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Studies on Pyridopyrimidines. I. Synthesis of Pyrazolo-[3′,4′:4,5]pyrido[2,3-*d*]pyrimidine Derivatives

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Pyrazolo[3′,4′:4,5]pyrido[2,3-*d*]pyrimidine derivatives were obtained from the reaction of tosylhydrazones of 6-allylaminopyrimidine-2,4(1*H*,3*H*)-dione-5-carbaldehydes with lead tetraacetate in good yields. In this reaction, the nitrile imide intermediates underwent an intramolecular 1,3-dipolar addition reaction to yield the tricyclic heterocycles. Pyrazolo[3,4-*d*]pyrimido[4,5-*b*]-azepine derivatives were also prepared by similar oxidation of tosylhydrazones of the corresponding 6-alkenylaminopyrimidine-2,4(1*H*,3*H*)-dione-5-carbaldehydes.

Keywords——pyrazolo[3′,4′:4,5]pyrido[2,3-*d*]pyrimidine; pyrazolo[3,4-*d*]pyrimido[4,5-*b*]-azepine; tosylhydrazone oxidation; nitrile imide intermediate; intramolecular 1,3-dipolar addition

There have been numerous investigations on pyrido[2,3-*d*]pyrimidines, and our attention has been focused on the synthesis of tricyclic heterocycles containing a pyrido[2,3-*d*]-pyrimidine structure because of their potential biological and pharmacological activities. Although the synthesis and pharmacological activities of pyrazolo[4,3-*c*]quinolines have been reported,[1] the pyrazolo[3′,4′:4,5]pyrido[2,3-*d*]pyrimidine ring system, one of the diaza-analogs of pyrazoloquinoline, has not yet been obtained.

We wish to describe here a novel preparation method for the octa- and hexahydro derivatives of pyrazolo[3′,4′:4,5]pyrido[2,3-*d*]pyrimidine and for the decahydro derivatives of its higher homolog, pyrazolo[3,4-*d*]pyrimido[4,5-*b*]azepine; the reaction of the tosylhydrazones of some 6-(substituted amino)-1,2,3,4-tetrahydro-2,4-dioxopyrimidine-5-carbaldehydes, bearing an olefinic or acetylenic dipolarophile at the amino moiety, with lead tetraacetate (LTA) leads to the nitrile imide intermediates and thence to the intramolecular 1,3-dipolar cycloadducts.

Results and Discussion

Since the first report by Fusco *et al.*[2a] several intramolecular cycloaddition reactions of nitrile imides have been reported.[2] However, in most cases the nitrile imide and the dipolarophile are situated at *ortho* positions of the benzene ring, and, therefore, their synthetic utility seems to be limited. We examined the application of the intramolecular cycloaddition reaction of nitrile imides to the synthesis of the pyrimidine-2,4-(1*H*,3*H*)-dione system.

The reaction of 1,3-disubstituted 6-chloro-1,2,3,4-tetrahydro-2,4-dioxopyrimidine-5-carbaldehydes (**1**) with the alkenylamines (**2**) in refluxing ethanol gave the corresponding 6-alkenylamino derivatives **3**, which were converted to their tosylhydrazones **4** by treatment with tosylhydrazine.

The nitrile imide intermediates **5** were generated by the oxidation of **4** with LTA; the reactions were sensitive to the conditions employed.[3] The results of preliminary experiments on the oxidation of **4a** with LTA under various conditions showed that the most suitable

procedure was as follows: a solution of LTA (1.5 equimol) in dry acetonitrile was added dropwise to a stirred and cooled solution of **4a** in dry acetonitrile at −5 °C during 1 h, and the reaction mixture was stirred for several hours more at the same temperature, then warmed gradually to room temperature. After usual purification, crystalline 5-allyl-3,3a,4,5,6,7,8,9-octahydro-6,8-dimethyl-7,9-dioxo-2-tosyl-2*H*-pyrazolo[3′,4′ : 4,5]pyrido[2,3-*d*]-pyrimidine (**6a**) was obtained in 56% yield together with **3a** (32%), a hydrolytic product of **4a**,

