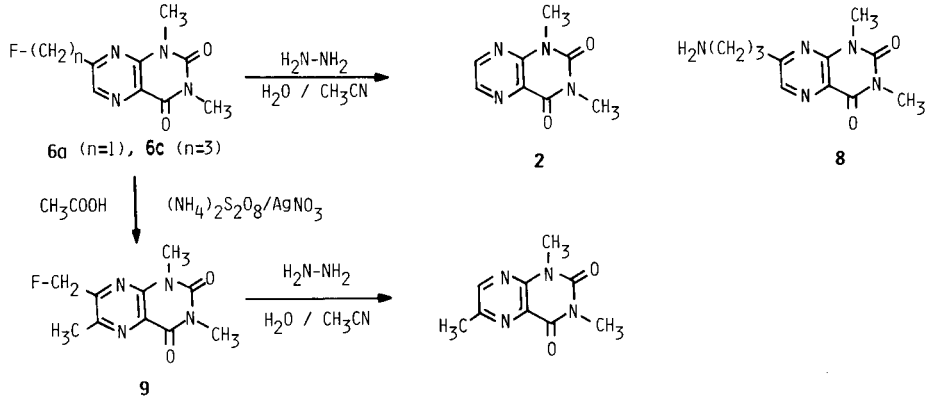
Alkyl and acyl radicals have nucleophilic character in the substitution reaction on the pyridinium or the quinolinium ion [1-5]. In these reactions SOMO (singly occupied molecular orbital) of radical and LUMO (lowest unoccupied molecular orbital) of the heterocycle interact to initiate the reaction. Pyrazine and lumazine are typical π-deficient heterocycles having a low energy level LUMO,

Scheme II

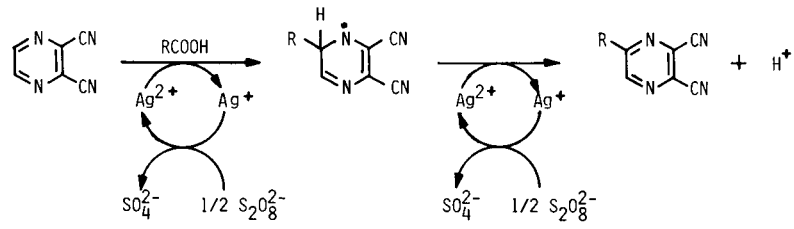


3a, **6a** : n=0, R=H **3b**, **6b** : n=1, R=H
3c, **6c** : n=2, R=H **3d**, **6d**, **7d** : n=0, R=CH_3

Scheme III



Scheme IV

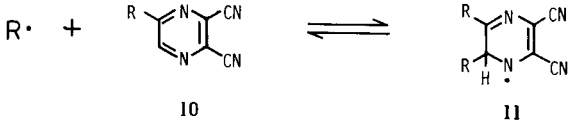


and we can expect strong interaction with the SOMO of the radical species. This concept was realized by the observed high reactivity of pyrazine-2,3-dicarbonitrile (**1**) and 1,3-dimethyllumazine (**2**).

These radical reactions require two equivalents of the oxidation reagent (Scheme IV), and the 1:2 molar mixture of peroxodisulfate and **1** gave the product in not over 50% yield even when a large excess of phthalimidoalkanoic acid was used.

Primary radicals from **3a-3c** gave both mono-, **4**, and di-substituted products **5** from **1** whereas the radical from **3d** gave only the mono-substituted product **4**. This feature is accounted for by reversibility of the radical addition (Equation 2) [11,12]. When the radical R· is secondary, a radical intermediate **11** is sterically crowded and the equilibrium must be favored for **10**. In simple radical alkylations, the *t*-butyl radical causes only mono-substitution. The 1-phthalimidoethyl radical from **3d** is secondary but is considered to be more bulky than the isopropyl radical.

Equation 2



10 11

1,3-Dimethyllumazine (**2**) undergoes radical substitution but causes only mono-substitution. This feature is accounted for by the reduced radicophilicity of **2** compared to **1**, and the mono-substituted products, **6** and **7** are further less radicophilic due to the rise of LUMO by alkyl substitution. Preferential formation of **6** over **7** must be due to the difference in radicophilicity of C-6 and C-7 of **2**. The position *para* to carbonyl (C-7) must be more reactive to the nucleophilic radicals, but the secondary radical is more nucleophilic than the primary radical and gives also the (C-6)-substitution product in a lower amount.

