Synthesis of 7-Alkyl-2,4-dimethoxy-5-oxo-5*H*-pyrano[4,3-*d*]pyrimidines

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October 3, 1989

A convenient synthesis of 7-alkyl-2,4-dimethoxy-5-oxo-5*H*-pyrano[4,3-*d*]pyrimidines from methyl 2,4-dimethoxy-6-phenylselenylmethyl (or 6-phenylthiomethyl)-5-pyrimidinecarboxylate with alkylaldehydes is described.

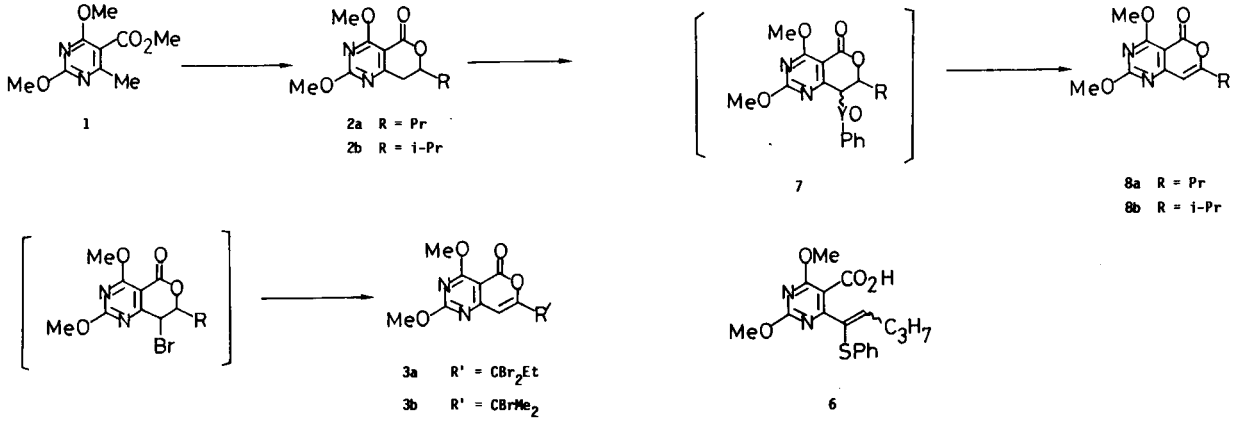
J. Heterocyclic Chem., **27**, 1899 (1990).

Previously, we reported a convenient synthetic procedures of 7-aryl-2,4-dimethoxy-5-oxo-5*H*-pyrano[4,3-*d*]-pyrimidines *via* the anionic cycloaddition of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate (**1**) with arylaldehydes [1]. Continuing this study, we attempted to prepare the 7-alkyl analogs by application of this methodology.

Treatment of the lithium salt, generated from **1** and lithium diisopropylamide (LDA), with *n*-butyraldehyde and *i*-butyraldehyde in ether at −70° under nitrogen and worked up at 0° afforded cycloadducts **2a** and **2b** in 85% and 74% yields, respectively. The ^{1}H nmr, ir, mass spectra data and elemental analysis were consistent with the indicated structures of **2a** and **2b**.

According to the previous report, when the adduct **2a** was refluxed with *N*-bromosuccinimide (NBS) in carbon tetrachloride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN), three equivalents of NBS were consumed before the complete disappearance of **2a** (monitored by thin layer chromatography) and the dibrominated 5-oxo-5*H*-pyrano[4,3-*d*]pyrimidine **3a** was obtained in 61% yield. Similarly, in the case of **2b**, two equivalents of NBS were required for the completion of the reaction and the monobromo derivative **3b** was obtained in 57% yield. Presumably, these products were generated from the benzylic brominations of aromatized 5-oxo-5*H*-pyrano[4,3-*d*]-pyrimidines, and it seemed to be difficult to stop these reactions at the aromatized stage (Scheme 1).

Scheme 1



It is well known that phenylselenyl and phenylsulfenyl groups facilitate oxidative eliminations to afford olefinic compounds [2,3]. Therefore, we focused our attention on the reaction of lithium salts of **4a** and **4b** with aldehydes in order to obtain 7-alkyl-5-oxo-5*H*-pyrano[4,3-*d*]pyrimidines without bromo- substitution. The introduction of phenylselenyl or phenylthio groups was achieved from the reaction of **1** with phenylselenyl chloride or diphenyl disulfide according to the previously reported method [4].