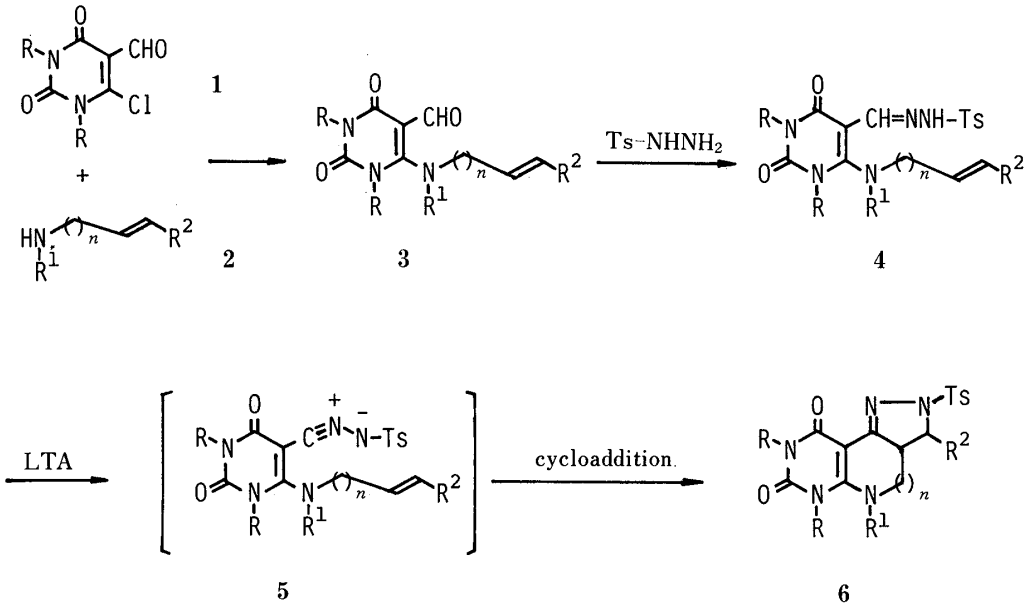


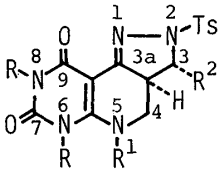
Chart 1

TABLE I. Preparation of Pyrazolo[3′,4′ : 4,5]pyrido[2,3-*d*]pyrimidines (**6a**—**6f**) and Pyrazolo[3,4-*d*]pyrimido[4,5-*b*]azepines (**6g**—**6i**)

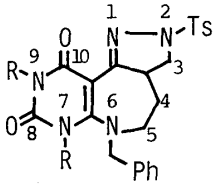
Compd.	*n*	R	R^1	R^2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
6a[a]	1	CH_3	CH_2–CH=CH_2	H	56	214—215	$C_{20}H_{23}N_5O_4S$	55.94	5.40	16.31
								(55.42	5.37	16.01)
6b[b]	1	CH_3	CH_2–Ph	CH_3	58	225—226	$C_{25}H_{27}N_5O_4S$	60.84	5.51	14.19
								(60.55	5.55	13.83)
6c[b]	1	CH_3	CH_2–Ph	Ph	56	218—220	$C_{30}H_{29}N_5O_4S$	64.85	5.26	12.61
								(64.85	5.29	12.65)
6d[b]	1	CH_3	CH_3	Ph	54	225—227	$C_{24}H_{25}N_5O_4S$	60.12	5.26	14.61
								(60.04	5.29	14.34)
6e[b]	1		CH_2–Ph	CH_3	58	228—229	$C_{35}H_{43}N_5O_4S$	66.75	6.88	11.12
								(66.76	7.02	10.93)
6f[a]	1	Ph	CH_2–Ph	CH_3	66	220—221	$C_{35}H_{31}N_5O_4S$	68.06	5.06	11.34
								(68.26	5.08	11.25)
6g[b]	2	CH_3	CH_2–Ph	H	9	184—186	$C_{25}H_{27}N_5O_4S$	60.84	5.51	14.19
								(60.60	5.46	13.90)
6h[a]	2		CH_2–Ph	H	28	178—179	$C_{35}H_{43}N_5O_4S$	66.75	6.88	11.12
								(66.60	6.94	11.13)
6i[b]	2	Ph	CH_2–Ph	H	66	182—184	$C_{35}H_{31}N_5O_4S$	68.06	5.06	11.34
								(68.10	5.14	11.04)

a) Colorless prisms from ethanol. *b*) Colorless needles from ethanol.

TABLE II. Spectral Data for the Products (**6**)