Removal of the phthalimidomethyl group on hydrazine degradation is unexpected but the hydrazine degradation of **6c** gave an expected 7-(3'-aminopropyl)-1,3-dimethyllumazine (**8**) in 72% yield. We presently have no explanation for the loss of the phthalimidomethyl group but it opens a new utility of this group as a protecting group of the C-7 position of lumazine. Alkyl radical substitution of lumazine takes place preferentially at C-7 and the alkylated product at C-6 is difficult to prepare, but this difficulty is overcome by the alkylation of **6** at C-6 and removal of the protection group. Thus radical methylation of **6a** followed by hydrazine degradation gave 1,3,6-trimethyllumazine [10]. On the other hand, direct methylation of **2** by Minisci oxidation (acetic acid/ammonium peroxodisulfate/silver nitrate) gave 1,3,7-trimethyllumazine (8%) [13] and 1,3,6,7-tetramethyllumazine (54%) [13], but no 1,3,6-trimethyllumazine was obtained.

In conclusion pyrazine-2,3-dicarbonitrile and 1,3-dimethyllumazine react with phthalimidoalkyl radicals to give phthalimidoalkyl-substituted products. The reaction is promising for the introduction of an aminoalkyl group to π-deficient heterocycles, and further the present results open a new potential of the phthalimidomethyl group as a protecting group of π-deficient heterocycles.

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EXPERIMENTAL

Materials and Spectra.

Pyrazine-2,3-dicarbonitrile (**1**) [14] and 1,3-dimethyllumazine (**2**) [15] were prepared by reported methods. Phthalimidoalkanoic acids were prepared from phthalimide and the corresponding amino acids by the reported method [16].

All ir spectra were taken in chloroform solution and the nmr spectra were determined in deuteriochloroform solution. Chemical shifts and coupling constants are recorded in δ-value and Hz respectively.

Reaction of Pyrazine-2,3-dicarbonitrile (**1**).

All the reactions and work up of the reaction of the phthalimidoalkyl radical with pyrazine-2,3-dicarbonitrile (**1**) were carried out essentially in the same manner and one example is described as a representative.

In a 50 ml flask were placed compound **1** (3 mmoles), phthalimidoacetic acid (5 mmoles), ammonium peroxodisulfate (7.5 mmoles), and silver nitrate (0.6 mmole). Air in the system was replaced by argon and the mixture was refluxed for 5.5 hours after addition of 35 ml of an ethanenitrile-water (7:3) mixture. After cooling most of ethanenitrile was evaporated under reduced pressure and the resulting aqueous layer was extracted twice with 30 ml of chloroform. After washing with aqueous sodium hydrogen carbonate and drying over sodium sulfate, evaporation of the chloroform gave 0.7 g of solid residue. The residue was separated into 5-(phthalimidomethyl)pyrazine-2,3-dicarbonitrile (**4a**) and 5,6-di-(phthalimidomethyl)pyrazine-2,3-dicarbonitrile (**5a**) by the preparative tlc on silica gel eluting with dichloromethane.

Compound **4a** decomposed at 165-170°; ir: 1789, 1720 cm^{-1}; ^1H-nmr: 5.47 (2H, s), 7.70-8.02 (4H, m), 8.95 (1H, s).

Anal. Calcd. for $C_{15}H_7N_5O_2$: C, 62.28; H, 2.44; N, 24.21. Found: C, 62.08; H, 2.40; N, 23.91.

Compound **5a** decomposed at 256-257°; ir: 1780, 1730 cm^{-1}; ^1H-nmr: 5.53 (4H, s), 7.80-8.12 (8H, m).

Anal. Calcd. for $C_{24}H_{12}N_6O_4$: C, 64.28; H, 2.70; N, 18.74. Found: C, 64.00; H, 2.70; N, 18.33.

Compound **4b** decomposed at 175-178°; ir: 1780, 1718 cm^{-1}; ^1H-nmr: 3.34 (2H, t, J = 7), 4.16 (2H, t, J = 7), 7.63-7.94 (4H, m), 8.78 (1H, s).

Anal. Calcd. for $C_{16}H_9N_5O_2$: C, 63.36; H, 2.99; N, 23.09. Found: C, 63.45; H, 2.92; N, 22.78.

