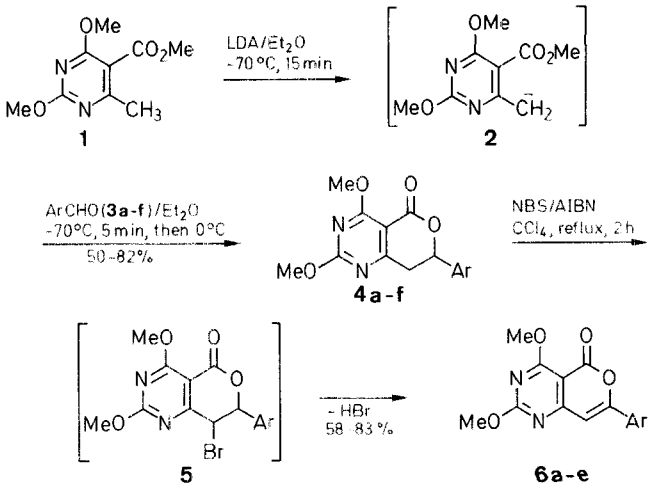

3-6	Ar	3-6	Ar
a	Ph	d	3-$MeOC_6H_4$
b	2-$O_2NC_6H_4$	e	4-$MeOC_6H_4$
c	2-$MeOC_6H_4$	f	4-$Me_2NC_6H_4$

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

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A convenient synthesis of 7-aryl-2,4-dimethoxy-5-oxo-5*H*-pyrano[4,3-*d*]pyrimidines **6** is described. The lithium salt of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate **(2)** reacts smoothly with aromatic aldehydes to afford cycloaddition products **4** in good yields. When **4** is treated with *N*-bromosuccinimide, aromatization occurs to give 5-oxo-5*H*-pyrano[4,3-*d*]pyrimidines **6** via dehydrobromination from the 8-bromo derivatives **5** in satisfactory yields.

Although a number of reports has appeared on anionic cycloaddition reactions using a benzylic carbanion,[1-4] little attention has been given to analogous reactions of heteroaromatics.[5] Recently,[6] we reported a brief and regiospecific synthesis of quinazoline derivatives from reactions of the lithium salt of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate **(2)** with some acetylenes and alkenes. This paper describes a convenient synthesis of 5-oxo-5*H*-pyrano[4,3-*d*]pyrimidines through reaction of **2** with aromatic aldehydes.

The lithium salt **2**, prepared by deprotonation of **1** with lithium diisopropylamide (LDA), reacted with aromatic aldehydes **3** in ether at −70 °C to afford cycloadducts **4** in good yields. The structure of **4** was determined from microanalytical and spectral data (Table 1). For example, the ^{1}H-NMR spectrum of **4a** showed a methine proton signal at $\delta = 5.58$ (dd, 1 H, $J = 9$, 5.5 Hz) and two benzylic proton signals at $\delta = 3.29$ (d, 1 H, $J = 9$ Hz) and 3.27 (d, 1 H, $J = 5.5$ Hz), which are characteristic of 2-oxo-5,6-dihydro-2*H*-pyran.[7] When **4a–e** were refluxed in carbon tetrachloride with 1.5 equivalents of *N*-bromosuccinimide (NBS) for 2 h in the presence of a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN),[8] aromatization occurred to give the corresponding 2,4-dimethoxy-5-oxo-5*H*-pyrano[4,3-*d*]pyrimidines **6** in moderate to good yields. These products are presumably formed via dehydrobromination of the initially formed 8-bromo derivatives **5** (Scheme, Table 2).

The novel anionic cycloaddition reaction described here provides a new and facile route for the synthesis of 5-oxo-5*H*-pyrano[4,3-*d*]pyrimidines in satisfactory yields.[9]

Table 1. Physical and Spectral Data of 5-Oxo-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidines **4**