6a—6f



6g—6i

Compd.	IR ν_{max}^{KBr} cm^{-1}	MS *m/z*	^{1}H-NMR δ (ppm)	Solvent[a]
6a	1700, 1650 (CO) 1350, 1160 (SO_2)	429 (M^+)	2.54 (3H, s, $-CH_3$), 3.37, 3.46 (3H each, 2s, $\geq N-CH_3$), 3.82 (2H, d, $J=10$ Hz, $-CH_2-CH=$), 4.10 (2H, m, 3a- and 4-H), 4.20 (1H, dd, $J=18$, 5 Hz, 3-H), 4.46 (1H, dd, $J=18$, 7 Hz, 3-H), 5.4—5.7 (2H, m, $=CH_2$), 5.8—6.1 (1H, m, $-CH=$), 7.56, 7.92 (2H each, 2d, $J=8$ Hz, phenyl)	T[b]
6b	1710, 1660 (CO) 1340, 1160 (SO_2)	493 (M^+)	1.46 (3H, d, $J=6$ Hz, $-CH_3$), 2.40 (3H, s, $-CH_3$), 2.64 (1H, dd, $J=13$, 5 Hz, 4-H), 2.76 (1H, br t, $J=13$ Hz, 4-H), 2.95 (1H, dq, $J=12$, 6 Hz, 3-H), 3.15 (1H, ddd, $J=13$, 12, 5 Hz, 3a-H), 3.22, 3.38 (3H each, 2s, $\geq N-CH_3$), 4.30, 4.42 (1H each, 2d, $J=15$ Hz, $-CH_2-Ph$), 7.2—7.4 (7H, m, phenyl), 7.76 (2H, d, $J=8$ Hz, phenyl)	C+D[b]
6c	1710, 1660 (CO) 1340, 1160 (SO_2)	399 (M^+ – Tol-SO_2H)	2.41 (3H, s, $-CH_3$), 2.78 (1H, dt, $J=12$, 6 Hz, 3a-H), 3.08 (1H, t, $J=12$ Hz, 4-H), 3.25 (1H, dd, $J=12$, 6 Hz, 4-H), 3.40 (6H, s, $\geq N-CH_3$), 4.04 (1H, d, $J=12$ Hz, 3-H), 4.12, 4.28 (1H each, 2d, $J=16$ Hz, $-CH_2-Ph$), 7.04 (2H, d, $J=8$ Hz, phenyl), 7.2—7.4 (10H, m, phenyl), 7.86 (2H, d, $J=8$ Hz, phenyl)	C[b]
6d	1710, 1660 (CO) 1350, 1170 (SO_2)	479 (M^+)	2.40, 2.80 (3H each, 2s, $-CH_3$), 3.0—3.4 (3H, m, 3a- and 4-H), 3.38 (6H, s, $\geq N-CH_3$), 4.18 (1H, d, $J=11$ Hz, 3-H), 7.30 (2H, d, $J=8$ Hz, phenyl), 7.4—7.5 (5H, m, phenyl), 7.85 (2H, d, $J=8$ Hz, phenyl)	C[b]
6e	1710, 1660 (CO) 1350, 1170 (SO_2)	473 (M^+ – Tol-SO_2H)	1.0—1.9 (23H, m, $-CH_2-$ and $-CH_3$), 2.44 (3H, s, $-CH_3$), 2.70 (1H, ddd, $J=13$, 12, 5 Hz, 3a-H), 3.00 (1H, t, $J=13$ Hz, 4-H), 3.22 (1H, dq, $J=12$, 6 Hz, 3-H), 3.28 (1H, dd, $J=13$, 5 Hz, 4-H), 3.9—4.1, 4.7—4.9 (1H each, m, $\geq CH$), 4.85 (2H, s, $-CH_2-Ph$), 7.2—7.5 (7H, m, phenyl), 7.92 (2H, d, $J=8$ Hz, phenyl)	C[b]
6f	1700, 1660 (CO) 1340, 1160 (SO_2)	461 (M^+ – Tol-SO_2H)	1.48 (3H, d, $J=6$ Hz, $-CH_3$), 2.40 (3H, s, $-CH_3$), 2.68 (1H, ddd, $J=13$, 12, 5 Hz, 3a-H), 2.95 (1H, t, $J=13$ Hz, 4-H), 3.15 (1H, dd, $J=13$, 5 Hz, 4-H), 3.22 (1H, dd, $J=12$, 6 Hz, 3-H), 3.90, 4.18 (1H each, 2d, $J=12$ Hz, $-CH_2-Ph$), 6.5—6.7 (12H, m, phenyl), 7.85 (2H, d, $J=8$ Hz, phenyl)	C[b]
6g	1680, 1640 (CO) 1340, 1160 (SO_2)	337 (M^+ – Tol-SO_2H)	0.8—1.2, 1.3—1.8 (1H each, m, 5-H), 2.60 (3H, s, $-CH_3$), 3.60, 3.80 (3H each, 2s, $\geq N-CH_3$), 3.3—4.1 (5H, m, 3-, 3a-, and 4-H), 4.68, 5.00 (1H each, 2d, $J=12$ Hz, $-CH_2-Ph$), 7.4—7.7 (7H, m, phenyl), 7.96 (2H, d, $J=8$ Hz, phenyl)	T[b]
6h	1710, 1660 (CO) 1350, 1160 (SO_2)	473 (M^+ – Tol-SO_2H)	0.9—2.9 (22H, m, $-CH_2-$ and 5-H), 2.56 (3H, s, $-CH_3$), 3.3—4.2 (6H, m, $\geq CH$, 3-, 3a-, and 4-H), 4.6—5.1 (3H, m, $\geq CH$, and $-CH_2Ph$), 7.3—7.6 (7H, m, phenyl), 7.90 (2H, d, $J=8$ Hz, phenyl)	T[c]

TABLE II. (continued)

Compd.	IR ν_{max}^{KBr} cm^{-1}	MS *m/z*	^{1}H-NMR δ (ppm)	Solvent[a]
6i	1710, 1660 (CO) 1340, 1160 (SO_2)	461 (M^+ – Tol-SO_2H)	0.6—1.1 (2H, m, 5-H), 2.04 (3H, s, $-CH_3$), 2.7—3.3 (5H, m, 3-, 3a-, and 4-H), 3.44, 4.08 (1H each, 2d, J=12 Hz, $-CH_2-$Ph), 6.6—7.2 (12H, m, phenyl), 7.30 (2H, d, J=8 Hz, phenyl)	T[c]

a) C, Deuteriochloroform; D, hexadeuteriodimethyl sulfoxide; T, trifluoroacetic acid. *b*) Measured at 200 MHz. *c*) Measured at 100 MHz.

as shown in Chart 1. Analogously, the reactions of **4b—4f** with LTA gave the 2*H*-pyrazolo[3′,4′:4,5]pyrido[2,3-*d*]pyrimidine derivatives **6b—6f** in good yields.

The structural confirmation of **6a—6f** was accomplished on the basis of the analytical data and spectroscopic properties; the infrared (IR) spectra lacked the NH-stretching vibrations of the hydrazone observed in **4a—4f**.