In the reaction of the lithium salt of **4a** with *n*-butyraldehyde, it was found that the products were dependent upon the reaction temperature. Thus, the workup at 0° afforded a 1:1 mixture of the pyrano[4,3-*d*]pyrimidine **5a** and the pyrimidine-5-carboxylic acid **6** [5]. On the contrary, the workup at −70° gave the desired product **5a** exclusively. Similarly, treatment of **4a** with *i*-butyraldehyde or **4b** with *n*-butyraldehyde at −70° afforded cycloadducts **5b** or **5c** in 63% and 66% yields, respectively. These cycloadducts **5** were isolated as a mixture of *cis* and *trans* isomers, and used in subsequent reactions without further purification.

Scheme 2

Treatment of **5c** under oxidative elimination conditions, using *m*-chloroperbenzoic acid (*m*-CPBA) in methylene chloride at room temperature, gave 2,4-dimethoxy-7-*n*-propyl-5*H*-pyrano[4,3-*d*]pyrimidin-5-one (**8a**) in 55% yield. On the other hand, for the oxidative elimination of the phenyl thio groups, a higher temperature was required and sulfinyl intermediates **7**, produced from the reaction of **5a** and **5b** with *m*-CPBA, were refluxed in toluene to afford **8a** and **8b** in 71% and 70% yields, respectively (Scheme 2).

EXPERIMENTAL

All melting points were determined by using a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270 spectrometer. Proton magnetic resonance spectra were determined on a JEOL JNM-MH-100 instrument using tetramethylsilane as the internal standard. Mass spectra were obtained with a JEOL JMS-100 instrument.

General Procedure for the Reaction of Pyrimidines **1** and **4** with Aldehydes, Diphenyl Disulfide and Phenylselenyl Chloride.

A solution of diisopropylamine (550 mg, 5.5 mmoles) and *n*-butyllithium (3.4 ml, 1.6 moles in hexane, 5.5 mmoles) in dry ether (20 ml) was stirred under nitrogen atmosphere at 0° for 20 minutes. The resulting solution was cooled at −70°, followed by the addition of an ether (30 ml) solution of **1** or **4** (5 mmoles), and stirred for 15 minutes. The appropriate aldehyde, diphenyl disulfide, or phenylselenyl chloride (5 mmoles) dissolved in ether (10 ml) was added dropwise over a 5 minute period. The resulting mixture was warmed slowly to 0° and quenched by the addition of a 5% hydrochloric acid solution (50 ml). After separating the layers, the aqueous layer was further extracted with ether (2 x 60 ml). The combined organic layers were washed with aqueous saturated sodium chloride (80 ml) and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (chloroform/ethyl acetate, 9/1) to afford the product.

7,8-Dihydro-2,4-dimethoxy-7-propyl-5*H*-pyrano[4,3-*d*]pyrimidin-5-one (**2a**).

This compound was synthesized from **1** (300 mg, 1.4 mmoles) and *n*-butyraldehyde (140 mg, 2.0 mmoles) in 85% yield (304 mg), mp 120-121° (petroleum ether); ir (chloroform): 1725, 1580, 1565 cm^{-1}; ^1H nmr (deuteriochloroform): 1.04 (3H, t, J = 7 Hz, Me), 1.3-2.1 (4H, m, 2 CH_2), 2.97 (2H, d, J = 8 Hz, CH_2), 4.09 (3H, s, OMe), 4.18 (3H, s, OMe), 4.4-4.7 (1H, m, C*H*) ppm; ms: m/z 252 (M^+).

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.22; H, 6.41; N, 11.31.

7,8-Dihydro-2,4-dimethoxy-7-(1-methyl)ethyl-5*H*-pyrano[4,3-*d*]-pyrimidin-5-one (**2b**).

This compound was synthesized from **1** (300 mg, 1.4 mmoles) and *i*-butyraldehyde (140 mg, 2.0 mmoles) in 85% yield (304 mg), mp 87-89° (petroleum ether); ir (chloroform): 1720, 1585, 1565 cm^{-1}; ^1H nmr (deuteriochloroform): 1.04 (3H, d, J = 7 Hz, Me), 1.08 (3H, d, J = 7 Hz, Me), 1.9-2.1 (1H, m, CH), 2.91 (1H, d, J = 6 Hz, CH_2), 2.92 (1H, d, J = 8 Hz, CH_2), 4.03 (3H, s, OMe), 4.09 (3H, s, OMe), 4.3-4.5 (1H, m, C*H*) ppm; ms: m/z 252 (M^+).

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.15; H, 6.32; N, 11.27.

Methyl 2,4-Dimethoxy-6-(phenylthio)methylpyrimidine-5-carboxylate (**4a**).

This compound was synthesized from **1** (670 mg, 3.2 mmoles) and diphenyl disulfide (670 mg, 3.2 mmoles) in 62% yield (612 mg), mp 75-76° (petroleum ether); ir (chloroform): 1725, 1580 cm^{-1}; ^1H nmr (deuteriochloroform): 3.78 (3H, s, OMe), 3.85 (3H, s, OMe), 3.93 (3H, s, OMe), 4.21 (2H, s, CH_2), 7.1-7.5 (5H, m, Ph) ppm; ms: m/z 320 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.25; H, 5.04; N, 8.75. Found: C, 56.15; H, 5.32; N, 8.81.