Product	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c]	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
4a	82	101–102 (PE[d])	$C_{15}H_{14}N_2O_4$ (286.3)	1730, 1585	3.28 (d, 1 H, $J = 5.5$); 3.29 (d, 1 H, $J = 9$); 4.04 (s, 3 H); 4.12 (s, 3 H); 5.58 (dd, 1 H, $J = 9$, 5.5); 7.3–7.6 (m, 5 H)
4b	76	162–164 (CH_2Cl_2/MeOH)	$C_{15}H_{13}N_3O_6$ (331.3)	1735, 1585	3.08 (dd, 1 H, $J = 16$, 11); 3.37 (dd, 1 H, $J = 16$, 4); 4.08 (s, 3 H); 4.17 (s, 3 H); 6.12 (dd, 1 H, $J = 11$, 4); 7.4–8.2 (m, 4 H)
4c	62	154–156 (CH_2Cl_2/PE)	$C_{16}H_{16}N_2O_5$ (316.3)	1730, 1580	3.0–3.3 (m, 1 H); 3.83 (s, 3 H); 4.07 (s, 3 H); 4.15 (s, 3 H); 5.81 (d, 1 H, $J = 10.5$); 6.88 (d, 1 H, $J = 8$); 7.02 (t, 1 H, $J = 8$); 7.39 (t, 1 H, $J = 8$); 7.56 (d, 1 H, $J = 8$)
4d	50	105–106 (PE)	$C_{16}H_{16}N_2O_5$ (316.3)	1730, 1585	3.0–3.3 (m, 2 H); 3.78 (s, 3 H); 4.06 (s, 3 H); 4.11 (s, 3 H); 5.46 (dd, 1 H, $J = 9$, 5); 6.7–7.4 (m, 4 H)
4e	69	184–185 (CH_2Cl_2/MeOH)	$C_{16}H_{16}N_2O_5$ (316.3)	1730, 1580	3.1–3.4 (m, 2 H); 3.83 (s, 3 H); 4.07 (s, 3 H); 4.16 (s, 3 H); 5.48 (dd, 1 H, $J = 11$, 5); 6.91 (d, 2 H, $J = 8$); 7.38 (d, 2 H, $J = 8$)
4f	58	152–153 (MeOH)	$C_{17}H_{19}N_3O_4$ (329.4)	1730, 1580	2.95 (s, 6 H); 3.1–3.5 (m, 2 H); 4.07 (s, 3 H); 4.12 (s, 3 H); 5.43 (dd, $J = 10$, 5); 6.68 (d, 2 H, $J = 8$); 7.28 (d, 2 H, $J = 8$)

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.14, H ±0.12, N ±0.21.
[d] PE = petroleum ether (bp 30–70 °C).

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Table 2. Physical and Spectral Data of 5-Oxo-5*H*-pyrano[4,3-*d*]pyrimidines **6**

Product	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c]	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
6a	83	201–202 (CH_2Cl_2/PE[d])	$C_{15}H_{12}N_2O_4$ (284.3)	1745, 1635, 1570	4.08 (s, 3H); 4.17 (s, 3H); 6.89 (s, 1H); 7.3–8.1 (m, 5H)
6b	79	217–218 (MeOH)	$C_{15}H_{11}N_3O_6$ (329.3)	1750, 1645, 1575	4.09 (s, 3H); 4.19 (s, 3H); 6.64 (s, 1H); 7.5–8.2 (m, 4H)
6c	72	202–204 (CH_2Cl_2/MeOH)	$C_{16}H_{14}N_2O_5$ (314.3)	1740, 1630, 1575	3.95 (s, 3H); 4.10 (s, 3H); 4.18 (s, 3H); 7.36 (s, 1H); 6.9–7.6 (m, 3H); 7.98 (d, 1H, J = 8)
6d	72	168–169 (MeOH)	$C_{16}H_{14}N_2O_5$ (314.3)	1745, 1635, 1575	3.85 (s, 3H); 4.07 (s, 3H); 4.18 (s, 3H); 6.82 (s, 1H); 7.41 (s, 1H); 6.7–7.6 (m, 3H)
6e	58	225–226 (CH_2Cl_2/MeOH)	$C_{16}H_{14}N_2O_5$ (314.3)	1740, 1635, 1570	3.88 (s, 3H); 4.09 (s, 3H); 4.17 (s, 3H); 6.78 (s, 1H); 6.96 (d, 2H, J = 8); 7.85 (d, 2H, J = 8)

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.20, H ±0.15, N ±0.11.
[d] PE = petroleum ether (bp 30–70 °C).

IR absorption spectra were recorded on a Hitachi 270 spectrophotometer, and ^{1}H-NMR spectra on a JEOL JNM-MH-100 spectrometer (with TMS as internal standard). Mass spectra were obtained with a JEOL JMS-100 instrument.