The stereochemistry of the above adducts **6b—6f** was assigned on the basis of the following observations. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **6a** in trifluoroacetic acid shows two ABX patterns due to the methylene protons at the 3- and 4-positions and a multiplet due to the methine proton at the 3a-position; δ: 4.0—4.2 (m, 3a- and 4-H), 4.20 (dd, 3-H, J=17.5, 5.0 Hz), 4.46 (dd, 3-H, J=17.5, 4.1 Hz), and 4.64 (dd, 4-H, J=12.0, 7.0 Hz). On the other hand, the spectra of **6b—6f** show two double doublets due to the diastereotopic methylene protons at the 4-position and a doublet and a multiplet due to the methine protons at the 3- and 3a-positions, respectively. The vicinal coupling constants of the 3- and 3a-positions of **6b—6f** are 10—12 Hz, which are almost identical with the reported values[2a,c] for *trans* configuration between the 4- and 5-positions of 3,4-fused 2-pyrazoline systems. Furthermore, the substituent (methyl or phenyl) at the 3-position of **6b—6f** caused an apparent change of the chemical shift of the methine proton at the 3a-position; the 3a-H signal of **6b—6f** was observed at higher field ($\Delta\delta$=0.6—0.9 ppm) than that of **6a** in the same solvent (Table II).

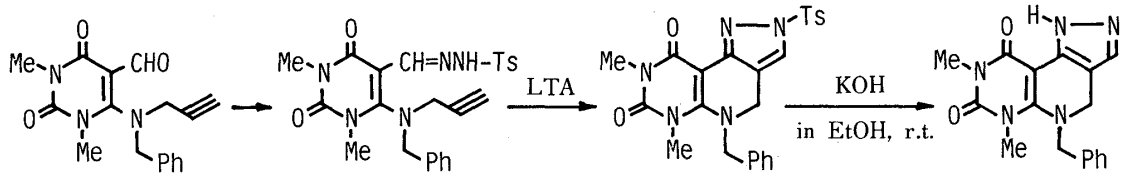
These findings suggest that the configuration between the methyl (or phenyl) group and 3a-H is *cis*[4] and, therefore, the configuration of the two methine protons at the 3- and 3a-positions is deduced to be *trans*.

This means that the 1,3-dipolar addition of nitrile imide intermediates **5** proceeded predictably with the retention of the stereochemistry of the olefinic dipolarophile.

Next, the tosylhydrazones of 1,3-disubstituted 6-*N*-(3-butenyl)benzylamino-2,4-dioxopyrimidine-5-carbaldehydes **4g—4i** were allowed to react with LTA in dry acetonitrile at −30 °C to afford 7,9-disubstituted 6-benzyl-2,3,3a,4,5,6,7,8,9,10-decahydro-8,10-dioxopyrazolo[3,4-*d*]pyrimido[4,5-*b*]azepines (**6g—6i**) in fair yields. The structures of **6g—6i** were also determined on the basis of their analytical and spectral data.[5] These results and spectral data for **6** are summarized in Tables I and II, respectively.

In order to prepare 4,5,6,7,8,9-hexahydro derivatives of the pyrazolopyridopyrimidine, the oxidation of the 2-pyrazoline rings of **6** to pyrazole ones was investigated. However, several attempts to dehydrogenate the 2-pyrazoline ring using various oxidizing reagents, *e.g.*, *N*-bromosuccinimide, chloranil, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, were unsuccessful.

The tosylhydrazone of 1,3-dimethyl-6-(*N*-3-propargyl)benzylamino-2,4-dioxopyrimidine-5-carbaldehyde (**7**) was prepared similarly and treated with LTA in dry acetonitrile below −30 °C to give the pyrazolopyridopyrimidine (**9**). The detosylation of **9** was performed with 5% ethanolic potassium hydroxide at room temperature to give the ex-



7 8 9 10

r.t., room temperature

Chart 2

pected 5-benzyl-4,5,6,7,8,9-hexahydro-6,8-dimethyl-7,9-dioxo-1*H*-pyrazolo[3′,4′ : 4,5]-pyrido[2,3-*d*]pyrimidine (**10**) in fair yield (Chart 2).

The IR spectrum of **10** shows broad NH-stretching vibrations in the vicinity of 3200 cm^{-1} (characteristic of pyrazole) and the NH proton signal of **10** was observed in the region of 9 ppm in the ^{1}H-NMR spectrum.

In conclusion, the intramolecular 1,3-dipolar addition reaction of these systems proved to be an effective route for the preparation of the fused pyridopyrimidine derivatives and their homologs.

Experimental

General——All melting points are uncorrected. The IR spectra were measured on a JASCO IRA-1 spectrometer as potassium bromide pellets. ^{1}H-NMR spectra were determined on JEOL JMN-MH-100 and FX-200 spectrometers with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with JEOL JMS-D and JMS-01SG-2 mass spectrometers with direct inlet systems and at an ionization energy of 75 eV. Elemental analyses were performed on a Hitachi 026 CHN analyzer. The thin-layer chromatography was accomplished on 0.2 mm precoated plates of Silica gel $60F_{254}$ (Merck) or on 0.2 mm precoated plates of Aluminium oxide $60F_{254}$ type E (Merck). Visualization was done under ultraviolet light (254 and 365 nm). For preparative column chromatography, Wakogel C-300 was used.

Preparation of 1,3-Disubstituted 6-Aminopyrimidine-2,4(1*H*,3*H*)-dione-5-carbaldehydes 3. Typical Procedure——A mixture of 6-chloro-5-formyl-1,3-dimethyluracil[6] (5.5 g, 27 mmol) and diallylamine (**2a**) (6.65 g, 70 mmol) in ethanol (80 ml) was refluxed for 12 h. The ethanol was removed *in vacuo* and the residue was poured into water, then extracted with chloroform (50 ml × 4). The organic layer was dried and the chloroform was evaporated off. The residue was purified by column chromatography (silica gel–chloroform) to give 6.3 g (89%) of 6-diallylamino-5-formyl-1,3-dimethyluracil (**3a**).