Compound **5b** decomposed at 205-207°; ir: 1780, 1718 cm^{-1}; ^1H-nmr: 3.38 (4H, t, J =7), 4.20 (4H, t, J = 7), 7.65-7.95 (8H, m).

Anal. Calcd. for $C_{26}H_{16}N_6O_4$: C, 65.54; H, 3.39; N, 17.64. Found: C, 65.51; H, 3.35; N, 17.60.

Compound **4c** decomposed at 117-118°; ir: 1776, 1716 cm^{-1}; ^1H-nmr: 2.28 (2H, quintet, J = 7), 3.09 (2H, t, J = 7), 3.80 (2H, t, J = 7), 7.67-7.89 (4H, m), 8.77 (1H, s).

Anal. Calcd. for $C_{17}H_{11}N_5O_2$: C, 64.35; H, 3.49; N, 22.07. Found: C, 64.26; H, 3.63; N, 22.44.

Compound **5c** decomposed at 165-166°; ir: 1776, 1714 cm^{-1}; ^1H-nmr: 2.28 (4H, quintet, J = 7), 3.02 (4H, t, J = 7), 3.83 (4H, t, J = 7), 7.63-7.92 (8H, m).

Anal. Calcd. for $C_{28}H_{20}N_6O_4$: C, 66.66; H, 4.00; N, 16.66. Found: C, 66.88; H, 4.25; N, 16.43.

Compound **4d** decomposed at 163-164°; ir: 1782, 1720 cm^{-1}; ^1H-nmr: 1.90 (3H, d, J = 7), 5.73 (1H, q, J = 7), 7.80-8.00 (4H, m), 9.22 (1H, s).

Anal. Calcd. for $C_{16}H_9N_5O_2$: C, 63.36; H, 2.99; N, 23.09. Found: C, 63.34; H, 3.10; H, 22.75.

Reaction of 1,3-Dimethyllumazine (**2**).

The reactions were carried out essentially in the same manner and scale as described in the previous section for the reaction of pyrazine-2,3-dicarbonitrile (**1**). A work up procedure was also similar to the case of compound **1** but a mixed solvent of ethyl acetate-hexane (1:1) was used for the preparative tlc.

7-(Phthalimidomethyl)-1,3-dimethyllumazine (**6a**).

This compound was obtained in 80% yield and was recrystallized from ethanenitrile, mp 238-239°; ir: 1778, 1720, 1674 cm^{-1}; ^1H-nmr: 3.29 (3H, s), 3.30 (3H, s), 4.98 (2H, s), 7.56-7.89 (4H, m), 8.45 (1H, s).

Anal. Calcd. for $C_{17}H_{13}N_5O_4$: C, 58.12; H, 3.73; N, 19.94. Found: C, 58.35; H, 3.66; N, 19.58.

Compound **6b** was obtained in 79% yield and was recrystallized from ethanenitrile, mp 209-210°; ir: 1780, 1716, 1666 cm^{-1}; ^1H-nmr: 3.27 (2H, t, J = 7), 3.43 (3H, s), 3.50 (3H, s), 4.66 (2H, t, J = 7), 7.55-7.85 (4H, m), 8.36 (1H, s).

Anal. Calcd. for $C_{18}H_{15}N_5O_4$: C, 59.17; H, 4.14; N, 19.17. Found: C, 59.28; H, 4.00; N, 18.93.

Compound **6c** was obtained in 80% yield and was recrystallized from ethanenitrile, mp 196-197°; ir: 1778, 1718, 1670 cm^{-1}; ^1H-nmr: 2.25 (2H, quintet, J = 7), 2.97 (2H, t, J = 7), 3.45 (3H, s), 3.64 (3H, s), 3.79 (2H, t, J = 7), 7.50-7.85 (4H, m), 8.34 (1H, s).

Anal. Calcd. for $C_{19}H_{17}N_5O_4$: C, 60.15; H, 4.52; N, 18.46. Found: C, 60.15; H, 4.32; N, 18.33.