Methyl 2,4-Dimethoxy-6-(phenylselenyl)methylpyrimidine-5-carboxylate (**4b**).

This compound was synthesized from **1** (650 mg, 3.1 mmoles) and phenylselenyl chloride (590 mg, 3.1 mmoles) in 52% yield (590 mg), mp 61-62.5° (petroleum ether); ir (chloroform): 1725, 1580 cm^{-1}; ^1H nmr (deuteriochloroform): 3.80 (3H, s, OMe), 3.94 (3H, s, OMe), 4.07 (3H, s, OMe), 4.30 (2H, s, CH_2), 7.2-7.8 (5H, m, Ph) ppm; ms: m/z 367 (M^+).

Anal. Calcd. for $C_{15}H_{16}N_2O_4Se$: C, 49.01; H, 4.39; N, 7.62. Found: C, 49.12; H, 4.32; N, 7.76.

7,8-Dihydro-2,4-dimethoxy-8-phenylthio-7-propyl-5*H*-pyrano-[4,3-*d*]pyrimidin-5-one (**5a**).

This compound was obtained from **4a** (200 mg, 0.63 mmole) and *n*-butyraldehyde (100 mg, 1.4 mmoles) after working up at −70° in 50% yield (112 mg) as a mixture of *cis* and *trans* isomers (*cis*/*trans* = ½), mp 104-106° (petroleum ether); ir (chloroform): 1730, 1580, 1560 cm^{-1}; ^1H nmr (deuteriochloroform): 0.8-2.2 (7H, m, CH_2CH_2CH_3), 3.87 (1H, s, OMe *cis*), 3.95 (2H, s, OMe *trans*), 4.13 (3H, s, OMe *cis* and *trans*), 4.0-4.2 (1H, m, C*H*), 4.5-4.7 (1H, m, C*H*), 7.2-7.5 (5H, m, Ph) ppm; ms: m/z 392 (M^+).

Anal. Calcd. for $C_{18}H_{20}N_2O_4S$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.07; H, 5.41; N, 7.68.

7,8-Dihydro-2,4-dimethoxy-7-(1-methyl)ethyl-8-phenylthio-5*H*-pyrano[4,3-*d*]pyrimidin-5-one (**5b**).

This compound was obtained from **4a** (200 mg, 0.63 mmole) and *i*-butyraldehyde (100 mg, 1.4 mmoles) after working up at −70° in 66% yield (148 mg) as a mixture of *cis* and *trans* isomers (*cis*/*trans* = ½), mp 159-162° (petroleum ether); ir (chloroform): 1730, 1585, 1560 cm^{-1}; ^1H nmr (deuteriochloroform): 0.90 (3H, d, J = 7 Hz, Me), 1.03 (3H, d, J = 7 Hz, Me), 1.7-2.1 (1H, m, C*H*), 3.89 (1H, s, OMe *cis*), 3.98 (2H, s, OMe *trans*), 4.08 (1H, s, OMe *cis*), 4.16 (2H, s, OMe *trans*), 4.0-4.5 (2H, m, 2 C*H*), 7.3-7.5 (5H, m, Ph) ppm; ms: m/z 392 (M^+).

Anal. Calcd. for $C_{18}H_{20}N_2O_4S$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.02; H, 5.71; N, 7.82.

7,8-Dihydro-2,4-dimethoxy-8-phenylselenyl-7-propyl-5*H*-pyrano-[4,3-*d*]pyrimidin-5-one (**5c**).

This compound was obtained from **4b** (230 mg, 0.63 mmole) and *n*-butyraldehyde (100 mg, 1.4 mmoles) after working up at −70° in 63% yield (112 mg) as a mixture of *cis* and *trans* isomers (*cis*/*trans* = ½), mp 103-105° (petroleum ether); ir (chloroform): 1730, 1580, 1565 cm^{-1}; ^1H nmr (deuteriochloroform): 0.8-2.2 (1H, m, C*H*), 3.87 (1H, s, OMe *cis*), 3.94 (2H, s, OMe *trans*), 4.07 (1H, s, OMe *cis*), 4.09 (2H, s, OMe *trans*), 4.1-4.3 (1H, m, C*H*), 4.5-4.8 (1H,

m, C*H*), 7.2-7.7 (5H, m, Ph) ppm; ms: m/z 406, 408 (M^+).

Anal. Calcd. for $C_{18}H_{20}N_2O_4Se$: C, 53.07; H, 4.95; N, 6.88. Found: C, 53.21; H, 4.87; N, 6.69.