3a: A brown viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 3.26, 3.28 (3H each, 2s, $>N-CH_3$), 3.76 (4H, d, J=5 Hz, $-CH_2-CH=$), 5.2—5.4 (4H, m, $=CH_2$), 5.5—5.8 (2H, m, $-CH=$), 9.84 (1H, s, $-CH=O$).

3b: Yield 71%. A brown viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (3H, d, J=5 Hz, $-CH_3$), 3.26 (6H, br s, $>N-CH_3$), 3.54 (2H, d, J=5 Hz, $-CH_2-CH=$), 4.26 (2H, s, $-CH_2-Ph$), 5.3—5.7 (2H, m, $-CH=CH-$), 7.3 (5H, br s, phenyl), 10.01 (1H, s, $-CH=O$).

3c: Yield 60%. A brown viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 3.36 (6H, br s, $>N-CH_3$), 3.78 (2H, d, J=5 Hz, $-CH_2-CH=$), 4.32 (2H, s, $-CH_2-Ph$), 6.0—6.6 (2H, m, $-CH=CH-$), 7.1—7.4 (10H, m, phenyl), 10.04 (1H, s, $-CH=O$).

3d: Yield 68%. Yellow prisms (ethanol). mp 151—152 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.85, 3.25, 3.36 (3H each, 3s, $>N-CH_3$), 3.90 (2H, d, J=5 Hz, $-CH_2-CH=$), 5.9—6.2 (2H, m, $-CH=CH-$), 7.2—7.4 (5H, m, phenyl), 9.90 (1H, s, $-CH=O$). *Anal.* Calcd for $C_{16}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.22; H, 6.19; N, 13.44.

3e: Yield 56%. Pale yellow prisms (hexane). mp 145—146 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.6—2.6 (20H, m, $-CH_2-$), 1.76 (3H, d, J=5 Hz, $-CH_3$), 3.60 (2H, d, J=5 Hz, $-CH_2-CH=$), 4.28 (2H, s, $-CH_2-Ph$), 4.5—5.0 (2H, m, $>CH$), 5.3—5.9 (2H, m, $-CH=CH-$), 7.2—7.6 (5H, m, phenyl), 10.08 (1H, s, $-CH=O$). *Anal.* Calcd for $C_{28}H_{37}N_3O_3$: C, 72.54; H, 8.04; N, 9.06. Found: C, 72.81; H, 8.13; N, 9.07.

3f: Yield 32%. A yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (3H, d, J=5 Hz, $-CH_3$), 3.44 (2H, d, J=6 Hz, $-CH_2-CH=$), 3.92 (2H, s, $-CH_2-Ph$), 5.2—5.7 (2H, m, $-CH=CH-$), 7.0—7.4 (15H, m, phenyl), 10.12 (1H, s, $-CH=O$).

3g: Yield 32%. A yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 2.3—2.5 (2H, m, $-CH_2-CH=$), 3.1—3.2 (2H, m, $>N-CH_2-$), 3.36 (6H, s, $>N-CH_3$), 5.0—5.2 (2H, m, $=CH_2$), 5.5—5.8 (1H, m, $-CH=$), 7.2—7.4 (5H, m, phenyl), 10.04 (1H, s, $-CH=O$).

3h: Yield 45%. Pale yellow prisms (ethanol). mp 133—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.5 (22H, m, $-CH_2-$), 3.0—3.2 (2H, m, $>N-CH_2-$), 3.5—3.8 (1H, m, $>CH$), 4.32 (2H, s, $-CH_2-Ph$), 4.6—4.9 (1H, m, $>CH$), 4.9—5.2 (2H, m, $=CH_2$), 5.5—5.9 (1H, m, $-CH=$), 7.1—7.5 (5H, m, phenyl), 9.96 (1H, s, $-CH=O$). *Anal.* Calcd for $C_{28}H_{37}N_3O_3$: C,

72.54; H, 8.04; N, 9.04. Found: C, 72.65; H, 8.05; N, 9.13.

3i: Yield 40%. A brown viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.3 (2H, m, $-CH_2-CH=$), 2.7—2.9 (2H, m, $>N-CH_2-$), 4.08 (2H, s, $-CH_2-Ph$), 4.8—5.0 (2H, m, $=CH_2$), 5.3—5.8 (1H, m, $-CH=$), 7.0—7.5 (15H, m, phenyl), 10.12 (1H, s, $-CH=O$).

The oily products **3a**—**3c**, **3f**, **3g**, and **3i** were used for the next reaction with tosylhydrazine without further purification.

Preparation of Tosylhydrazones 4 from 3. Typical Procedure——Tosylhydrazine (1.90 g, 10 mmol) in methanol (10 ml) containing a few drops of conc. hydrochloric acid was added to a stirred and cooled solution of **3a** (2.60 g, 10 mmol) in methanol (20 ml) at 0 °C. After several hours, the resultant precipitate was collected by filtration. Recrystallization from ethanol gave 2.97 g (70%) of the tosylhydrazone **4a**.

