Synthesis of 3-Aminopyrazolo[3,4-*d*]pyrimidine Derivatives Using *N*-Bis(methylthio)methylene-*p*-toluenesulfonamide

Yoshinori Tominaga*, Mayumi Hara, Harumasa Honkawa and Akira Hosomi†

Faculty of Pharmaceutical Sciences, Nagasaki University,
Bunkyomachi 1-14, Nagasaki 852, Japan

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N-Bis(methylthio)methylene-*p*-toluenesulfonamide (**1**) reacted with active methylene compounds such as malononitrile (**2a**) and, cyanoacetamide (**2b**) to give the corresponding 3-methylthio-3-*p*-toluenesulfonylaminopropenenitrile derivatives **3a,b** which were found to be convenient starting materials for the synthesis of 3,5-diaminopyrazole derivatives. Reaction of **3a** and **3b** with hydrazines gave the corresponding 3,5-diaminopyrazoles **4a-e**, key intermediates for the synthesis of 3-aminopyrazolo[3,4-*d*]pyrimidine derivatives **5a-d**.

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N-Bis(methylthio)methylene-*p*-toluenesulfonamide (**1**), which is readily prepared by the reaction of *p*-toluenesulfonamide with carbon disulfide in the presence of an appropriate base and solvent followed by the methylation with dimethyl sulfate in good yield, is an active electrophilic reagent towards various nucleophiles such as amines [1-9]. Because of high reactivity, this reagent which is used for the synthesis of *p*-toluenesulfonylguanidines as drugs has attracted much attention of many medicinal chemists [10]. Specially, a variety of cimetidine derivatives which are known as antagonists are synthesized by using this reagent [11-15]. However, a few examples of the reaction of this reagent with active methylene compounds are known [1-9]. *S,N*-Acetals derived by the above reaction of **1** with active methylene compounds have been scarcely investigated.

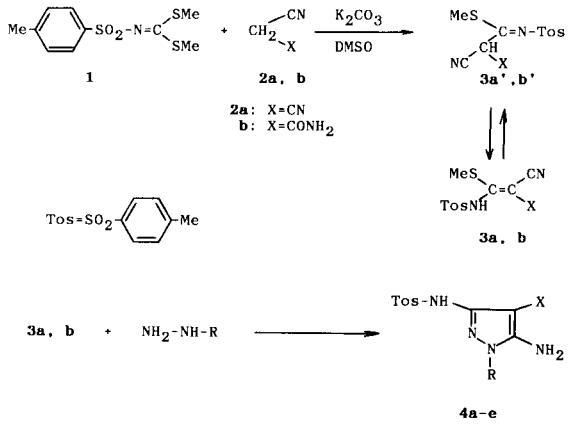
In general, the first displacement reaction of the methylthio group in ketene dithioacetals with amines smoothly occurs under a mild condition. While the second displacement reaction required harder conditions, it has been reported that the reaction of *N*-acetylketene *S,N*-acetals with amines smoothly occurs under the mild conditions to give the corresponding diamine derivatives in good results [17]. We reported that *N*-acetyl or *N*-aroylketene *S,N*-acetal derivatives which smoothly reacted with amines to give the corresponding diamine derivatives in good yields. But these diamines spontaneously transformed to pyrimidine derivatives. We tried the synthesis and reaction of *N*-tosylketene *N,S*-acetal derivatives from *N*-bis(methylthio)methylene-*p*-toluenesulfonamide.

It has been generally reported that the combination of potassium carbonate as a base and dimethyl sulfoxide as a solvent gives the most effective and successful results in the reaction of ketene dithioacetals with active methylene compounds [7]. So we applied the above reaction to the synthesis of *S,N*-acetals.

The reaction of **1** with malononitrile (**2a**) in the presence of potassium carbonate in dimethyl sulfoxide afforded the desired displacement product **3a** of the methylthio group of **1** in 93% yield. Similarly, the reaction of **1** with cyanoacetamide (**2b**) gave the corresponding propenamide derivative **3b** in 94% yield.