7-(1,1-Dibromo)propyl-2,4-dimethoxy-5*H*-pyrano[4,3-*d*]pyrimidin-5-one (**3a**).

A solution of **2a** (60 mg, 0.24 mmole) and AIBN (20 mg) in carbon tetrachloride (20 ml) was refluxed adding an equivalent of NBS in each hour until the disappearance of **2a**. After cooling, the reaction mixture was poured into ice-water (30 ml) and extracted with chloroform (3 x 20 ml). The combined extract was successively washed with aqueous sodium thiosulfate (40 ml), aqueous sodium chloride (40 ml) and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (chloroform/ethyl acetate, 19/1) to afford **3a** (60 mg, 61%), mp 132-134° (petroleum ether); ir (chloroform): 1755, 1640, 1575, 1555 cm^{-1}; ^1H nmr (deuteriochloroform): 1.12 (3H, t, J = 7 Hz, Me), 2.75 (2H, q, J = 7 Hz, CH_2), 4.08 (3H, s, OMe), 4.15 (3H, s, OMe), 7.12 (1H, s, Ar*H*) ppm; ms: m/z 406, 408, 410 (M^+).

Anal. Calcd. for $C_{12}H_{12}Br_2N_2O_4$: C, 35.32; H, 2.97; N, 6.87. Found: C, 35.41; H, 3.02; N, 6.85.

7-(1-Bromo-1-methyl)ethyl-2,4-dimethoxy-5*H*-pyrano[4,3-*d*]pyrimidin-5-one (**3b**).

Following the method described for the preparation of **3a**, this compound was synthesized from **2b** (60 mg, 0.24 mmole) in 61% yield (60 mg), mp 127.5-129° (petroleum ether); ir (chloroform): 1750, 1645, 1575, 1555 cm^{-1}; ^1H nmr (deuteriochloroform): 2.09 (6H, s, 2 CH_3), 4.11 (3H, s, OMe), 4.19 (3H, s, OMe), 7.58 (1H, s, Ar*H*) ppm; ms: m/z 328, 330 (M^+).

Anal. Calcd. for $C_{12}H_{13}BrN_2O_4$: C, 43.78; H, 3.98; N, 8.51. Found: C, 43.81; H, 3.94; N, 8.70.

2,4-Dimethoxy-7-propyl-5*H*-pyrano[4,3-*d*]pyrimidin-5-one (**8a**).

i) A solution of *m*-CPBA (40 mg, 0.21 mmole) in dichloromethane (3 ml) was added dropwise to a stirred solution of **5a** (75 mg, 0.23 mmole) in dichloromethane (10 ml) at room temperature, and stirring was continued for one hour. After removal of the solvent, toluene (15 ml) was added and the resulting mixture was refluxed for 2 hours, then poured into water. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3 x 15 ml). The organic layers were combined and successively washed with saturated sodium bicarbonate and sodium chloride solution, then dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate/dichloromethane, 1/9) to afford **8a** in 71% yield (37 mg), mp 110-111° (petroleum ether); ir (chloroform): 1740, 1650, 1575, 1550 cm^{-1}; ^1H nmr (deuteriochloroform): 1.01 (3H, t, J = 7 Hz, Me), 1.5-2.1 (2H, m, CH_2), 2.55 (3H, t, J = 7 Hz, CH_2), 4.10 (3H, s, OMe), 4.19 (3H, s, OMe), 6.27 (1H, s, Ar*H*) ppm; ms: m/z 250 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.65; H, 5.69; N, 11.34.

ii) A solution of *m*-CPBA (30 mg, 0.12 mmole) in dichloromethane (3 ml) was added dropwise to a stirred solution of **5c** (50 mg, 0.17 mmole) in dichloromethane (10 ml) at room temperature, and stirring was continued for an additional hour. After the workup according to the above procedure i), **8a** was obtained in 55% yield (17 mg).

2,4-Dimethoxy-7-(1-methyl)ethyl-5*H*-pyrano[4,3-*d*]pyrimidin-5-one (**8b**).

This compound was prepared from **5b** (115 mg, 0.30 mmole) and *m*-CPBA (55 mg, 0.33 mmole) by the procedure employed in the preparation of **8a** in 70% yield (57 mg), mp 129-131° (petroleum ether); ir (chloroform): 1740, 1650, 1575, 1550 cm^{-1}; ^1H nmr (deuteriochloroform): 1.03 (6H, d, J = 7 Hz, 2 Me), 1.7-2.2 (1H, m, CH), 4.09 (3H, s, OMe), 4.21 (3H, s, OMe), 6.29 (1H, s, ArH), ppm; ms: m/z 250 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.55; H, 5.73; N, 11.41.

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