4a: Pale yellow prisms. mp 164—165 °C. IR (KBr): 3140 (NH), 1680, 1620 (CO, $>C=N-$), 1320, 1150 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, $-CH_3$), 3.16, 3.25 (3H each, 2s, $>N-CH_3$), 3.36 (4H, d, $J=6$ Hz, $-CH_2-CH=$), 4.8—5.2 (4H, m, $=CH_2$), 5.4—5.8 (2H, m, $-CH=$), 7.32 (2H, d, $J=8$ Hz, phenyl), 7.72 (2H, d, $J=8$ Hz, phenyl), 7.84 (1H, s, $-CH=N-$), 11.60 (1H, s, $>NH$). *Anal.* Calcd for $C_{20}H_{25}N_5O_4S$: C, 55.67; H, 5.84; N, 16.23. Found: C, 55.62; H, 5.91; N, 16.20.

4b: Yield 64%. Colorless prisms (ethanol). mp 158—160 °C. IR (KBr): 3120 (NH), 1690, 1600 (CO, $>C=N-$), 1360, 1160 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.76 (3H, d, $J=5$ Hz, $-CH_3$), 2.40 (3H, s, $-CH_3$), 3.36 (6H, s, $>N-CH_3$), 4.24 (2H, s, $-CH_2-Ph$), 6.76 (1H, s, $-CH=N-$); 7.0—7.4 (7H, m, phenyl), 7.90 (2H, d, $J=8$ Hz, phenyl), 10.7 (1H, br s, $>NH$). *Anal.* Calcd for $C_{25}H_{29}N_5O_4S$: C, 60.34; H, 6.28; N, 14.08. Found: C, 60.73; H, 5.96; N, 13.95.

4c: Yield 58%. Colorless prisms (ethanol). mp 142—144 °C. IR (KBr): 3130 (NH), 1700, 1600 (CO, $>C=N-$), 1360, 1160 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s, $-CH_3$), 3.28, 3.32 (3H each, 2s, $>N-CH_3$), 3.68 (2H, d, $J=6$ Hz, $-CH_2-CH=$), 4.16 (2H, s, $-CH_2-Ph$), 5.8—6.5 (2H, m, $-CH=CH-$), 6.72 (1H, s, $-CH=N-$), 7.0—7.4 (7H, m, phenyl), 7.8 (2H, d, $J=8$ Hz, phenyl), 10.6 (1H, br s, $>NH$). *Anal.* Calcd for $C_{30}H_{31}N_5O_4S$: C, 64.62; H, 5.60; N, 12.56. Found: C, 64.67; H, 5.78; N, 12.43.

4d: Yield 22%. Colorless prisms (ethanol). mp 136—137 °C. IR (KBr): 3100 (NH), 1680, 1620 (CO, $>C=N-$), 1330, 1150 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.58 (3H, s, $-CH_3$), 2.29, 2.34, 2.38 (3H each, 3s, $>N-CH_3$), 3.90 (2H, d, $J=6$ Hz, $-CH_2-CH=$), 5.8—6.7 (2H, m, $-CH=CH-$), 6.92 (1H, s, $-CH=N-$), 7.2—7.4 (7H, m, phenyl), 7.90 (2H, d, $J=8$ Hz, phenyl), 10.74 (1H, s, $>NH$). *Anal.* Calcd for $C_{24}H_{27}N_5O_4S$: C, 59.86; H, 5.65; N, 14.55. Found: C, 59.95; H, 5.53; N, 14.39.

4e: Yield 60%. Colorless needles (ethanol). mp 142—144 °C. IR (KBr): 3020 (NH), 1710, 1620 (CO, $>C=N-$), 1330, 1160 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.8—2.6 (20H, m, $-CH_2-$), 1.76 (3H, s, $-CH_3$), 2.40 (3H, s, $-CH_3$), 3.50 (2H, d, $J=5$ Hz, $-CH_2-CH=$), 3.5—3.8 (1H, m, $\geqslant CH$), 4.24 (2H, s, $-CH_2-Ph$), 4.5—5.0 (1H, m, $\geqslant CH$), 6.88 (1H, s, $-CH=N-$), 7.0—7.4 (7H, m, phenyl), 7.95 (2H, d, $J=8$ Hz, phenyl), 10.08 (1H, s, $>NH$). *Anal.* Calcd for $C_{35}H_{45}N_5O_4S$: C, 66.54; H, 7.18; N, 11.09. Found: C, 66.23; H, 7.39; N, 11.23.

4f: Yield 78%. Pale yellow prisms (ethanol). mp 188—189 °C. IR (KBr): 3020 (NH), 1710, 1620 (CO, $>C=N-$), 1360, 1160 cm^{-1} (SO_2). ^{1}H-NMR (DMSO-d_6) δ: 1.58 (3H, d, $J=5$ Hz, $-CH_3$), 2.28 (3H, s, $-CH_3$), 3.20 (2H, d, $J=5$ Hz, $-CH_2-CH=$), 3.66 (2H, s, $-CH_2-Ph$), 5.1—5.5 (2H, m, $-CH=CH-$), 6.80 (1H, s, $-CH=N-$), 7.0—7.8 (19H, m, phenyl), 10.8 (1H, br s, $>NH$). *Anal.* Calcd for $C_{35}H_{33}N_5O_4S$: C, 67.84; H, 5.37; N, 11.30. Found: C, 68.03; H, 5.48; N, 11.21.

