Cyclocondensation of 2-Hydrazinoperimidine with Diethyl Oxalate and Ethyl Pyruvate

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Refluxing 2-hydrazinoperimidine (**1**) with excess amount of diethyl oxalate (**2a**) gave ethyl 1*H*-1,2,4-triazolo[4,3-*a*]perimidine-3-carboxylate (**4a**) in 84% yield. On the other hand, heating **1** with ethyl pyruvate (**2b**) in glacial acetic acid afforded 3-methyl-1,2,4-triazino[4,3-*a*]perimidin-4(1*H*)-one (**6b**) in 92% yield. Structures of the products were investigated by spectral and elemental analysis.

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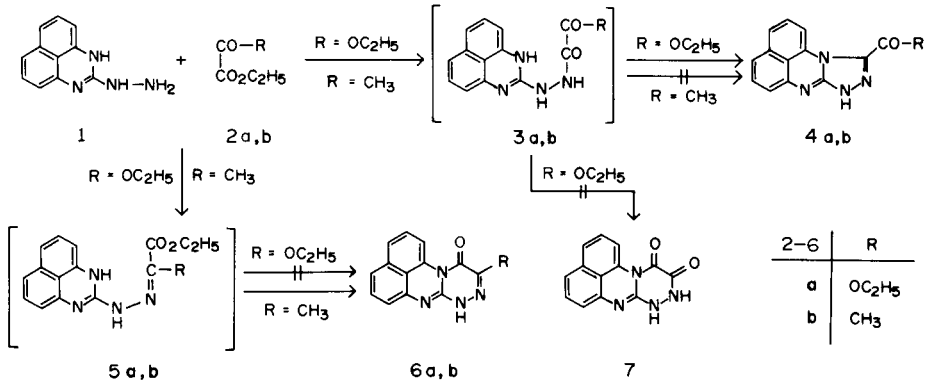
In the foregoing communications [1,2], we reported the cyclocondensation of 2-hydrazinoperimidine (**1**) with a representative 1,3-dielectrophile, acetylacetone and some monocarboxylic acid derivatives. In the first case, it gave 2-(3,5-dimethyl-1-pyrazolyl)perimidine in 73% yield. In the second case, 3-substituted 1*H*-1,2,4-triazolo[4,3-*a*]perimidines were produced in 43-68% yields. As a progressive continuation of our study in this series, we wish now to describe the cyclocondensation of **1** with two 1,2-dielectrophiles, diethyl oxalate (**2a**) and ethyl pyruvate (**2b**).

The cyclocondensations of oxalic acid or its derivatives with allied hydrazino nitrogen heterocycles have been investigated in many laboratories [3-7]. However, difficulties were often encountered or otherwise, products of ambiguous structures were isolated. We carried out the reaction by heating **1** with excess of **2a** at reflux for 5 hours. A greenish yellow crystalline product was obtained after recrystallized from ethanol. Theoretically, this reaction might be initiated as in case involving monocarboxylic acid derivatives [2] to form a hydrazide intermediate **3a** and then cyclodehydrated to give ethyl 1*H*-1,2,4-triazolo[4,3-*a*]-perimidine-3-carboxylate (**4a**). However, **3a** might also undergo acylative cyclization to afford 1,2-dihydro-1,2,4-triazino[4,3-*a*]perimidine-3,4-dione (**7**), since it was shown that in several hydrazine substituted nitrogen heterocycles cyclization involving **2a** proceeded with loss of two equivalent of ethanol to yield the corresponding diones [3,5,7]. In the present case the cyclization took very likely a different course forming **4a** instead and this fact was evidenced by the inconsistency of **7** with the molecular formula, $C_{15}H_{12}N_4O_2$ obtained by mass and elemental analysis of the isolated product. Consequently, another envisioned pathway *via* the hydrazone intermediate **5a** to give rise to 3-ethoxy-1,2,4-triazino[4,3-*a*]perimidin-4(1*H*)-one (**6a**) might also be taken into consideration. The discrimination of the plausible structure of **4a** and **6a** was made on the basis of spectral analysis. The ir spectrum showed the carbonyl stretching band at 1740 cm^{-1} corresponding to an ester group. The H-nmr spectrum exhibited the signals of all aromatic protons at δ 6.84 and 7.32-7.74 ppm, where no downfield shift could be seen. The mass fragmentation was characterized by the occurrence of M-OC_2H_5 and M-$CO_2C_2H_5$ fragment ion peaks at m/e 235 and 207 along with the base molecular ion peak at m/e 280. These data lead to the conclusion that the reaction of **1** and **2a** proceeded *via* the hydrazide intermediate **3a** to give the condensation product **4a** as shown in the reaction scheme.