7-Aryl-2,4-dimethoxy-5-oxo-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidines 4; General Procedure:

A solution of diisopropylamine (550 mg, 5.5 mmol) and *n*-BuLi (3.4 mL, 1.6 M in hexane, 5.5 mmol) in dry Et_2O (20 mL) is stirred under nitrogen atmosphere at 0 °C for 20 min. The resulting solution is cooled at −70 °C, followed by the addition of a solution of **1**[b] (5 mmol) in Et_2O (30 mL), and stirring for 15 min. The aromatic aldehyde **3** (5 mmol) dissolved in Et_2O (10 mL) is added dropwise over a period of 5 min. The resulting mixture is warmed slowly to 0 °C and quenched by 5% HCl (50 mL). After separating the layers, the aqueous layer is further extracted with Et_2O (2 × 60 mL). The combined organic layers are washed with brine (80 mL) and then dried (Na_2SO_4). The solvent is removed under reduced pressure, and the residue is chromatographed on silica gel ($CHCl_3$/EtOAc, 9:1) to afford **4** (Table 1).

7-Aryl-2,4-dimethoxy-5-oxo-5*H*-pyrano[4,3-*d*]pyrimidines 6; General Procedure:

A stirred mixture of the adduct **4** (1 mmol), AIBN (18 mg, 0.1 mmol), and NBS (270 mg, 1.5 mmol) in CCl_4 (30 mL) is refluxed for 2 h. After cooling, the reaction mixture is poured into ice/water (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined extract is successively washed with aqueous 10% $Na_2S_2O_3$ (70 mL), brine (70 mL), and then dried (Na_2SO_4). The solvent is removed under reduced pressure, and the residue is chromatographed on silica gel ($CHCl_3$/EtOAc, 19:1) to afford **6** (Table 2).

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(1) *o*-Toluate:
Hauser, F.M., Rhee, R.P. *J. Org. Chem.* **1978**, *43*, 178.
Evans, G.E., Leeper, F.J., Murphy, J.A., Staunton, J. *J. Chem. Soc. Chem. Commun.* **1979**, *205*, 206.
Dodd, J.H., Garigipati, R.S., Weinreb, S.M. *J. Org. Chem.* **1982**, *47*, 4045.
Hauser, F.M., Rhee, R.P., Prasana, S., Weinreb, S.M., Dodd, J.H. *Synthesis* **1980**, 72.

(2) Phthalide:
Broom, N.J.P., Sammes, P.G. *J. Chem. Soc. Perkin Trans. I* **1981**, 465.
Hauser, F.M., Prasanna, S., Combs, D.M. *J. Org. Chem.* **1983**, *48*, 1328, and references cited therein.

(3) (2-Carboxyphenyl)acetate:
Eisenmuth, W., Renfroe, H.B., Schmidt, H. *Helv. Chim. Acta* **1965**, *48*, 375.
Chenard, B.L., Dolson, M.G., Sercel, A.D., Swenton, J.S. *J. Org. Chem.* **1984**, *49*, 318.

(4) Isochroman-1,3-dione:
Tamura, Y., Sasho, M., Akai, S., Wada, A., Kita, Y. *Tetrahedron* **1984**, *40*, 4539.
Tamura, Y., Sasho, M., Akai, S., Kishimoto, H., Sekihachi, J., Kita, Y. *Tetrahedron Lett.* **1986**, *27*, 195, and references cited therein.

(5) Tamura, Y., Mohri, S., Maeda, H., Tsugoshi, T., Sasho, M., Kita, Y. *Tetrahedron Lett.* **1984**, *25*, 309.
Kita, Y., Mohri, S. Tsugoshi, T., Maeda, H., Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 4723.

(6) Wada, A., Yamamoto, H., Kanatomo, S. *Heterocycles* **1988**, *27*, 1345.

(7) Dugger, R.W., Heathcock, H. *J. Org. Chem.* **1980**, *45*, 1181.

(8) Smith, T.H., Fujiwara, A.N., Henry, D.W., Lee, W.W. *J. Am. Chem. Soc.* **1976**, *98*, 1969.

(9) Only one report is found for the synthesis of 5-oxo-5*H*-pyrano[4,3-*d*]pyrimidine: Ismail, A.G., Wibberley, D.G. *J. Chem. Soc. C* **1968**, 2706.

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