Synthesis and ^{13}C-NMR Study of Novel Pyrazolo[5′,1′:3,4][1,2,4]triazino[5,6-*d*]pyrimidines

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Received November 18, 1988

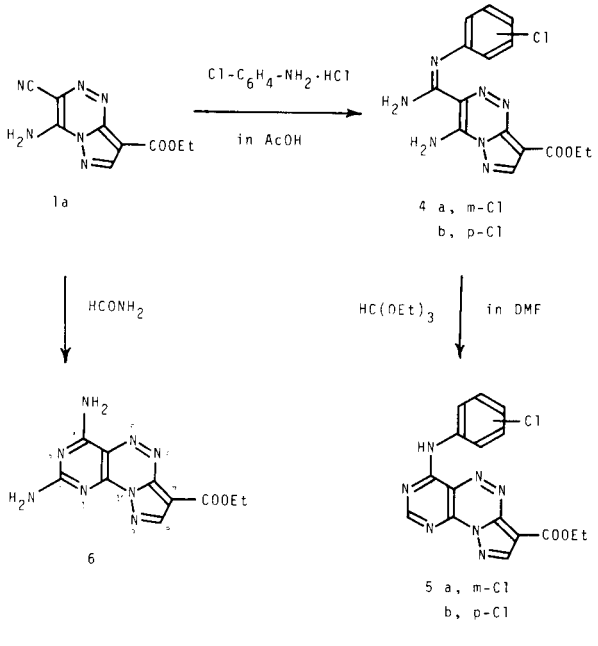
The pyrazolo[5′,1′:3,4][1,2,4]triazino[5,6-*d*]pyrimidines **5a-c,6** were synthesized from the pyrazolo[5,1-*c*]-[1,2,4]triazines **1a,c** and the ring carbon signals of **5a-c,6** were assigned by the aid of coupling constant [J(^{13}C-^{1}H)] data.

J. Heterocyclic Chem., **26**, 853 (1989).

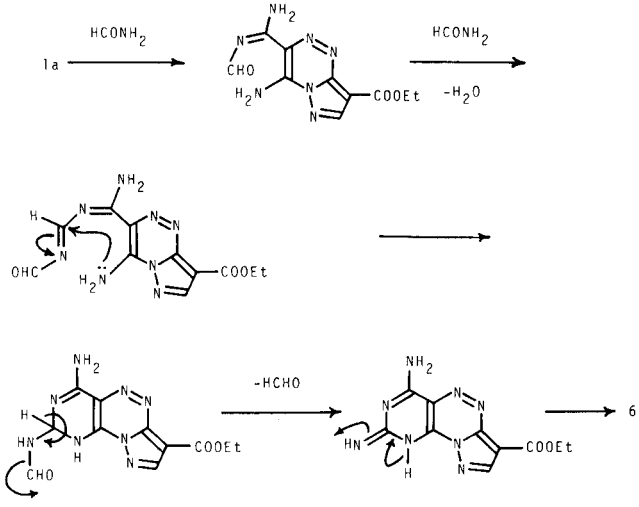
In previous papers [2,3], we reported the synthesis of the pyrazolo[5′,1′:3,4][1,2,4]triazino[5,6-*b*][1,5]benzodiazepines **2** and pyrazolo[5′,1′:3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepines **3** from the 3-substituted 4-amino-8-ethoxycarbonylpyrazolo[5,1-*c*][1,2,4]triazines **1a,b**. In continuation of these works, we undertook the synthesis of the pyrimidine ring condensed pyrazolo[5,1-*c*][1,2,4]triazines **5a-c**, **6**. The studies on the synthesis of condensed pyrimidines have numerously been reported [4-6], but pyrazolo[5′,1′:3,4]-[1,2,4]triazino[5,6-*d*]pyrimidines synthesized are less than ten derivatives between 1967 and 1988 [7-9]. This paper describes the synthesis of new pyrazolo[5′,1′:3,4][1,2,4]triazino[5,6-*d*]pyrimidines **5a-c**, **6** and the ^{13}C-nmr study to assign their ring carbon signals.