4g: Yield 78%. Pale yellow prisms (ethanol). mp 174—176 °C. IR (KBr): 3120 (NH), 1710, 1600 (CO, $>C=N-$), 1360, 1160 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.9—2.2 (2H, m, $>N-CH_2-$), 2.26 (3H, s, $-CH_3$), 2.7—2.9 (2H, m, $-CH_2-CH=$), 3.16, 3.20 (3H each, 2s, $>N-CH_3$), 3.90 (2H, s, $-CH_2-Ph$), 4.7—5.0 (2H, m, $=CH_2$), 5.3—5.7 (1H, m, $-CH=$), 6.9—7.3 (8H, m, phenyl, $>NH$), 7.70 (2H, d, $J=8$ Hz, phenyl), 7.92 (1H, s, $-CH=N-$). *Anal.* Calcd for $C_{25}H_{29}N_5O_4S$: C, 60.59; H, 5.90; N, 14.13. Found: C, 60.43; H, 5.96; N, 13.90.

4h: Yield 34%. Pale yellow prisms (ethanol). mp 181—182 °C. IR (KBr): 3140 (NH), 1690, 1620 (CO, $>C=N-$), 1340, 1160 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.8—2.6 (22H, m, $-CH_2-$), 2.38 (3H, s, $-CH_3$), 3.0—3.2 (2H, m, $>N-CH_2-$), 3.5—3.8 (1H, m, $\geqslant CH$), 4.26 (2H, s, $-CH_2-Ph$), 4.6—4.9 (1H, m, $\geqslant CH$), 5.0—5.3 (2H, m, $=CH_2$), 5.5—5.8 (1H, m, $-CH=$), 6.86 (1H, s, $-CH=N-$), 7.1—7.4 (7H, m, phenyl), 7.94 (2H, d, $J=8$H, phenyl), 10.8 (1H, br s, $>NH$). *Anal.* Calcd for $C_{35}H_{45}N_5O_4S$: C, 66.54; H, 7.18; N, 11.09. Found: C, 66.29; H, 7.15; N, 11.10.

4i: Yield 33%. Colorless prisms (ethanol). mp 198—201 °C. IR (KBr): 3050 (NH), 1720, 1630 (CO, $>C=N-$), 1320, 1160 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.4 (2H, m, $-CH_2-CH=$), 2.28 (3H, s, $-CH_3$), 2.8—3.0 (2H, m, $>N-CH_2-$), 3.88 (2H, s, $-CH_2-Ph$), 4.8—5.1 (2H, m, $=CH_2$), 5.3—5.6 (1H, m, $-CH=$), 6.92 (1H, s, $-CH=N-$), 7.0—7.4 (17H, m, phenyl), 7.80 (2H, d, $J=8$ Hz, phenyl), 10.56 (1H, s, $>NH$). *Anal.* Calcd for $C_{35}H_{33}N_5O_4S$: C, 67.84; H, 5.37; N, 11.30. Found: C, 68.05; H, 5.44; N, 11.30.

Preparation of Pyrazolopyridopyrimidines (6) by the Oxidation of 4 with LTA. Typical Procedure——LTA (2.3 g, 5.21 mmol) in dry acetonitrile (30 ml) was added dropwise to a stirred and cooled solution of **4a** (1.5 g, 3.48 mmol) in dry acetonitrile (100 ml) at -5 °C during 1 h. After completion of the addition, the reaction mixture was allowed to stand at the same temperature. The resultant precipitate was filtered off and the filtrate was evaporated to dryness. The residue was poured into water and extracted with dichloromethane (50 ml × 4). The organic layer was washed with water several times, dried, and evaporated to afford a residue. Crystallization of the residue from ethanol gave

0.84 g (56%) of **6a**. The ethanol filtrate was evaporated to dryness, and the residue was subjected to short column chromatography (silica gel–chloroform) to give 0.29 g (32%) of **3a**.

For the preparation of the pyrazolopyrimidoazepines **6g**—**6i**, the oxidation of **4g**—**4i** with LTA (1.5 equimol) was carried out in dry acetonitrile at −30 °C. The results of these reactions and the physical properties and spectral data of **6** are summarized in Tables I and II, respectively.

Preparation of Pyrazolopyridopyrimidines (10). Typical Procedure——As described in the procedure for the preparation of **6**, 6-(*N*-propargyl)benzylaminopyrimidine-2,4(1*H*,3*H*)-dione-5-carbaldehyde **7** was prepared and converted to the hydrazone **8**. The oxidation of **8** with LTA (1.5 equimol) was performed below −30 °C to give **9** in 40% yield. Compound **9** (0.2 g, 0.42 mmol) was treated with 5% ethanolic potassium hydroxide (40 ml) at room temperature for 1 h and the ethanol was removed *in vacuo* to give a residue. The residue was poured into water and extracted with dichloromethane (30 ml × 2). The organic layer was dried and evaporated to give 70 mg of the expected product (**10**).

7: Yield 82%. A brown viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (1H, t, J=3 Hz, ≡CH), 3.30, 3.46 (3H each, 2s, ≻N–CH_3), 3.88 (2H, d, J=3 Hz, –CH_2–C≡), 4.46 (2H, s, –CH_2–Ph), 7.3 (5H, m, phenyl), 9.94 (1H, s, –CH=O).