The further reaction of **3a,b** with various hydrazines (hydrazine hydrate, phenylhydrazine, *p*-chlorophenylhydrazine, *p*-nitrophenylhydrazine) gave the corresponding 5-aminopyrazole derivatives **4a-e** in good yields. The results are shown in Table 1.

Scheme 1

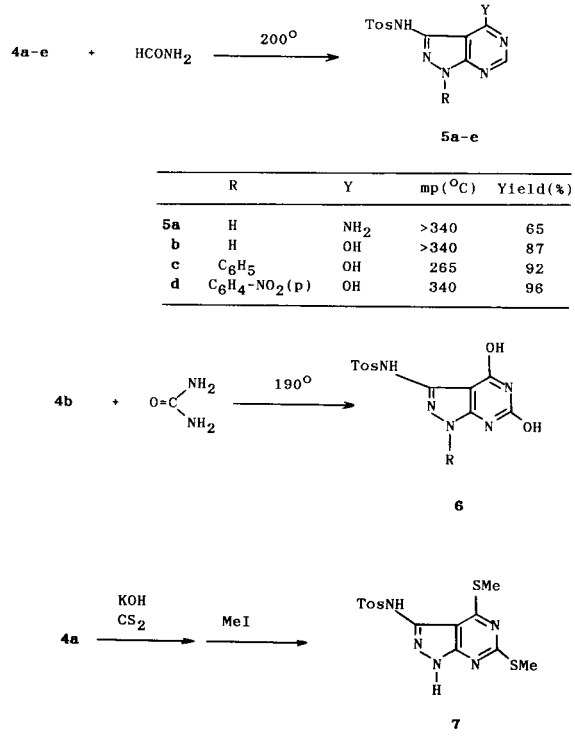


	R	X	mp(°C)	Yield(%)
4a	H	CN	213	66
b	H	$CONH_2$	282	76
c	C_6H_5	$CONH_2$	230	70
d	C_6H_4-Cl(p)	$CONH_2$	302	98
e	C_6H_4-NO_2(p)	$CONH_2$	322	66

5-Amino- (or 3-amino-) pyrazole-4-carbonitrile is a useful intermediate for the preparation of pyrazolo[3,4-*d*]pyrimidine derivatives. Therefore compounds **4a-e** may be key intermediates for the synthesis of 3-aminopyrazolo[3,4-*d*]-pyrimidine. Treatment of **4a** with formamide at 200° for 1 hour gave 4-amino-3-*p*-toluenesulfonylaminopyrazolo[3,4-*d*]pyrimidines (**5a**) in 65% yield. Similarly, 4-hydroxy-3-*p*-toluenesulfonylaminopyrazolo[3,4-*d*]pyrimidines **5b-d** were also synthesized by the reaction of **4b,c,e** with formamide. Compound **4b** was allowed to react with urea to give 4-hydroxypyrazolo[3,4-*d*]pyrimidines **6**. Carbon disulfide

can be also used for the preparation of pyrazolo[3,4-*d*]-pyrimidine derivative. Thus, compound **4a** was allowed to react with carbon disulfide in the presence of potassium hydroxide in dimethyl sulfoxide (DMSO), followed by treatment with methyl iodide to give desired product, 4,6-bis(methylthio)pyrazolo[3,4-*d*]pyrimidines **7** in 73% yield.

Scheme 2



	R	Y	mp(°C)	Yield(%)
5a	H	NH_2	>340	65
b	H	OH	>340	87
c	C_6H_5	OH	265	92
d	C_6H_4-NO_2(p)	OH	340	96

In conclusion, a new ketene *N,S*-acetal, 3-methylthio-3-*p*-toluenesulfonylaminopropenenitrile derivatives which are prepared by the reaction of **1a** with active methylene compounds (malononitrile, cyanoacetamide), was found to be a useful starting materials for synthesis of pyrazole and pyrazolo[3,4-*d*]pyrimidine derivatives.