The reaction of **1a** [2] with *m*-chloroaniline hydrochloride in acetic acid gave 4-amino-3-(*m*-chlorophenyl)amidino-8-ethoxycarbonylpyrazolo[5,1-*c*][1,2,4]triazine hydrochloride (74%), whose treatment with pyridine furnished the free base **4a** (Scheme 1). The reaction of **4a** and **4b** [2] with triethyl orthoformate provided 4-(*m*-chlorophenyl)-amino-7-ethoxycarbonylpyrazolo[5′,1′:3,4][1,2,4]triazino-[5,6-*d*]pyrimidine **5a** (81%) and 4-(*p*-chlorophenyl)amino-7-ethoxycarbonylpyrazolo[5′,1′:3,4][1,2,4]triazino[5,6-*d*]-pyrimidine **5b** (88%), respectively. Refluxing of **1a** in formamide afforded 2,4-diamino-7-ethoxycarbonylpyrazolo[5′,1′:3,4][1,2,4]triazino[5,6-*d*]pyrimidine **6** (78%). Ordinary reaction of *o*-aminonitrile with formamide furnished 4-aminopyrimidine derivative [10,11], but compound **1a** was converted into the 2,4-diaminopyrimidine derivative **6**. Its plausible reaction mechanism is shown in Scheme 2.

Scheme 1

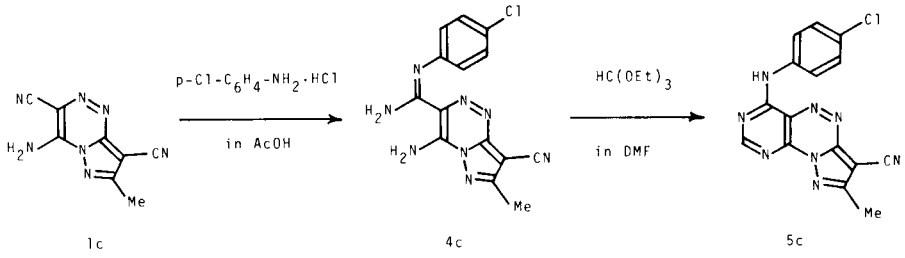


Scheme 2



In order to prepare other derivative of **5**, 4-amino-3,8-dicyano-7-methylpyrazolo[5,1-*c*][1,2,4]triazine **1c** was synthesized in 67% yield by a known method [2]. The reaction of **1c** with *p*-chloroaniline hydrochloride gave 4-amino-3-(*p*-chlorophenyl)amidino-8-cyano-7-methylpyrazolo[5,1-*c*]-

Scheme 3



[1,2,4]triazine hydrochloride **4c**, whose reaction with triethyl orthoformate in *N,N*-dimethylformamide afforded 4-(*p*-chlorophenyl)amino-7-cyano-8-methylpyrazolo[5′,1′:3,4]-[1,2,4]triazino[5,6-*d*]pyrimidine **5c** (83%) (Scheme 3).

The structural assignments of the above compounds were based on the analytical and spectral data. Especially, the ^{13}C-nmr spectral data were helpful for the structural assignments of the pyrimidines **5a-c**, **6**. Fortunately, compounds **5a** and **5b** had protons at C_2 and C_8 carbons, and hence the ring carbon signals of **5a** and **5b** could be easily assigned by the data of the coupling constants [^{1}J-^{3}J (^{13}C-^{1}H)] (Table 1). The doublet signals of C_2 (^{1}J), C_4 (^{3}J) and C_{10a} (^{3}J) carbons in the pyrimidine ring were due to the coupling with the C_2-H proton, and the doublet signals of the C_{6a} (^{3}J), C_7 (^{2}J) and C_8 (^{1}J) carbons in the pyrazole ring were due to the coupling with the C_8-H proton. The C_{4a} carbon signal was observed as the singlet.

The chemical shifts of the C_2 carbon signals in **5a-c** were similar to those of pteridine derivatives [12] (Chart 2). In comparison with compound **6**, the shielding of C_4 carbon signals in **5a-c** by 5 ppm is observed, presumably due *to an influence of the chlorophenyl group connecting with* the C_4-amino group. Moreover, the C_2 carbon signal of the 3,4-dihydro-4-oxo-pteridine derivative (Chart 2) was observed at δ 157.4 ppm, which was different from the C_2 carbon chemical shifts of **5a-c** by 5 ppm. These data supported the aromatized pyrimidine structure for **5a-c**.