Refluxing a solution of equimolar amount of **1** and **2b** in glacial acetic acid for 5 hours gave a pale yellow crystalline powder after recrystallized from dimethylformamide and then from methanol. The analytical data established the molecular formula as $C_{14}H_{10}N_4O$ corresponding to a 1:1 adduct. Presumably this reaction might proceed in similar fashion *via* the hydrazide intermediate **3b** to give



the condensate, 3-acetyl-1*H*-1,2,4-triazolo[4,3-*a*]perimidine (**4b**). More preferentially, the condensation might be initiated between the hydrazine group which is more nucleophilic than the ring nitrogen atom in **1** and the more electrophilic keto center of the 1,2-dielectrophile in **2b** to form the hydrazone intermediate **5b** and then led to 3-methyl-1,2,4-triazino[4,3-*a*]perimidin-4(1*H*)-one (**6b**). This pathway, as demonstrated for the first time by Druey and Ringier [8] by interconversion of the hydrazone intermediate and the cyclized product of a 1,2,4-triazino[3,4-*a*]-phthalazine ring system, was readily confirmed by the spectral analysis of our product. In the ir region, the carbonyl stretching band was observed at 1640 cm^{-1} corresponding to a six-membered lactam structure. The H-nmr spectrum contained one of the aromatic protons shifted to considerably lower field at δ 8.52 ppm. This fact implied that carbonyl function was present in close proximity to the naphthalene ring. The mass fragmentation showed the molecular ion peak at m/e 250 as expected; it was further accompanied by two prominent fragment ion peaks at m/e 222 and 181. These were obviously resulted by successive cleavage of CO and CH_3CN from the parent molecule and such cleavage could never occur in compound **4b**. In addition, a negative iodoform reaction of the product provided further evidence for the structure assignment.

Reaction Scheme

The cyclocondensation of pyruvic acid with a very similar hydrazino heterocycle, for example, 2-hydrazinobenzimidazole was also reported [9]. The reaction was performed in alcohol solution and required more extreme conditions of temperature and pressure to produce 3-methyl-1,2,4-triazino[4,3-*a*]benzimidazol-4(10*H*)-one up to 85% yield. Another acylative cyclization involving a methyl ester function in the preformed hydrazone of the same ring system under the influence of triethylamine gave the condensate only in 23% yield [10]. In comparison with these, the cyclocondensation in our experiment was achieved more conveniently and it afforded the product in more satisfactory yield (92%).

So far as these results showed, it might be understood that the reaction of 2-hydrazinoperimidine with 1,2-dicarboxylic acid esters proceeds *via* a hydrazide intermediate to give 1*H*-1,2,4-triazolo[4,3-*a*]perimidine-3-carboxylates. On the other hand, reaction of the same compound with α-keto esters occurs *via* a hydrazone intermediate to afford 3-alkyl-1,2,4-triazino[4,3-*a*]perimidin-4(1*H*)-ones. Above all, compounds produced from these reactions could be isolated simply and resulted in excellent yields.

EXPERIMENTAL

All melting points were determined with Tottoli apparatus and are uncorrected. The ultraviolet and infrared spectra were measured with Shimadzu 210 A ultraviolet and Perkin Elmer M 577 infrared spectrophotometer, respectively. Nuclear magnetic resonance spectra were recorded on JEOL FX 100 spectrometer. Mass spectra were obtained with Hitachi RMS 4 spectrometer. Elemental analyses were carried out in Chungshan Institute of Science and Technology, Taoyuan, Taiwan, China.

2-Hydrazinoperimidine (**1**).

Compound **1** was prepared from 6.0 g (0.03 mole) of 2-mercaptoperimidine [11] and 29 ml (0.06 mole) of 99% hydrazine hydrate according to a procedure described previously [1], yield, 5.4 g (91%), mp 188-191°.

Ethyl 1*H*-1,2,4-Triazolo[4,3-*a*]perimidine-3-carboxylate (**4a**).