8: Colorless needles (ethanol). mp 152—154 °C. IR (KBr): 3230 (≡CH), 3120 (NH), 2100 (–C≡CH), 1700, 1610 (CO, ≻C=N–), 1320, 1160 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s, –CH_3), 2.48 (1H, t, J=3 Hz, ≡CH), 3.24, 3.30 (3H each, 2s, ≻N–CH_3), 3.62 (2H, d, J=3 Hz, –CH_2–C≡), 4.28 (2H, s, –CH_2–Ph), 6.80 (1H, s, –CH=N–), 7.1—7.4 (7H, m, phenyl), 7.84 (2H, d, J=8 Hz, phenyl), 10.72 (1H, s, ≻NH). *Anal.* Calcd for $C_{24}H_{25}N_5O_4S$: C, 60.12; H, 5.26; N, 14.61. Found: C, 60.03; H, 5.24; N, 14.40.

9: Colorless needles (ethanol). mp 187—189 °C. IR (KBr): 1690, 1660 (CO, ≻C=N–), 1350, 1170 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s, –CH_3), 3.38, 3.52 (3H each, 2s, ≻N–CH_3), 3.98 (2H, s, 4-H), 4.02 (2H, s, –CH_2–Ph), 7.2—7.4 (7H, m, phenyl), 7.58 (1H, s, 3-H), 7.80 (2H, d, J=8 Hz, phenyl). MS *m/z* (relative intensity): 477 (M^+, 17), 322 (M^+ −Ts, 7), 244 (9), 231 (M^+ −Ts−CH_2Ph, 3), 91 ($C_7H_7^+$, base peak). *Anal.* Calcd for $C_{24}H_{23}N_5O_4S$: C, 60.37; H, 4.86; N, 14.67. Found: C, 60.07; H, 4.79; N, 14.41.

10: Colorless needles (ethanol). mp 222—224 °C. IR (KBr): 3220 (NH), 1700, 1640 cm^{-1} (CO, ≻C=N–). ^{1}H-NMR ($CDCl_3$) δ: 3.50, 3.60 (3H each, 2s, ≻N–CH_3), 4.20, 4.30 (2H each, 2s, 4-H, –CH_2–Ph), 7.2—7.6 (6H, m, 3-H, phenyl), 8.6—9.2 (1H, br s, ≻NH). MS *m/z* (relative intensity): 323 (M^+, 43), 232 (M^+ −CH_2Ph, 20), 202 (M^+ −CH_2Ph−2×CH_3, 8), 91 ($C_7H_7^+$, base peak). *Anal.* Calcd for $C_{27}H_{17}N_5O_2$: C, 63.14; H, 5.30; N, 21.66. Found: C, 62.91; H, 5.33; N, 21.43.

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References and Notes

1) W. Oppolzer, *Tetrahedron Lett.*, **1970**, 3091; R. Hull, P. J. van den Broek, and M. L. Swain, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 2271; M. Gál, Ö. Fehér, E. Tihanyi, G. Horváth, and G. Jerkovich, *Tetrahedron*, **38**, 2933 (1982); N. Yokoyama, U. S. Patent 4312870 (1982) [*Chem. Abstr.*, **96**, 18128*v* (1982)].

2) *a*) R. Fusco, L. Garaniti, and G. Zecchi, *Tetrahedron Lett.*, **1974**, 269; *b*) L. Garaniti and G. Zecchi, *ibid.*, **1976**, 1339; *c*) *Idem, J. Org. Chem.*, **42**, 1389 (1977); *idem, ibid.*, **43**, 2077 (1978); *d*) A. Padwa, S. Nahm, and E. Sato, *ibid.*, **43**, 1664 (1978); *e*) H. Meir, H. Meimgartner, and H. Schmidt, *Helv. Chim. Acta*, **60**, 1078 (1978); H. Meir and H. Meimgartner, *ibid.*, **60**, 3035 (1978); *f*) T. Shimizu, Y. Hayashi, Y. Nagano, and K. Teramura, *Bull. Chem. Soc. Jpn.*, **53**, 429 (1980); T. Shimizu, Y. Hayashi, Y. Kitora, and K. Teramura, *ibid.*, **55**, 2450 (1982); T. Shimizu, Y. Hayashi, S. Ishikawa, and K. Terashima, *ibid.*, **55**, 2456 (1982) and references cited therein.

3) The generation of nitrile imide intermediates by the oxidation of hydrazones with LTA was reported.[2f,7] However, the reported method gave unsatisfactory results in our cases; a lower yield of **6** and the formation of acetylated products.

4) The inspection of molecular models of **6b**—**6f** showed that the proton at the 3a-position is situated in the shielding area of methyl[8] or phenyl group at the 3-position.

5) Other structures for **6g**—**6i**, pyrazolo[4,5-*b*]pyrimido[3,4,5-*de*]azocine derivatives, are ruled out because of the similarity of the spectral data to those of **6a**—**6f** and a consideration of the transition states leading to the pyrazolopyrimidoazocines (steric repulsion between the terminal olefin protons and the 6-amino group of **5g**—**5i** would become serious as the reaction progressed).

6) S. Senda, K. Hirota, G. N. Yang, and M. Shiraishi, *Yakugaku Zasshi*, **91**, 1372 (1971).

7) W. A. Gladstone, J. B. Aylward, and R. O. C. Norman, *J. Chem. Soc.* (*C*), **1969**, 2587.

8) A. G. Moritz and N. Sheppard, *Mol. Phys.*, **5**, 361 (1962).