Compound **6d** was obtained in 58% yield and was recrystallized from ethanenitrile, mp 205-205.5°; ir: 1778, 1716, 1676 cm^{-1}; ^1H-nmr: 1.97 (3H, d, J = 7), 3.47 (6H, s), 5.69 (1H, q, J = 7), 7.61-7.95 (4H, m), 8.57 (1H, s); ^{13}C-nmr: 28.7, 28.8, 48.7, 123.2, 126.1, 131.1, 134.1, 137.7 (C-7), 146.8, 150.2, 157.8 (C-6), 159.4, 167.8.

Anal. Calcd. for $C_{18}H_{15}N_5O_4$: C, 59.17; H, 4.14; N, 19.17. Found: C, 59.44; H, 4.10; N, 19.13.

Compound **7d** was obtained in 58% yield and was recrystallized from ethanol, mp 183.5-184°; ir: 1778, 1718, 1672 cm^{-1}; ^1H-nmr: 2.02 (3H, d, J = 7), 3.52 (3H, s), 3.70 (3H, s), 5.81 (1H, q, J = 7), 7.62-7.96 (4H, m), 8.79 (1H, s); ^{13}C-nmr: 28.8, 29.2, 48.8, 123.2, 126.1, 131.6, 134.0, 145.7 (C-6), 146.8, 149.8, 150.3 (C-7), 159.3, 167.4.

Anal. Calcd. for $C_{18}H_{15}N_5O_4$: C, 59.17; H, 4.14; N, 19.17. Found: C, 58.95; H, 4.12; N, 19.07.

Methylation of 7-(Phthalimidomethyl)-1,3-dimethyllumazine (**6a**).

7-(Phthalimidomethyl)-1,3-dimethyllumazine (**6a**) (5 mmoles) was treated with ten molar equivalents of acetic acid, ammonium peroxodisulfate, and silver nitrate (0.5 mmole) in 35 ml of ethanenitrile-water (7:3). After reflux for 15 hours the same work up as described in the previous section gave 7-(phthalimidomethyl)-1,3,6-trimethyllumazine (**9**) in 35% yield. Product **9** was recrystallized from ethanol-ethanenitrile, mp 204-204.5°; ir: 1776, 1720, 1672 cm^{-1}; ^1H-nmr: 2.79 (3H, s), 3.18 (3H, s), 3.43 (3H, s), 5.09 (2H, s), 7.71-8.02 (4H, m).

Anal. Calcd. for $C_{18}H_{15}N_5O_4$: C, 59.19; H, 4.14; N, 19.17. Found: C, 59.19; H, 4.08; N, 18.81.

Hydrazine Degradation of 7-(3'-Phthalimidopropyl)-1,3-dimethyllumazine (**6c**) and 7-(Phthalimidomethyl)-1,3,6-trimethyllumazine (**9**).

A mixture of compound **6c** (0.7 mmole) and 50% hydrazine hydrate (1 mmole) in 10 ml of ethanenitrile was refluxed for 1 hour. After most of ethanenitrile was evaporated under reduced pressure, the residue was added with 10 ml of saturated sodium hydrogen carbonate solution and extracted with dichloromethane. Dichloromethane was evaporated after drying over sodium sulfate and the residue was chromatographed on an alumina column (1 x 30 cm) using dichloromethane as eluent.

7-(3'-Aminopropyl)-1,3-dimethyllumazine (**8**).

This compound was obtained in 72% yield, mp 242-243° dec; ir: 3380, 3325, 1720, 1670 cm^{-1}; ^1H-nmr: 1.90 (2H, quintet, J = 7), 2.41-2.93 (4H, m, $-CH_2NH_2$), 2.96 (2H, t, J = 7), 3.36 (3H, s), 3.59 (3H, s), 8.41 (1H, s).

The same procedure starting from compound **9** gave 1,3,6-trimethyllumazine in 34% yield, whose spectroscopic data were identical with those reported [10].

Methylation of 1,3-Dimethyllumazine (**2**).

The reaction was carried out essentially in the same manner as the phthalimidoalkylation described earlier. A mixture of compound **2** (3 mmoles), acetic acid (6 mmoles), ammonium peroxodisulfate (6 mmoles), and silver nitrate (0.03 mmole) was heated to 80° for 5 hours. Tlc separation (silica gel/ethyl acetate-hexane) gave 1,3,7-trimethyllumazine and 1,3,6,7-tetramethyllumazine in 8 and 54% yield respectively. Spectroscopic data of these products are identical to the data reported [13].

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