A mixture of 2.0 g (0.01 mole) of **1** and 29.2 g (0.20 mole) of **2a** was heated under reflux for 5 hours. After removal of excess amount of **2a** under reduced pressure, the crude product was recrystallized from ethanol to give 2.4 g (84%) of greenish yellow crystals, mp 235-236°; uv (methanol): λ max (log ϵ) 218 (4.53), 252 (4.16), 314 (4.07) nm; λ min (log ϵ) 241 (4.09), 283 (3.65) nm; ir (potassium bromide): 3500 (N-H), 3020 (=C-H), 1740 (C=O), 1660, 1595 (C=N/C=C), 1450 (C-N), 1175 (C-O), 820, 760 (=C-H) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ (ppm) 1.02 (t, CH_3, J = 6.0 Hz), 4.03 (q, CH_2, J = 6.0 Hz), 6.84 (m, H-6, 9), 7.32-7.74 (m, H-5, 7, 8, 10), 10.62 (s, broad, NH); ms: (70 eV), m/e 280 (M^+, 100), 235 ($M-OC_2H_5$, 15), 207 ($M-CO_2C_2H_5$, 60), 166 ($C_{11}H_6N_2$, 40), 154 ($C_{10}H_6N_2$, 25), 140 ($C_{10}H_6N$, 12), 126 ($C_{10}H_6$, 22).

Anal. Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.41; H, 4.08; N, 19.73.

3-Methyl-1,2,4-triazino[4,3-*a*]perimidin-4(1*H*)-one (**6b**).

A solution of 2.0 g (0.01 mole) of **1** and 1.2 g (0.01 mole) of **2b** in 20 ml of glacial acetic acid was heated under reflux for 5 hours. After cooling the solid product was collected by filtration and recrystallized from dimethylformamide and then from methanol to give 2.4 g (92%) of pale yellow crystalline powder, mp 232-233°; uv (methanol): λ max (log ϵ) 228 (4.19), 269 (3.86), 313 (3.74) nm; λ min (log ϵ) 248 (3.71), 292 (3.73) nm; ir (potassium bromide): 3370 (N-H), 3040 (=C-H), 1640 (C=O), 1605, 1585 (C=N/C=C), 1370 (C-N), 810, 750 (=C-H) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ (ppm) 2.14 (s, CH_3), 6.63 (m, H-7, 10), 7.14-7.53 (m, H-8, 9, 11), 8.52 (d, H-6, J = 6.0 Hz), 10.52 (s, broad, NH); ms: (70 eV), m/e 250 (M^+, 100), 222 (M-CO, 65), 181 (222-CH_3CN, 18), 166 ($C_{11}H_6N_2$, 10), 154 ($C_{10}H_6N_2$, 12), 140 ($C_{10}H_6N$, 10), 126 ($C_{10}H_6$, 65).

Anal. Calcd. for $C_{14}H_{10}N_4O$: C, 67.19; H, 4.03; N, 22.39. Found: C, 66.85; H, 4.15; N, 22.20.

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REFERENCES AND NOTES

[1] K. C. Liu and H. H. Chen, *J. Heterocyclic Chem.*, **21**, 911 (1984).

[2] K. C. Liu and H. H. Chen, *Arch. Pharm.* (Weinheim), **318**, 468 (1985).

[3] T. K. Kauffmann, H. Hacker, C. Kosel and K. Vogt, *Z. Naturforsch.*, **14(b)**, 601 (1959); *Chem. Abstr.*, **54**, 4584e (1960).

[4] K. T. Potts and H. R. Burton, *J. Org. Chem.*, **31**, 251 (1966).

[5] H. Zimmer, J. M. Koskosa and K. J. Shah, *ibid.*, **40**, 2901 (1975).

[6] S. W. Schneller and D. G. Bartholomew, *J. Heterocyclic Chem.*, **15**, 439 (1978).

[7] K.-H. Ongania, *Chem. Ber.*, **114**, 1200 (1981).

[8] J. Druey and B. H. Ringier, *Helv. Chim. Acta*, **34**, 195 (1951); *Chem. Abstr.*, **45**, 10248c (1951).

[9] M. V. Postyanoi, E. V. Logachev and P. M. Kochergin, *Ukr. Khim. Zh.*, **43**, 746 (1977); *Chem. Abstr.*, **87**, 167984g (1977).

[10] D. J. Le Count and A. T. Greer, *J. Chem. Soc., Perkin Trans. I*, 1974, 297.

[11] K. C. Liu, J. Y. Tuan and B. J. Smith, *Arch. Pharm.* (Weinheim), **309**, 928 (1976).