Chart 1

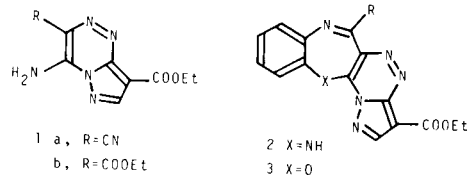
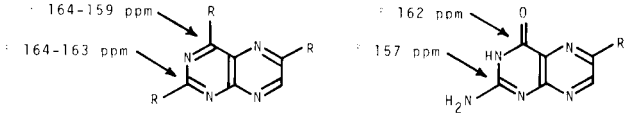


Chart 2



EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The pmr and ^{13}C-nmr spectra were measured in deuteriodimethylsulfoxide with a VXR-300 spectrometer at 300 MHz. Chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

Table

^{13}C-NMR Spectral Data for **5a-c** and **6**

Compound	Ring Carbon Signals (δ) (J in Hz)						
	C_2	C_4	C_{4a}	C_{6a}	C_7	C_8	C_{10a}
5a	162.49 (d, ^{1}J = 204.5)	157.50 (d, ^{3}J = 11.0)	122.41 (s)	148.60 (d, ^{3}J = 5.0)	107.64 (d, ^{2}J = 8.5)	147.40 (d, ^{1}J = 192.0)	140.72 (d, ^{3}J = 12.3)
5b	162.45 (d, ^{1}J = 205.0)	157.35 (d, ^{3}J = 11.0)	122.43 (s)	148.57 (d, ^{3}J = 5.5)	107.53 (d, ^{2}J = 8.5)	147.35 (d, ^{1}J = 192.0)	140.68 (d, ^{3}J = 12.5)
6	164.16 (s)	162.19 (s)	120.60 (s)	148.72 (d, ^{3}J = 5.0)	104.40 (d, ^{2}J = 8.5)	146.82 (d, ^{1}J = 190.5)	143.14 (s)
5c	162.77 (d, ^{1}J = 205.0)	157.30 (d, ^{3}J = 11.0)	123.28 (s)	151.88 (s)	86.30 (q, ^{3}J = 3.5)	158.53 (q, ^{2}J = 7.0)	140.32 (d, ^{3}J = 10.0)

4-Amino-3-(*m*-chlorophenyl)amidino-8-ethoxycarbonylpyrazolo-[5,1-*c*][1,2,4]triazine **4a**.

A solution of **1a** (10 g, 35.95 mmoles) and *m*-chloroaniline hydrochloride (8.85 g, 53.79 mmoles) in acetic acid (500 ml) was refluxed in an oil bath for 2 hours. The reaction mixture was cooled to room temperature to precipitate colorless needles (hydrochloride of **4a**), which were collected by suction filtration (9.50 g, 74%). Trituration with hot pyridine/ethanol provided analytically pure yellow needles **4a**, mp 278-279°; ir: ν cm^{-1} 3480, 3270, 2990, 1720, 1630; ms: m/z 359 (M^+), 361 ($M^+ + 2$); pmr: 10.55 (s, 1H, NH), 9.60 (s, 1H, NH), 8.72 (s, 1H, C_7-H), 7.42-6.95 (m, 4H, aromatic) and (2H, NH_2), 4.34 (q, J = 7 Hz, 2H, CH_2), 1.35 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{14}ClN_7O_2$: C, 50.08; H, 3.92; Cl, 9.85; N, 27.25. Found: C, 49.90; H, 3.85; Cl, 9.73; N, 27.32.

4-Amino-3,8-dicyano-7-methylpyrazolo[5,1-*c*][1,2,4]triazine **1c**.

A solution of sodium nitrite (6.38 g, 92.4 mmoles) in water (40 ml) was added to a solution of 5-amino-4-cyano-3-methyl-1*H*-pyrazole [13] (10 g, 92.4 mmoles) in acetic acid (360 ml) with stirring in an ice-water bath to give a clear solution, to which malononitrile (9.57 g, 184 mmoles) was added portionwise. Stirring was carried out for additional 30 minutes to precipitate colorless crystals. Ethanol (300 ml) was added to the above reaction mixture and the whole mixture was refluxed for 1 hour on a boiling water bath. The solvent was evaporated *in vacuo* to about 200 ml, and water (150 ml) and ethanol (100 ml) were added to this reaction mixture. The mixture was allowed to stand at room temperature overnight to afford yellow needles, which were collected by suction filtration (12.25 g, 67%). Trituration with hot ethanol furnished an analytically pure sample **1c** as monohydrate, mp above 320°; ir: ν cm^{-1} 3530, 3340, 2230, 1660, 1640; ms: m/z 199 (M^+); pmr: 9.80 (s, 2H, NH_2), 2.58 (s, 3H, CH_3).