EXPERIMENTAL

All melting points were determined in a capillary tube and uncorrected. Infrared (ir) spectra were recorded in potassium bromide pallets on a JASCO IRA-2 spectrometer and ultraviolet (UV) absorption spectra were determined in 95% ethanol on a Hitachi EP-S2 spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained on JNM-PS-(100 MHz) and JNM-FX-90Q(90 MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on a JEOL JMS-01SG mass spectrometer.

2-Cyano-3-methylthio-3-*p*-toluenesulfonylaminopropenenitrile (**3a**).

A mixture of 1.98 g (30 mmoles) of malononitrile, 5.51 g (20 mmoles) of *N*-bis(methylthio)methylene-*p*-toluenesulfonamide, 5.52 g (40 mmoles) of potassium carbonate, and 60 ml of dimethyl sulfoxide was stirred for 2 hours at room temperature. The reaction mixture was poured into 300 ml of ice water and then acidified with 10% hydrochloric acid. The precipitate was collected by the filtration and recrystallized from methanol to give 5.45 g (18.6 moles) of colorless needles, mp 134° [lit [2] mp 132-134°] in 93% yield; ^{1}H-nmr (deuteriochloroform): δ 2.28 (3H, s, SMe), 2.47 (3H, s, CH_3), 6.30 (2H, d, J = 8.0 Hz, phenyl-H), 7.67 (2H, d, J = 8.0 Hz, phenyl-H), 10.90 (1H, bs, NH).

2-Cyano-3-methylthio-3-*p*-toluenesulfonylaminopropenamide (**3b**).

This compound (5.84 g, 18.8 mmoles) was prepared from **1** (5.51 g, 20 mmoles) and cyanoacetamide (**2b**) (1.68 g, 20 mmoles) in 94% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 138°; ir (potassium bromide): ν max cm^{-1} 3445, 3335, 3190 (NH), 2210 (CN), 1669 (CO); ^{1}H-nmr (deuteriochloroform): δ 2.42 (3H, s, CH_3), 2.58 (3H, s, SCH_3), 6.02 (2H, bs, NH_2), 7.27 (2H, d, J = 8.0 Hz, phenyl-H), 7.80 (2H, d, J = 8.0 Hz, phenyl-H), 12.96 (1H, bs, NH).

Anal. Calcd. for $C_{12}H_{13}N_3O_3S_2$: C, 46.29; H, 4.21; N, 13.49; S, 20.59. Found: C, 46.13; H, 4.20; N, 13.34; S, 20.45.

5-Amino-3-*p*-toluenesulfonylaminopyrazole-4-carbonitrile (**4a**).

A mixture of 2.98 g (10 mmoles) of **3a** and 0.76 g (15 mmoles) of hydrazine hydrate was heated at 100° for 1 hour. After cooling, a crystallized product was washed with water and recrystallized from methanol to give 1.82 g (6.57 mmoles) of yellow needles, mp 213°, in 66% yield; ir (potassium bromide): ν max cm^{-1} 3440, 3320 (NH), 2200 (CN); uv (ethanol): λ max nm (log ϵ) 230 (4.23); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.36 (3H, s, CH_3), 6.30 (2H, bs, NH), 7.33 (2H, d, J = 8.5 Hz, phenyl-H), 7.68 (2H, d, J = 8.5 Hz, phenyl-H), 10.18 (1H, bs, NH), 11.54 (1H, bs, NH).

Anal. Calcd. for $C_{11}H_{11}N_5O_2S$: C, 47.65; H, 4.00; N, 25.25; S, 11.66. Found: C, 47.58; H, 3.87; N, 25.32; S, 11.37.