Anal. Calcd. for $C_8H_5N_7 \cdot H_2O$: C, 44.24; H, 3.25; N, 45.14. Found: C, 44.41; H, 3.20; N, 45.04.

4-(*m*-Chlorophenyl)amino-7-ethoxycarbonylpyrazolo[5',1':3,4]-[1,2,4]triazino[5,6-*d*]pyrimidine **5a**.

A solution of **4a** (3 g, 8.34 mmoles) and triethyl orthoformate (20 ml) in *N,N*-dimethylformamide (30 ml) was refluxed in an oil bath for 2 hours. The reaction mixture was cooled to room temperature to precipitate analytically pure yellow needles **5a**, which were collected by suction filtration (2.49 g, 81%), mp 283-284°; ir: ν cm^{-1} 3310, 3120, 2980, 1690; ms: m/z 369 (M^+), 371 ($M^+ + 2$); pmr: 11.73 (s, 1H, NH), 8.93 (s, 1H, C_2-H), 8.89 (s, 1H, C_8-H), 8.19 (dd, J = 2 Hz, J = 2 Hz, 1H, phenyl C_2-H), 7.97 (dd, J = 8 Hz, J = 2 Hz, 1H, phenyl C_4-H), 7.48 (dd, J = 8 Hz, J = 8 Hz, 1H, phenyl C_5-H), 7.30 (dd, J = 8 Hz, J = 2 Hz, 1H, phenyl C_6-H), 4.42 (q, J = 7 Hz, 2H, CH_2), 1.40 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{12}ClN_7O_2$: C, 51.97; H, 3.27; Cl, 9.59; N, 26.52. Found: C, 51.90; H, 3.33; Cl, 9.74; N, 26.38.

4-(*p*-Chlorophenyl)amino-7-ethoxycarbonylpyrazolo[5',1':3,4]-[1,2,4]triazino[5,6-*d*]pyrimidine **5b**.

A solution of **4b** (2.4 g, 6.68 mmoles) and triethyl orthoformate (20 ml) in *N,N*-dimethylformamide (30 ml) was refluxed in an oil bath for 2 hours. The reaction mixture was cooled to room temperature to precipitate yellow crystals **5b**, which were collected by suction filtration (1.18 g). Evaporation of the filtrate *in vacuo* gave additional yellow crystals **5b** (1 g). Total yield, 2.18 g (88%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp 281-282°; ir: ν cm^{-1} 3310, 3100, 2880, 1690; ms: m/z 369 (M^+), 371 ($M^+ + 2$); pmr: 11.73 (s, 1H, NH), 8.89 (s, 1H, C_8-H), 8.88 (s, 1H, C_2-H), 8.02 (d, J = 9 Hz, 2H, phenyl C_3- and C_5-H), 7.57 (d, J = 9 Hz, 2H, phenyl C_2- and C_6-H), 4.42 (q, J = 7 Hz, 2H, CH_2), 1.39 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{12}ClN_7O_2$: C, 51.97; H, 3.27; Cl, 9.59; N, 26.52. Found: C, 52.18; H, 3.43; Cl, 9.56; N, 26.56.

4-Amino-3-(*p*-chlorophenyl)amidino-8-cyano-7-methylpyrazolo-[5,1-*c*][1,2,4]triazine **4c** and 4-(*p*-Chlorophenyl)amino-7-cyano-8-methylpyrazolo[5',1':3,4][1,2,4]triazino[5,6-*d*]pyrimidine **5c**.

A solution of **1c** (5.0 g, 25.1 mmoles) and *p*-chloroaniline hydrochloride (5.67 g, 34.6 mmoles) in acetic acid (250 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* afforded an oily product, which was dissolved in ethanol and then evaporated *in vacuo*. This procedure was repeated 3 times to give yellow needles **4c**, which were triturated with ethanol/hexane and then collected by suction filtration (4.59 g, 61%). This sample was pure enough for the next step; ir: ν cm^{-1} 3440, 3380, 2220, 1630; ms: m/z 326 (M^+), 328, ($M^+ + 2$).