5-Amino-3-*p*-toluenesulfonylaminopyrazole-4-carboxamide (**4b**).

This compound (2.24 g, 7.6 mmoles) was prepared from **3b** (3.11 g, 10 moles) and hydrazine hydrate (0.76 g, 15 mmoles) in 76% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 282°; ir (potassium bromide): ν max cm^{-1} 3450, 3400, 3330, 3280 (NH), 1680 (CO); uv (ethanol): λ max nm (log ϵ) 222 (4.43), 258 (4.12); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.33 (3H, s, CH_3), 6.27 (2H, bs, NH_2), 6.93 (2H, bs, NH_2), 7.29 (2H, d, J = 8.0 Hz, phenyl-H), 7.67 (2H, d, J = 8.0 Hz, phenyl-H), 11.40 (1H, bs, NH).

Anal. Calcd. for $C_{11}H_{13}N_5O_3S$: C, 44.74; H, 4.44; N, 23.71; S, 10.86. Found: C, 45.07; H, 4.45; N, 23.77; S, 10.78.

5-Amino-3-*p*-toluenesulfonylamino-1-phenylpyrazole-4-carboxamide (**4c**).

This compound (2.60 g, 7.0 mmoles) was prepared from **3b** (3.11 g, 10 moles) and phenylhydrazine (1.08 g, 10 mmoles) in 70% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 230°; ir (potassium bromide): ν max cm^{-1} 3440, 3320, 3040 (NH), 1636 (CO); uv (ethanol): λ max nm (log ϵ) 236 (4.52); ^{1}H-nmr (deuteriochloroform): δ 2.38 (3H, s, CH_3), 6.46 (2H, bs, NH_2), 6.95 (2H, bs, NH_2), 7.25-7.50 (7H, m, phenyl-H), 7.75 (2H, d, J = 8.0 Hz, phenyl-H).

Anal. Calcd. for $C_{17}H_{17}N_5O_3S$: C, 54.96; H, 4.61; N, 18.86; S, 8.63. Found: C, 54.98; H, 4.60; N, 18.71; S, 8.59.

5-Amino-1-*p*-chlorophenyl-3-*p*-toluenesulfonylaminopyrazole-4-carboxamide (**4d**).

This compound (1.07 g, 2.65 mmoles) was prepared from **3b** (3.11 g, 10 moles) and *p*-chlorophenylhydrazine (1.43 g, 10 mmoles) in 98% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 302°; ir (potassium bromide): ν max cm^{-1} 3440-3280 (NH), 1645 (CO); uv (ethanol): λ max nm (log ϵ) 236 (4.47), 310 (3.41); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.40 (3H, s, CH_3), 6.51 (2H, bs, NH_2), 6.85 (2H, bs, NH_2), 7.30-7.52 (6H, m, phenyl-H), 7.78 (2H, d, J = 8.0 Hz, phenyl-H).

Anal. Calcd. for $C_{17}H_{16}ClN_5O_3S$: C, 50.31; H, 3.97; N, 17.26; S, 7.90. Found: C, 50.11; H, 4.01; N, 17.13; S, 7.98.

5-Amino-1-*p*-nitrophenyl-3-*p*-toluenesulfonylaminopyrazole-4-carboxamide (**4e**).

This compound (2.74 g, 6.58 mmoles) was prepared from **3b** (3.11 g, 10 mmoles) and *p*-nitrophenylhydrazine (1.53 g, 10 mmoles) in 66% yield in a manner similar to that described for the preparation of **4a**. An analytical sample was recrystallized from methanol to give tan needles, mp 322°; ir (potassium bromide): ν max cm^{-1} 3440-3280 (NH), 1645 (CO); uv (ethanol): λ max nm (insufficient solubility) 225, 300, λ min 310; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.40 (3H, s, SCH_3), 6.70 (1H, bs, NH), 7.00 (1H, bs, NH), 7.38 (2H, d, J = 8.0 Hz, phenyl-H), 7.61 (2H, d, J = 8.0 Hz, phenyl-H), 7.77 (2H, d, J = 8.0 Hz, aromatic-H), 8.31 (2H, d, J = 8.0 Hz, phenyl-H).

Anal. Calcd. for $C_{17}H_{16}N_6O_5S$: C, 49.03; H, 3.87; N, 20.18; S, 7.70. Found: C, 48.90; H, 3.92; N, 19.97; S, 7.42.

4-Amino-3-*p*-toluenesulfonylaminopyrazolo[3,4-*d*]pyrimidine (**5a**).

A mixture of 1.0 g (3.6 mmoles) of **4a** and 1.0 ml of formamide was heated 200° for 1 hour. After cooling, the solid was washed with 50 ml of water and recrystallized from methanol to give 0.71 g (2.34 mmoles) of colorless needles, mp >340°, in 65% yield; ir (potassium bromide): ν max cm^{-1} 3390-3300 (NH); uv (ethanol): λ max nm (log ϵ) 227 (4.30), 252 (4.13), 330 (3.44); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.34 (3H, s, CH_3), 7.20 (1H, bs, NH), 7.36 (2H, d, J = 8.0 Hz, phenyl-H), 7.70 (2H, d, J = 8.0 Hz, phenyl-H), 8.13 (1H, s, 6-H), 10.80 (1H, bs, NH), 13.40 (1H, bs, NH).

Anal. Calcd. for $C_{12}H_{12}N_6O_2S$: C, 47.36; H, 3.98; N, 27.62; S, 10.54. Found: C, 47.21; H, 3.75; N, 27.84; S, 10.48.

4-Hydroxy-3-*p*-toluenesulfonylaminopyrazolo[3,4-*d*]pyrimidine (**5b**).

This compound (0.90 g, 2.96 mmoles) was prepared from **4b** (1.0 g, 3.40 moles) and 1 ml of formamide in 87% yield in a manner similar to that described for the preparation of **5a**. An analytical sample was recrystallized from methanol to give tan needles, mp >340°; ir (potassium bromide): ν max cm^{-1} 3250-3020 (NH or OH), 1650 (CO); uv (ethanol): λ max nm (log ϵ) 213 (4.40); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.37 (3H, s, CH_3), 7.33 (2H, d, J = 8.1 Hz, 3', 5'-H), 7.80 (2H, d, J = 8.1 Hz, 2', 6'-H), 7.93 (1H, d, J = 3.7 Hz, 6-H), 10.23 (1H, bs, NH), 11.93 (1H, bs, NH).

Anal. Calcd. for $C_{12}H_{11}N_5O_3S$: C, 47.21; H, 3.63; N, 22.95. Found: C, 46.98; H, 3.69; N, 22.92.

4-Hydroxy-1-phenyl-3-*p*-toluenesulfonylaminopyrazolo[3,4-*d*]-pyrimidine (**5c**).

This compound (0.94 g, 2.47 mmoles) was prepared from **4c** (1.0 g, 2.69 moles) and 1 ml of formamide in 92% yield in a manner similar to that described for the preparation of **5a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 265°; ir (potassium bromide): ν max cm^{-1} 3250-3020 (NH or OH), 1675 (CO); uv (ethanol): λ max nm (log ϵ) 235 (4.71), 295 (4.10); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.35 (3H, s, CH_3), 7.28-7.58 (5H, m, phenyl-H), 7.80-7.96 (4H, m, phenyl-H), 8.11 (1H, d, J = 2.5 Hz, 6-H), 10.30 (1H, s, NH or OH), 12.04 (1H, bs, NH).

Anal. Calcd. for $C_{18}H_{15}N_5O_3$: C, 56.68; H, 3.96; N, 18.36. Found: C, 56.48; H, 3.95; N, 18.32.