A solution of **4c** (5 g) and triethyl orthoformate (50 ml) in *N,N*-dimethylformamide (150 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* afforded yellow crystals, which was triturated with ethanol/water and then collected by suction filtration (4.29 g, 83%). Recrystallization from *N,N*-dimethylformamide/ethanol/water provided yellow needles **5c**, mp 332-334°; ir: ν cm^{-1} 3270, 3200, 2240, 1605; ms: m/z 336 (M^+), 338 ($M^+ + 2$); pmr: 11.80 (s, 1H, NH), 8.84 (s, 1H, C_2-H), 7.95 (d, J = 9 Hz, 2H, phenyl C_3- and C_5-H), 7.49 (d, J = 9 Hz, 2H, phenyl C_2- and C_6-H), 2.70 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_9ClN_8$: C, 53.50; H, 2.69; Cl, 10.53; N, 33.28. Found: C, 53.20; H, 2.86; Cl, 10.60; N, 32.99.

2,4-Diamino-7-ethoxycarbonylpyrazolo[5',1':3,4][1,2,4]triazino-[5,6-*d*]pyrimidine **6**.

A solution of **1a** (5 g) in formamide (50 ml) was refluxed in an oil bath for 5 hours. The solution was cooled to room temperature to precipitate crystals. The reaction mixture was poured into water to precipitate crystals, which were collected by suction filtration (3.63 g, 78%). Recrystallization from *N,N*-dimethylformamide/ethanol gave yellow needles as half hydrate, mp above 340°; ir: ν cm^{-1} 3300, 3140, 1700, 1610; ms: m/z 274 (M^+); pmr: 8.66 (s, 1H, NH), 8.59 (s, 1H, C_8-H), 8.19 (s, 1H, NH), 8.03 (s, 1H, NH), 7.72 (s, 1H, NH), 4.33 (q, J = 7 Hz, 2H, CH_2), 1.34 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{10}H_{10}N_8O_2 \cdot \frac{1}{2}H_2O$: C, 42.40; H, 3.91; N, 39.56. Found: C, 42.30; H, 3.66; N, 39.81.

REFERENCES AND NOTES

[1] Permanent position: Department of Chemistry, Teacher's College, Hyosung Women's University, Gyongsan 713-900, Korea.

[2] Y. Kurasawa, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.*, **24**, 1799 (1987); Y. Kurasawa, M. Kanoh, Y. Kamigaki, M. Okiyama, A. Takada and Y. Okamoto, *ibid.*, **25**, 1015 (1988).

[3] Y. Kurasawa, M. Okiyama, Y. Kamigaki, M. Kanoh, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.*, **24**, 1805 (1987); Y. Kurasawa, M. Okiyama, Y. Kamigaki, M. Kanoh, A. Takada and Y. Okamoto, *ibid.*, **25**, 1259 (1988).

[4] D. J. Brown, "The Chemistry of Heterocyclic Compounds. Fused Pyrimidines", E. C. Taylor, ed, John Wiley and Sons, New York, Chichester, Brisbane, Toronto, Singapore, 1988.

[5] D. J. Brown, "The Chemistry of Heterocyclic Compounds. Fused Pyrimidines, Part I. Quinazolines", by A. Weissberger, ed, Interscience Publishers, New York, London, Sydney, 1967.

[6] D. J. Brown, "The Chemistry of Heterocyclic Compounds. Fused Pyrimidines, Part II. Purines", by A. Weissberger and E. C. Taylor, eds, Wiley-Interscience, New York, London, Sydney, Toronto, 1971.

[7] J. Slouka, V. Bekarek and J. Kubata, *Monatsh. Chem.*, **105**, 535 (1974).

[8] S. A. S. Ghozlan, E. M. Zayed and M. H. Elnagdi, *Gazz. Chim. Ital.*, **113**, 219 (1983).

[9] E. M. Zayed, S. A. S. Ghozlan and A. A. H. Ibrahim, *Pharmazie*, **39**, 432 (1984).

[10] E. C. Taylor and A. McKillop, "Advances in Organic Chemistry. The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles", by E. C. Taylor, ed, by Interscience Publishers, New York, London, Sydney, Toronto, 1970.

[11] E. J. Gray, M. F. G. Stevens, G. Tennant and R. J. S. Vevers, *J. Chem. Soc., Perkin Trans. I*, 1496 (1976).

[12] U. Ewers, H. Guenther and L. Jaenicke, *Chem. Ber.*, **106**, 3951 (1973).

[13] C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).