4-Hydroxy-*p*-nitrophenyl-3-*p*-toluenesulfonylaminopyrazolo[3,4-*d*]pyrimidine (**5d**).

This compound (1.06 g, 2.50 mmoles) was prepared from **4e** (1.0 g, 2.40 moles) and 1 ml of formamide in 96% yield in a manner similar to that described for the preparation of **5a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 340°; ir (potassium bromide): ν max cm^{-1} 3160-2860 (NH or OH), 1680 (CO); uv (ethanol): λ max nm (log ϵ) 229 (4.53), 344 (4.13); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.33 (3H, s, CH_3), 7.30 (2H, d, J = 8.0 Hz, phenyl-H), 7.92 (2H, d, J = 8.0 Hz, phenyl-H), 8.18 (1H, s, 6-H), 8.28 (4H, bs, phenyl-H).

Anal. Calcd. for $C_{18}H_{14}N_6O_5S$: C, 50.70; H, 3.31; N, 19.71; S, 7.52. Found: C, 50.47; H, 3.31; N, 19.87; S, 7.37.

4,6-Dihydroxy-3-*p*-toluenesulfonylaminopyrazolo[3,4-*d*]pyrimidine (**6**).

A mixture of 1.48 g (5 mmoles) of **4b** and 1.20 g (10 mmoles) of urea was heated at 160° for 20 minutes. The clear solution went mushy and heating was continued for another 1 hour at 190° until the mushy melt became too solid to stir. The resulting solid was dissolved in hot dilute sodium hydroxide and the boiling basic solution was then carefully acidified with acetic acid. The solution was collected to stand approximately ten minutes and was then filtered. The crude yield of **6** was 1.28 g (4.0 mmoles, 80%), mp 323°. Further purification was accomplished by reprecipitation from hot basic solution with acetic acid. A small amount was recrystallized from a large volume of water and dried at 150° for analysis; ir (potassium bromide): ν max cm^{-1} 3440-3380 (NH or OH), 1705, 1665 (CO); uv (ethanol): λ max nm (insufficient solubility) 216, 249.

Anal. Calcd. for $C_{12}H_{10}N_5O_4S$: C, 44.86; H, 3.45; N, 21.80; S, 9.96. Found: C, 44.60; H, 3.19; N, 21.97; S, 9.95.

4,6-Bis(methylthio)-3-*p*-toluenesulfonylaminopyrazolo[3,4-*d*]-pyrimidine (**7**).

To a solution of 1.49 g (5 mmoles) of **4a** and 20% solution of potassium hydroxide (KOH: 1.12 g, H_2O: 4.5 ml) in 20 ml of dimethyl sulfoxide, stirred at 0°, 0.76 g (10 mmoles) of carbon disulfide was added in several portions during 30 minutes. After another 1 hour at room temperature, 2.13 g (5 mmoles) of methyl iodide was slowly added to the stirring solution over a period of 30 minutes and stirring was continued for 1 hour at room temperature. The reaction mixture was poured into 10 ml of ice-water. The precipitate was collected by filtration and washed several times with water. This crude product was recrystallized from methanol to give 1.31 g (3.67 mmoles) of colorless needles, mp 289°, in 73% yield; ir (potassium bromide): ν max cm^{-1} 3190 (NH); uv (ethanol): λ max nm (log ϵ) 223 (4.34), 255 (4.46), 306

(4.06); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.36 (3H s, CH_3), 2.53 (3H, s, SCH_3), 2.60 (3H, s, SCH_3), 7.30 (2H, d, J = 8.0 Hz, phenyl-H), 7.68 (2H, d, J = 8.0 Hz, phenyl-H), 10.04 (1H, bs, NH), 13.51 (1H, bs, NH).

Anal. Calcd. for $C_{14}H_{15}N_5O_2S_3$: C, 44.08; H, 4.07; N, 18.36; S, 25.51. Found: C, 44.04; H, 4.07; N, 18.33; S, 25.19.

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